Sympathetic Nerve Traffic Activation in Essential Hypertension and Its Correlates

Systematic Reviews and Meta-Analyses

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Abstract—Muscle sympathetic nerve activity (MSNA) has shown that sympathetic activation may occur in essential hypertension (EHT). However, the small sample size of the studies, the heterogeneity of the patients examined, and the presence of confounders represented major weaknesses not allowing to draw definite conclusions. Among the 432 studies identified providing information in EHT on MSNA, 63 were eligible (1216 patients) and meta-analyzed grouping them on the basis of clinically relevant questions: (1) Is MSNA increased in hypertension of mild/moderate-to-severe degree? (2) Does sympathetic activation occur in borderline, white-coat, and masked EHT? (3) Is MSNA related to clinic and ambulatory blood pressure and target organ damage? (4) Are heart rate and venous plasma norepinephrine valuable surrogate markers of MSNA in clinical practice? The results show that MSNA was significantly greater (1.5×; $P<0.001$) in mild-to-moderate and severe EHT as compared with normotensive controls and that this was the case also in borderline, white-coat, and masked hypertension as well. Interestingly, MSNA was significantly greater in both untreated and treated hypertension ($P<0.001$ for both), related to clinic and ambulatory blood pressure ($r=0.67$ and $r=0.83$; $P<0.001$ for both), inversely related to heart rate ($r=-0.38$; $P<0.001$) and directly to venous plasma norepinephrine ($r=0.28$; $P<0.001$) and left ventricular mass index ($r=0.27$; $P<0.001$). Thus, EHT is a condition characterized by a sustained sympathetic overdrive, whose magnitude is proportional to its clinical severity. This is more clearly manifest when MSNA rather than indirect markers of adrenergic drive, such as heart rate and plasma norepinephrine, are used. **(*Hypertension*. 2018;72:483-491. DOI: 10.1161/HYPERTENSIONAHA.118.11038.)** ● **Online Data Supplement**

Key Words: essential hypertension ■ heart rate ■ humans ■ meta-analysis ■ sample size

In the past 3 decades, microneurographic recording of efferent postganglionic sympathetic nerve traffic to the skeletal muscle circulation (muscle sympathetic nerve activity [MSNA]) has been increasingly used for the direct assessment of the neuroadrenergic cardiovascular drive in healthy human beings and in patients with cardiovascular, metabolic, and renal diseases. This has been particularly the case for essential hypertension (EHT), in which microneurographic studies have investigated the participation of sympathetic neural factors in both the development and the progression of the high blood pressure state.[1–63] The results, however, suffer from limitations. First, conclusions on the existence and importance of sympathetic overdrive in hypertension have not been univocal, particularly with regard to the initial and more mild hypertensive states.[17,30,32,33,35,54–58,61–63] Second, microneurographic data have shown variable discrepancies with less direct adrenergic markers, such as resting heart rate (HR) and venous plasma norepinephrine (NE), sometimes making interpretation of the data controversial.[2,4,6,7,10,15,16,18,20,27,31,35,39,42,47,50,53] Third, all available studies have been based on a small number of subjects, largely because of the difficulty to obtain stable MSNA recordings with optimal signal-to-noise ratios in many patients. The last limitation has made it difficult to safely generalize the results to the large hypertensive population.

The present meta-analysis was aimed at minimizing some of the above limitations, by determining MSNA from many studies and thus from an overall large sample. Because of the larger number of available studies, the analysis was

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primarily based on MSNA quantification in essential hypertensive forms of different severity, but data from less widely addressed conditions (eg, prehypertension, family history of hypertension, and white-coat and masked hypertension) were also considered, and assessment was extended to the relationship of MSNA with other neuroadrenergic markers (NE and HR), metabolic variables, and markers of target organ damage.

Methods

A detailed Methods section is available in the online-only Data Supplement. The data of the meta-analysis are available from the corresponding author at reasonable request.

Data Source and Search Strategy

Ovid-MEDLINE database was looked for English language articles without time restriction up to March 1, 2017, through focused, highly sensitive searching strategies (Table S1 in the online-only Data Supplement). References from relevant studies were screened for supplementary articles. The search was designed by C.Z. and D.B. and performed by A.P. and D.B.

Study Selection and Data Extraction

We included any observational (cross-sectional or longitudinal) or interventional study providing information on MSNA by multifiber nerve traffic recordings. Titles and abstracts were screened independently by 2 authors (C.Z. and G.S.) and studies were excluded if they (1) focused on secondary forms of hypertension or treatment-resistant hypertension, diabetes mellitus, heart failure, renal insufficiency, and obesity; (2) did not provide data on the parameters of interest (see below); and 3) did not base MSNA quantification on microneurography. Case reports, reviews, editorials, letters, and studies performed in subjects aged <18 years were also excluded, although screened for potential additional references. Interventional or longitudinal studies were considered only for their baseline data. Studies in which at least part of the population did not display exclusion criteria were included, limited to the relevant patients. Two authors (C.Z. and G.S.) to confirm the study eligibility critically assessed the full text of the retrieved studies.

The main variable to analyze was MSNA burst incidence over time (bursts per minute) and corrected for HR (bursts per 100 heartbeats). Additional variables of interest included (1) office and 24-hour systolic and diastolic blood pressure (SBP and DBP, respectively); (2) resting HR; (3) echocardiographic data, including left ventricular mass index; (4) venous plasma NE and plasma NE spillover (systemic, renal, or cardiac); (5) renal function parameters, such as serum creatinine, creatinine clearance or estimated glomerular filtration rate, and albuminuria or proteinuria; (6) anthropometric data, such as body mass index, waist circumference and waist-to-hip ratio, as well as other biochemical data related to patients' metabolic profile (plasma or serum glucose, cholesterol and triglycerides, serum insulin levels, and homeostatic model assessment index); (7) information on familial background for hypertension and cardiovascular disease; and (8) ongoing pharmacological treatment.

Data Analysis

Data are expressed as means±SD or SE. In statistical analyses, all studies were weighted for sample size. The equality of variances was evaluated by Levene test. Comparison between 2 groups was analyzed by Student *t* test, whereas association between variables was assessed by Pearson correlation coefficient and *P* value. Multiple regression models were used to adjust for potential confounders, such as age and sex, when available. One-way ANOVA followed by Dunnett post hoc test was used to compare data among groups. *P* values <0.05 are considered statistically significant. Statistical analyses were performed by G.D. and A.P. using IBM SPSS, version 22. Recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement were adhered to the study by Page et al.[64]

Results

Search Results

The flowchart of the studies selection process is shown in Figure S1. Four hundred and thirty-two potentially relevant references were initially retrieved. Twelve additional citations were added by personal search. By title and abstract screening, 360 citations were excluded because of search overlap, focus on patients other than those of interest (see above), focus on end points other than those of interest (see above), or because the articles were review articles or case reports. Among the remaining 72 articles, 9 were excluded because they reported post-treatment data only or because baseline MSNA data suitable to quantification were not available. Thus, a total of 63 articles were selected and used for analysis. The main characteristics of the included studies are reported in Tables S2 (essential hypertensive patients) and S3 (borderline hypertensives and offspring of hypertensive individuals).

Main Study Features

Among the 63 studies reviewed,[1–63] 24 were observational,[1,2,4,6,14,16,17,22,24–26,29,32–34,36–38,40,44,46,48,49,52] and 33 had an interventional design.[3,5,7,9–13,15,18–21,23,27,28,30,31,35,39,41–43,45,47,54,56–58,60–63] Six[8,50,51,53,55,59] were clinical trials, of which 5 were randomized.[50,51,53,55,59] Twenty-seven studies[1–18,54–62] were performed before year 2000. Fifty articles included normotensive subjects as control group[1–7,10,11,13,14,16–20,24–27,29–37,39,40,42,43,45–50,52,54–63]; 4 studies compared ≥2 groups of hypertensive subjects with different clinical stage[8] or presence/absence of comorbidities[22] and risk factors.[9,44] The remaining were cohort studies, with no data from a control group.[12,15,21,23,28,38,41,51,53]

Fifty-three studies reported on essential hypertensive patients.[1–53] Eight studies focused on borderline, high-normal, or white-coat and masked hypertensive patients,[54–58,61–63] and 2 on normotensive individuals with or without family history of hypertension.[59,60] Five studies performed in EHT included also patients fulfilling the criteria defining borderline hypertension or offspring hypertensive state.[17,30,32,33,35]

Characteristics of the Essential Hypertensive Population

The sample size was extremely variable across studies, ranging from 7[11] to 113[16] subjects. The overall study population included 1216 patients. The mean age of participants ranged from 22[4] to 67[19] years with a predominance of men (50%[8,25,32] to 87.5%[30]). A comparison between premenopausal and postmenopausal women was made in 1 study,[49] whereas in the remaining ones, sex information was not provided.[4,13,14,21,24]

The severity of hypertension (World Health Organization classification) varied from mild (stage I),[5,7,10,14,24,30,45,47,50,51] mild/moderate (stage I/II),[4,6,9,12,15,16,18,23,38,43] and moderate/severe or more severe (stages II and III),[13,22,41] while 4 studies covered the full range of hypertension severity.[8,17,32,33] All studies were conducted on whites, whereas comparison between black and white hypertensive subjects was done in 1 study.[9]

Thirty-seven of 53 studies were eligible for quantitative synthesis.[2–7,10,11,13,14,16,17,19,20,24–27,29–32,34–37,39,40,42,43,45–50,52] Two studies reported information on 4 hypertensive subgroups, stratifying population by sex,[36,40] whereas in other 2 studies, patients were stratified by age.[4,6] In 3 studies, data were provided according to stage of hypertension (7 subgroups)[13,17,32] and in 4 according to presence/absence of cardiovascular comorbidities.[27,31,34,42] In 1 study, patients were stratified by both age and hypertension background.[30]

Variables of Interest

Resting MSNA values quantified both as bursts per minute or as bursts per 100 heartbeats were available in 40 studies.[1,2,4,6,7,9–14,17,19–32,34–37,39,42–45,47,48,50,52,53] Thirteen studies reported MSNA expressed as burst incidence over time or as burst incidence corrected for HR only.[3,5,8,15,16,18,33,38,40,41,46,49,51] MSNA was recorded in the peroneal nerve of supine or semisupine subjects in 34 studies,[1,2,7,9–17,19–53] whereas in the remaining 6 studies, MSNA was recorded in the tibial nerve.[3–6,8,18] Thirty-three studies reported MSNA after a period (at least 12–24 hours) of abstinence from smoking, alcohol, coffee, and strenuous physical exercise.[4,6,7,10,14,15,17,19,20,22,24–28,30–34,36,37,39,40,42–44,46,47,49–51,53] No smoking habits, no history of excessive alcohol consumption, and no strenuous physical exercise habits were reported in 7 studies.[12,13,16,23,35,38,52]

Thirty-one studies were performed on treated hypertensive subjects.[1,3–11,13,14,16–20,22,24,26,27,29–31,37,41,43,45,48,52,53] Twenty-four studies quantified MSNA after a washout period (from 12–24 hours to 4 weeks) from antihypertensive drug treatment.[1,3–11,13,14,16–20,22,24,27,30,31,37,45] In a study by Greenwood et al,[22] treatment was discontinued only on the study day. In 2 other studies,[43,53] patients continued their antihypertensive therapy during the study. Washout information was not available in 5 studies.[26,29,41,48,52]

The remaining 22 studies reported MSNA in untreated essential hypertensive patients.[2,12,15,21,23,25,28,32–36,38–40,42,44,46,47,49–51]

Blood pressure and HR were recorded simultaneously with MSNA in 30 studies,[1,4–8,10–16,18–20,23,25,29,35,38,39,42–44,47,48,50,52,53] but this information was not available in the remaining ones.[2,3,9,17,21,22,24,26–28,30–34,36,37,40,41,45,46,49,51] Blood pressure was measured by a standard sphygmomanometer in 25 studies[3,7,8,10,18,19,21,25,26,28,29,32–34,36,37,39–41,44–46,48,49,53] and by a finger photoplethysmographic device (beat-to-beat measurement) in 12 studies.[9,11,16,17,22,30,38,43,47,50–52] Twelve studies reported blood pressure as measured by both devices,[4–6,12–15,20,23,24,35,42] whereas 3 used intra-arterial measurements. No information on blood pressure measurement modalities was reported by Morlin et al.[2] Only 4 studies reported data on 24-hour ambulatory SBP and DBP.[35,39,42,63]

Major echocardiographic variables, such as left ventricular mass and left ventricular mass index, were available in 12 studies,[7,10,13,19,22,25,27,31,34,35,42,52] whereas other echocardiographic parameters were reported in 10 studies.[16,19,22,24,25,27,31,42,52,53] Among the anthropometric variables, body mass index was reported by the majority of the studies reviewed,[9,11,13,14,16,17,19–22,24–37,39–47,49–53] whereas information on weight, waist circumference, and waist-to-hip ratio was provided in 17,[7,9–12,17,20–23,25,26,28,32–34,49] 5,[29,35–36,39–40] and 4[29,46,51,52] studies, respectively.

Information on other markers of sympathetic activity, such as plasma NE, were was in 17 microneurographic studies,[2,4,6,7,10,15,16,18,20,27,31,35,39,42,47,50,53] of which 13 were eligible for quantitative analysis. Only 2 microneurographic studies provided concomitant data on NE spillover (systemic, renal, or cardiac).[27,31] Information on serum creatinine, creatinine clearance, or estimated glomerular filtration rate was reported in few studies,[39,47,50,52,53] and data on albuminuria, proteinuria, or carotid vascular structure were provided in none. Few studies referred to other biochemical parameters, such as plasma glucose or insulin, and homeostatic model assessment index (8 studies).[26,29,35,39,47,50,52,53] Lipid biomarkers (total cholesterol, high density lipoproteins, low density lipoproteins, and triglycerides) were reported by 7 studies.[27,29,31,39,43,47,50]

Results

MSNA in EHT Versus Normotension

Among the 53 articles focused on EHT, 37 reported suitable data to perform quantitative analyses.[2–7,10,11,13,14,16,17,19,20,24–27,29–32,34–37,39,40,42,43,45–50,52]

Overall, MSNA values were significantly greater (1.5×) in hypertensive patients as compared with normotensive controls (Figure 1). MSNA did not differ among essential hypertensive and normotensive women in 1 study,[11] whereas in another study, not included in the global analysis, MSNA values reported to be greater than in normotensive subjects separately in stage I, II, and III EHT[33] (P<0.001). Compared with normotensive subjects, MSNA values were significantly greater in untreated and treated essential hypertensive patients (P<0.001 for both). In the latter, MSNA was usually assessed

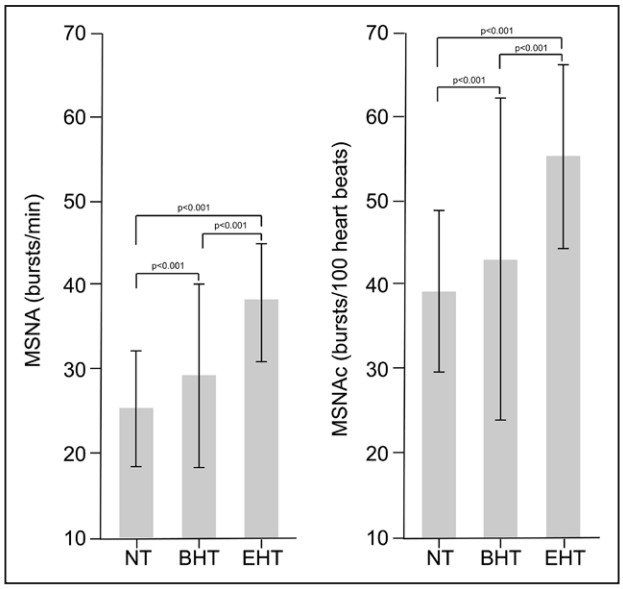

Figure 1. Muscle sympathetic nerve activity (MSNA; means±SD) expressed as burst incidence over time (bursts per minute, **left**) and as bursts corrected for heart rate (bursts per 100 heartbeats, **right**) in normotensive (NT) subjects, borderline essential hypertensives (BHT), and established essential hypertensive (EHT) patients. Differences between groups were highly statistically significant (always P<0.001). Data from 1216 individuals evaluated in 63 microneurographic studies. MSNAc indicates muscle sympathetic nerve activity, values corrected for heart rate.

after washout period of variable duration from antihypertensive drugs, but an increased MSNA value was reported also in the study performed on treated mild-to-moderate essential hypertensive male patients who did not discontinue antihypertensive treatment during the study.[43] Of note is that in the vast majority of cases, patients were studied in the absence (at least 12–24 hours) of smoking, alcohol, coffee, or strenuous physical exercise.

Correlates of MSNA

Correlations with anthropometric data were available in 41 studies. MSNA showed a significant positive association with body mass index (r=0.17 and r=0.25, respectively, for the association uncorrected and corrected for HR; P<0.001 for both). MSNA was also significantly related to clinic SBP and DBP, although in general with not elevated correlation coefficient values (Figure 2). The correlation coefficients were much consistent, however, for 24-hour ambulatory SBP and DBP values (r=0.83 and r=0.82; P<0.001 for both), although data were available in 4 study groups only.[35,39,42,63] Separate analyses, stratified by status, confirmed these associations, particularly between MSNA corrected for HR and the majority of blood pressure measurements (data not shown). There was also a positive significant association between MSNA and age both when data were uncorrected (SBP, β=0.82; DBP, β=0.75; P<0.001 for both) and when corrected for HR (SBP, β=0.86; DBP, β=0.77; P<0.001 for both). Finally, MSNA corrected for HR was signficantly and directly related to plasma glucose and insulin levels (r=0.58 and r=0.64; P<0.01 for both), although data were available in 8 studies only.

In the population including both normotensive and hypertensive patients, MSNA was significantly and directly related to HR, particularly when the data were expressed as burst incidence corrected for HR (Figure 3, top). The association was not significant, however, in the normotensive group, but it was significant in the hypertensive group separately considered. In the latter, however, MSNA exhibited an inverse relationship with HR (MSNA uncorrected: r=–0.16, P<0.001; MSNA corrected for HR: r=–0.38, P<0.001), also after adjustments for age and male sex (β=0.17; P<0.001 for both MSNA expressions). In hypertensives, daytime, nighttime, and 24-hour HR were also significantly but again

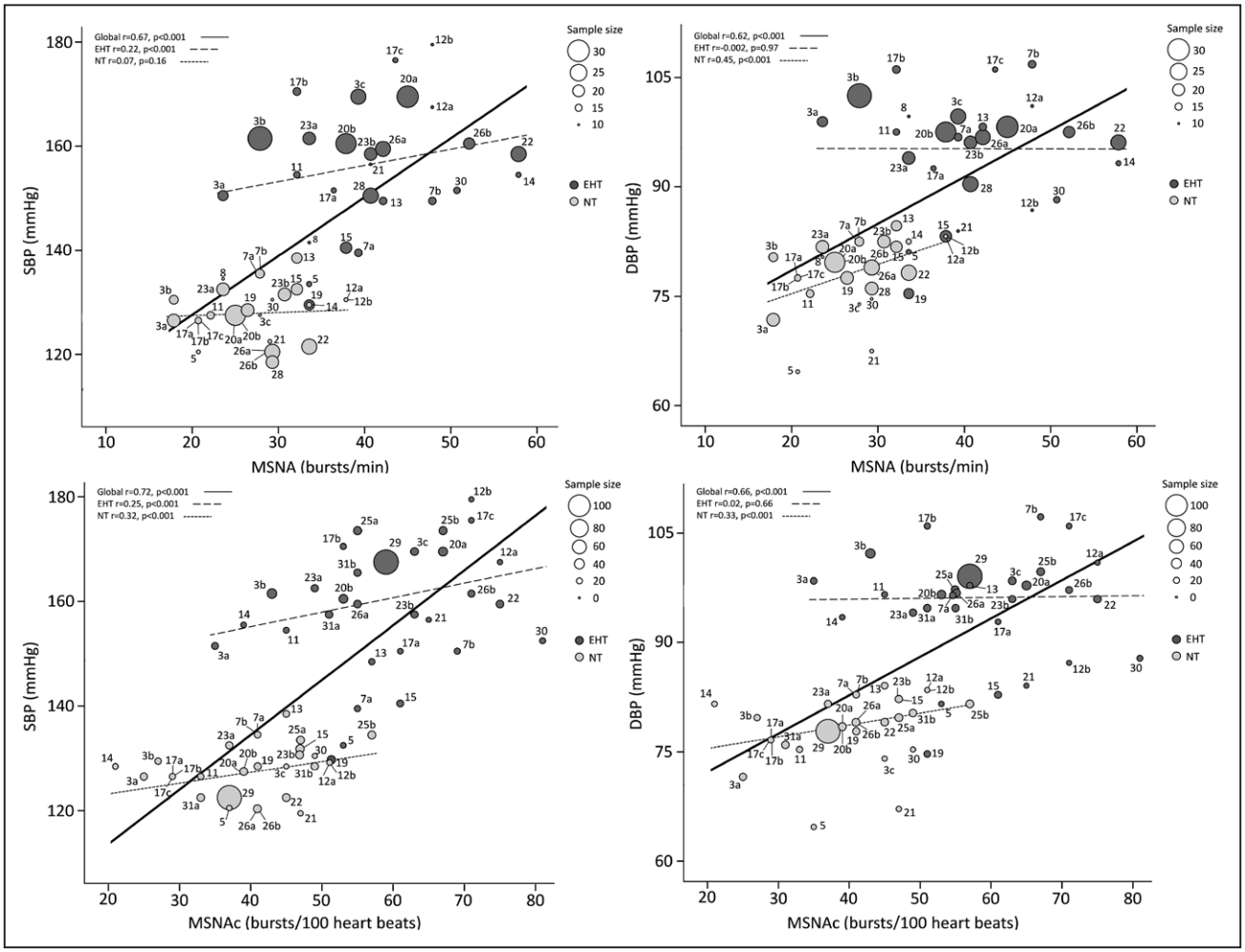

Figure 2. Relationships between systolic blood pressure (SBP, **left**), diastolic blood pressure (DBP, **right**) and muscle sympathetic nerve activity (MSNA), expressed as burst incidence over time (bursts per minute, **top**) and burst incidence corrected for heart rate (bursts per 100 heartbeats, **bottom**) in normotensive (NT) subjects, essential hypertensive (EHT) patients, and in the global population sample. Circles represent individual studies (each numbered according to the references) and have a diameter proportional to the sample size of the studies. MSNAc indicates muscle sympathetic nerve activity, values corrected for heart rate.

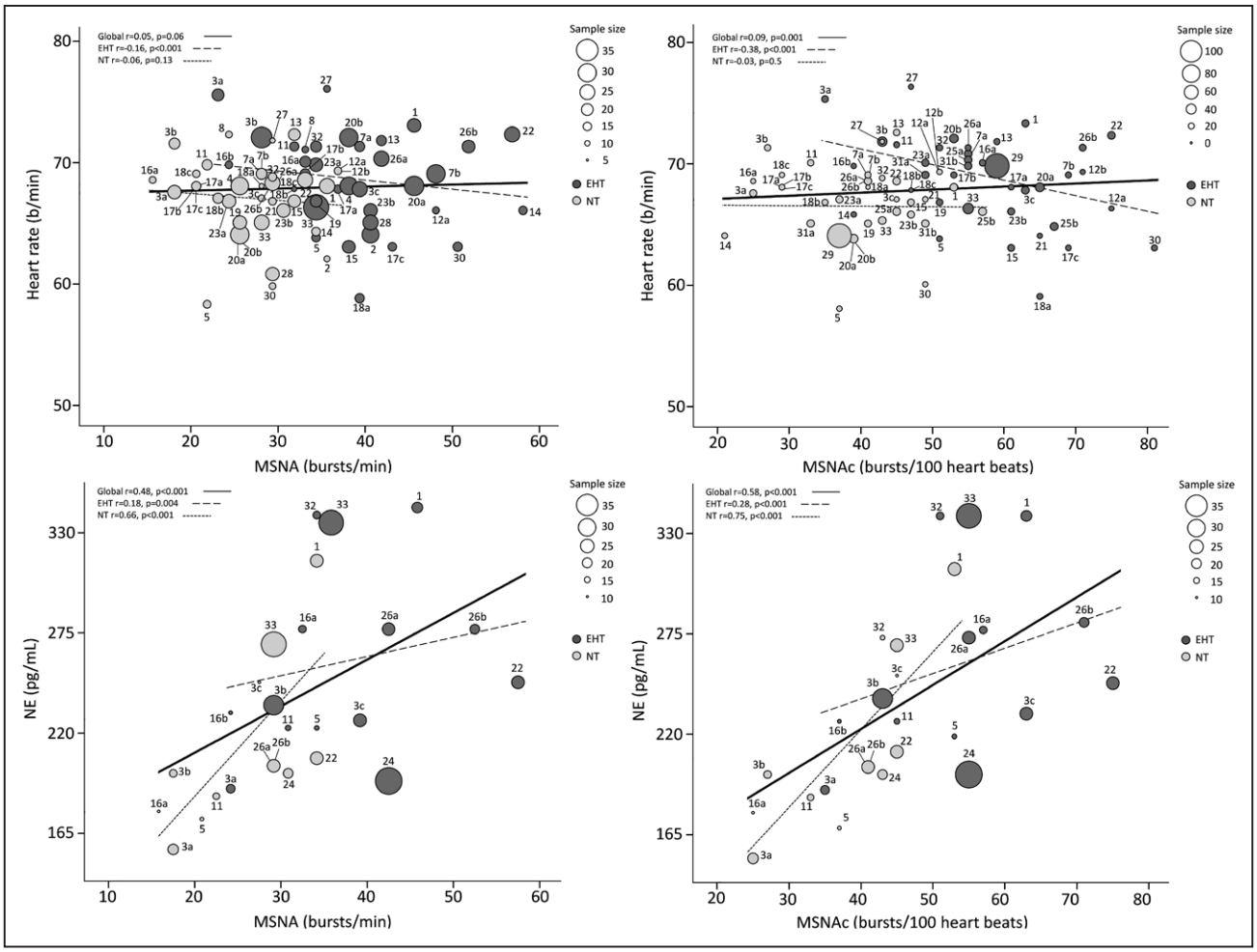

Figure 3. Relationships between different markers of sympathetic activity. **Top**, Relationships between heart rate and muscle sympathetic nerve activity (MSNA), expressed as burst incidence over time (bursts per minute, **left**) and burst incidence corrected for heart rate (bursts per 100 heartbeats, **right**) in normotensive (NT) subjects, essential hypertensive (EHT) patients, and in the global population sample. **Bottom**, Relationships between venous plasma norepinephrine (NE) and MSNA, expressed as burst incidence over time (bursts per minute, **left**) and burst incidence corrected for heart rate (bursts per 100 heartbeats, **right**) in NT, EHT, and in the global population sample. Circles represent individual studies (each numbered according to the references) and have a diameter proportional to the sample size of the studies. MSNAc indicates muscle sympathetic nerve activity, values corrected for heart rate.

inversely related with MSNA, but data were reported only by few study groups (data not shown). Similar results were obtained when MSNA values were replaced by venous plasma NE (data not shown).

MSNA was also significantly and directly related to venous plasma NE (Figure 3, bottom). Separate analyses, stratified by status, confirmed this association, which was also confirmed after data adjustment for age and male sex (MSNA uncorrected: β=0.49; MSNA corrected for HR: β=0.61; $P<0.001$ for both). Also including in the models clinic SBP or DBP, as well as including HR, both the associations remained significant (P at least 0.01).

Finally, MSNA was significantly related to left ventricular mass index, both when expressed as burst incidence over time and corrected for HR ($r=0.51$ and $r=0.38$, respectively; $P<0.001$ for both; Figure 4). After adjustment for age and male sex, the results were confirmed for both variables (β=0.43 and β=0.34, respectively; $P<0.001$ for both), this being the case also after adjustments for blood pressure and HR.

Comparison of Borderline Hypertensives, High-Normal Individuals, and Offsprings of Hypertensive Patients Versus Normotensive Controls

Twelve studies provided information on borderline or high-normal or white-coat or masked hypertensive population.[17,32,33,35,54–58,61–63] All the retrieved studies reported that MSNA was significantly higher in borderline hypertensives than in normotensives, the values being significantly lower than those detected in moderate-to-severe essential hypertensive patients (Figure 1). Exceptions were the studies by Schobel et al,[61,62] in which MSNA was higher in normotensive than in borderline hypertensive men. In white-coat and in masked hypertensives, MSNA values were significantly greater than those reported in true normotensive controls.[32,35] To maximize information on MSNA, we also reported 4 studies performed on individuals with an optimal or high-normal blood pressure,[63] the latter being characterized by a significant ($P<0.01$) elevation in MSNA. On the other hand, no difference in MSNA was detected when comparing normotensives with and without family history of hypertension.[30,54,59,60]

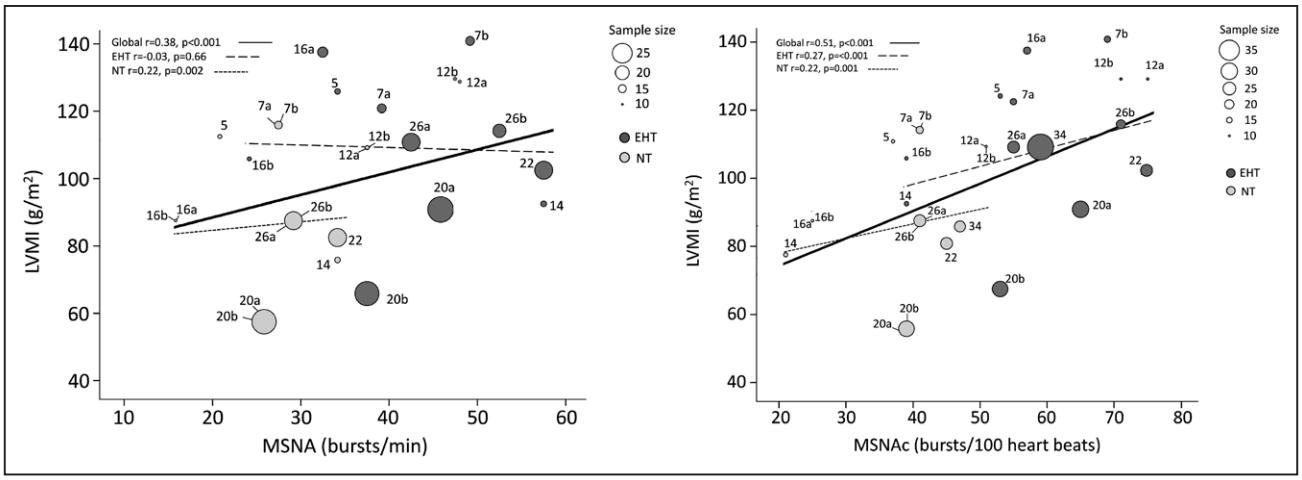

Figure 4. Relationships between left ventricular mass index (LVMI) and muscle sympathetic nerve activity (MSNA), expressed as burst incidence over time (bursts per minute, **left**) and burst incidence corrected for heart rate (bursts per 100 heartbeats, **right**) in normotensive (NT) subjects, essential hypertensive (EHT) patients, and in the global population sample. Circles represent individual studies (each numbered according to the references) and have a diameter proportional to the sample size of the studies. MSNAc indicates muscle sympathetic nerve activity, values corrected for heart rate.

Discussion

The present meta-analyses provide 4 sets of information. First, the only direct and most sensitive marker for the assessment of neuroadrenergic drive, that is, MSNA, is significantly increased in the essential hypertensive state of moderate and more severe degree as compared with the normotensive condition. Second, patients with EHT exhibit sympathetic hyperactivity both when untreated and when under antihypertensive drug treatment, which, therefore, cannot reestablish normalization of sympathetic circulatory drive. Third, the data also show that a direct and significant relationship exists between MSNA and SBP and DBP data conventionally collected in the office environment or via ambulatory blood pressure monitoring throughout the 24-hour period, although in the latter case, based on a much smaller number of patients. Fourth, when compared with age-matched normotensive controls, borderline hypertensives, prehypertensive individuals, as well as patients with white-coat and masked hypertension are also characterized by significant MSNA elevations, although to a degree less marked than that detected in the stable and more severe hypertensive states. It can be thus concluded that essential hypertensive patients are characterized by sympathetic overactivity regardless the hypertension severity, the initial or later stage of the hypertension condition, and the presence or absence of treatment. It seems also clear that in these patients, the magnitude of the sympathetic activation mirrors the degree of the blood pressure increase, both when evaluated in the clinical setting or when assessed via 24-hour ambulatory monitoring in conditions closer to daily life. These conclusions are strengthened by the fact that data were obtained from a large database ever (>1200 patients).

Several other results of the present article deserve to be discussed. In our hypertensive patients, MSNA was inversely related to HR; that is, that elevated MSNA values were associated with lower HR and vice versa. This may imply that in EHT there is some dissociation between the changes of cardiac and peripheral sympathetic activity, namely that any time peripheral or (vascular) sympathetic activity is increased cardiac sympathetic drive tends to show a reduction, possibly because of the influence of the baroreflex.[65] It may also be regarded, however, as further evidence that HR is a somewhat insensitive marker of adrenergic cardiovascular drive, as it has been shown in studies on much smaller population samples.[16] This may be ascribed to the fact that HR is modulated not only by sympathetic drive but also, and to a greater extent, by vagal influences on the sinus node.[16] A further possibility refers to the fact that normalization of MSNA values for HR may in some way interfere with the relationships between the 2 variables.

In the patients of our meta-analyses, venous plasma NE was directly related to MSNA values not only in the population as a whole but also separately in the normotensive and in the hypertensive group. This provides a large-scale demonstration that plasma NE represents a satisfactory indicator of the existence of an increased generalized sympathetic activity, thereby validating the results of an old meta-analysis that concluded that a sympathetic overdrive occurs in 40% of hypertensive patients, based on plasma NE values.[66] It should be mentioned, however, that the correlation between MSNA and NE found in our meta-analysis remains weak, suggesting that NE and other surrogate markers of adrenergic drive, such as HR, have limitations in reflecting adrenergic drive (particularly the one characterizing regional cardiovascular districts, such as in the renal and coronary circulation) and its changes elicited by therapeutic interventions, such as renal denervation.[65,67] The profound differentiation and heterogeneity in the behavior of the sympathetic drive in different cardiovascular districts in hypertensive patients should be also considered when assessing sympathetic responses, which may not be uniform in different cardiovascular districts.[65] In this regard, it should be emphasized that at variance from the regional NE spillover approach, which allows to provide information on sympathetic outflow in different organs, microneurography allows to directly assess sympathetic drive in a specific neural district only, that is, the skeletal mucle one.[65] Our results finally indicate, however,

that in EHT, the sympathetic hyperactivity does not depend on peripheral abnormalities (increased release of NE from sympathetic nerve terminals, decreased neuronal reuptake of NE, and reduced NE tissue clearance in the synaptic clefts) but that central activation is involved. It has been hypothesized that the increased central sympathetic neural outflow may originate from an excessive hypothalamic drive because of excessive environmental chronic stimuli or inherent subcortical hyperresponsivness to an otherwise normal environment[65].

Finally, our meta-analysis shows that in the whole population sample, as well as in the normotensive and hypertensive groups, there is a direct relationship between MSNA and left ventricular mass index. Confirming the results obtained in experimental models, this provides evidence that sympathetic influences participate in the growth of cardiac mass (a finding previously limited to 2 small studies[22,27]) and that this is the case not only when blood pressure is elevated but also when it is still normal. Whether the promoting role of sympathetic hyperactivity on organ damage includes large and small vessels remains to be seen because no study on this issue has been performed to date.

Perspectives

Our meta-analysis has some limitations but also some strengths. The first limitation, which is shared by all the meta-analytic investigations, includes the fact that the evaluation we did depends on the number, size, and design of the various studies included in the analysis, and this may have affected to some extent the results. However, the homogeneity of the data obtained (>90% of the studies displayed greater MSNA values in hypertensive patients as compared with normotensive controls) speaks against this possibility. The second limitation refers to the fact that comparisons were made without correction for multiple testing, not excluding the possibility that some of the significant differences may be because of chance. The strengths are the number of studies and patients included in the meta-analysis, which makes the present evaluation the largest never done before, as well as the rigid selection criteria for inclusion and analysis of the microneurographic studies included in the present study. The clinical implication is that EHT is by no means a condition characterized by a sustained increase in sympathetic cardiovascular drive, whose magnitude is proportional to the degree of the blood pressure elevation, as well as to the clinical severity of the disease. This should be taken into account in setting the therapeutic approach to the hypertensive state, both when based on nonpharmacological or pharmacological interventions.

Disclosures

None.

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Novelty and Significance

What Is New?

- This article provides data on the first meta-analysis ever done on the behavior of muscle sympathetic nerve traffic in essential hypertension.
- Data related to the relationships between office blood pressure, ambulatory blood pressure, target organ damage, and sympathetic nerve traffic are reported.

What Is Relevant?

- The results of the meta-analysis, involving 1216 patients, show that sympathetic nerve traffic is significantly increased in the essential hypertensive state of moderate and more severe degree as compared with the normotensive condition. This is the case also for borderline hypertension and prehypertension as well.
- The data also show that patients with essential hypertension exhibit sympathetic overactivity both when untreated and when under antihypertensive drug treatment.
- Finally, the results of the meta-analysis show that sympathetic nerve traffic is closely related to clinic, 24-hour ambulatory blood pressure, and cardiac organ damage as well.

Summary

Essential hypertension is a condition characterized by a sustained increase in sympathetic cardiovascular drive, whose magnitude is proportional to the degree of the blood pressure elevation, as well as to the clinical severity of the disease.

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Sympathetic Nerve Traffic Activation in Essential Hypertension and Its Correlates: Systematic Reviews and Meta-Analyses

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SYMPATHETIC NERVE TRAFFIC ACTIVATION IN ESSENTIAL HYPERTENSION AND ITS CORRELATES: SYSTEMATIC REVIEWS AND META-ANALYSES.

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S1. Focused search strategy in MEDLINE database

Ovid-MEDLINE
1. muscle sympathetic nerve activity.tw.
2. sympathetic nerve traffic.tw.
3. sympathetic nervous system.tw.
4. microneurography.tw.
5. 1 or 2 or 3 or 4
6. essential hypertension.tw.
7. primary hypertension.tw.
8. idiopathic hypertension.tw.
9. hypertension essential.tw.
10. systemic primary arterial hypertension.tw.
11. 6 or 7 or 8 or 9 or 10
12. 5 and 11
13. limit 12 to human
14. (comment or editorial or historical_article or review or letter).pt.
15. 13 not 14

S2. Summary of main characteristics and findings of the studies reviewed

Study, year (ref)	Study design	-Inclusion criteria -Exclusion criteria	Population characteristics	Control group	MSNA technique	Variables
Wallin and Sundlof, 1979 (1)	Observational	-Essential hypertensive subjects	-N=8 -Men (%)= 75 -Age (yrs)= 41.3±11.2 -Intra-arterial SBP (mmHg)= 179.3±26.9 -Intra-arterial DBP (mmHg)= 110.6±10.8 -HR (b/min)= 73.6±5.6	-N=33 -Normotensives -Men (%)= 75.7 -Age (yrs)= range (18-54)	Records performed on peroneal nerve at the fibular head or in median nerve at the elbow level	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)
Morlin et al., 1983 (2)	Observational	-Untreated essential hypertensive subjects	-N=18 -Men (%)= 77.8 -Age (yrs)= 41.6±9.8 -HR (b/min)= 73.1±8.9	-N=20 -Normotensives -Men (%)= 85 -Age (yrs)= 34.7±10.2 -HR (b/min)= 68.2±10.2	Records performed on peroneal nerve	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats) Plasma Noradrenaline (nmol/L)
Matsukawa et al., 1988 (3)	Interventional	-Uncomplicated essential hypertensive subjects	-N=12 -Men (%)= 58.3 -Age (yrs)= 49±2.0 -MAP (mmHg)= 104±3.0 -HR (b/min)= 64±3.0	-N=9 -Normotensives -Men (%)= 55.6 -Age (yrs)= 50±3.0 -MAP (mmHg)= 86±3.0 -HR (b/min)= 62±2.0	Records performed on tibial nerve at the popliteal fossa in supine subjects	Burst rate (bursts/min) PRA (ng/mL/h)
Yamada et al., 1989 (4) Miyajima et al., 1991 (6)	Observational	-Stage I or II (WHO classification) uncomplicated essential hypertensive subjects with sitting BP≥160/95 mmHg -Secondary hypertension	-N=16 -Young (≤30 yrs) hypertensives -Age (yrs)= 22.3±0.9 -SBP (mmHg)= 150.5±3.4 -DBP (mmHg)= 98.8±2.6 -HR (b/min)= 75.5±1.9 -N=27 -Middle-aged (31-50 yrs) hypertensives -Age (yrs)= 41.6±0.9 -SBP (mmHg)= 161.1±3.4 -DBP (mmHg)= 102.2±2.0 -HR (b/min)= 72.0±1.7 -N=20 -Older (≥51 yrs) hypertensives -Age (yrs)= 58.5±0.9 -SBP (mmHg)= 169.8±4.3 -DBP (mmHg)= 99.0±2.0 -HR (b/min)= 67.8±2.3	-N=18 -Young (≤30 yrs) normotensives -Age (yrs)= 22.6±0.8 -SBP (mmHg)= 126.1±2.6 -DBP (mmHg)= 71.3±2.2 -HR (b/min)= 67.7±1.9 -N=15 -Middle-aged (31-50 yrs) normotensives -Age (yrs)= 42.5±1.7 -SBP (mmHg)= 130.4±2.7 -DBP (mmHg)= 80.3±1.4 -HR (b/min)= 71.5±2.4 -N=10 -Older (≥51 yrs) normotensives -Age (yrs)= 57.0±1.7 -SBP (mmHg)= 128.3±3.2 -DBP (mmHg)= 74.1 ±2.6 -HR (b/min)= 67.0±1.9	Records performed on tibial nerve at the popliteal fossa in prone subjects who had been supine for 30-60 minutes	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)

						Spike frequency (spikes/min)	
						Plasma Norepinephrine (pg/mL)	
Matsukawa et al., 1991 (5)	Interventional	-Uncomplicated, mild essential hypertensive subjects (DBP≥95 mmHg) -Secondary hypertension	-N=23 -Men (%)= 56.5 -Age (yrs)= 41.3±1.7 -MAP (mmHg)= 106±2.0 -HR (b/min)= 68±1.0	-N=23 -Normotensives -Men (%)= 52.2 -Age (yrs)= 41.1±2.0 -MAP (mmHg)= 84±2.0 -HR (b/min)= 68±2.0	Records performed on tibial nerve at the popliteal fossa in prone subjects who had been supine for 30-60 minutes	Burst rate (bursts/min)	
Matsukawa et al., 1993 (8)	Trial	-Both benign (sitting DBP>95 mmHg) and accelerated (DBP>130 mmHg) essential hypertensive subjects	-N=8 -Benign essential hypertensives -Men (%)= 50 -Age (yrs)= 40±3 -SBP (mmHg)= 161±4 -DBP (mmHg)= 91±2	-N=7 -Accelerated essential hypertensives -Men (%)= 57.1 -Age (yrs)= 39±2 -SBP (mmHg)= 210±3	Records performed on tibial nerve at the popliteal fossa in supine	Burst rate (bursts/min)	

		-Secondary hypertension	-HR (b/min)= 60±2	-DBP (mmHg)= 126±3 -HR (b/min)=68±5	subjects	PRA (ng/mL/h)
Floras and Hara, 1993 (7) Hara and Floras, 1995 (10)	Interventional	-Young, untrained, mild essential hypertensive subjects (sitting SBP/DBP range, 140-170/90-105) -Secondary hypertension, concurrent illness and use of medication	-N=12 -Men (%)= 83.3 -Age (yrs)= 31±6 -Weight (Kg)= 81±14 -LVM (g)= 247±86 -LVMI (g/m^2)= 125±33 -SBP (mmHg)= 132.8±9.7 -DBP (mmHg)= 81.3±8.4 -HR (b/min)= 63.8±12.2	-N=11 -Normotensives -Men (%)= 100 -Age (yrs)= 26±6 -Weight (Kg)= 79±11 -LVM (g)= 215±39 -LVMI (g/m^2)= 111±22 -SBP (mmHg)= 119.8±7.2 -DBP (mmHg)= 64.6±8.9 -HR (b/min)= 58.2±10.8	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats) Plasma Noradrenaline (nmol/L) ANF (pg/mL)
Calhoun et al. 1994 (9)	Interventional	-Mild to moderate essential hypertensive subjects	-N=13 -African-American hypertensives -Men (%)= 69.2 -Age (yrs)= 47±2 -Weight (kg)=92±6 -BMI (kg/m^2)=31±2 -Finger SBP (mmHg)= 177±4 -Finger DBP (mmHg)= 100±2 -Finger MAP (mmHg)= 125±3 -HR (b/min)= 68±4	-N=12 -American Caucasian hypertensives -Men (%)= 75 -Age (yrs)= 48±4 -Weight (kg)=91±5 -BMI (kg/m^2)=31±3 -Finger SBP (mmHg)= 173±5 -Finger DBP (mmHg)= 95±2 -Finger MAP (mmHg)= 121±3 -HR (b/min)= 67±3	Records performed on peroneal nerve at the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)
Schobel et al., 1996 (11)	Interventional	-Essential hypertensive women	-N=7 -Age (yrs)= 27±2 -Weight (kg)= 67±6 -BMI (kg/m^2)= 23.9±0.2 -Finger MAP (mmHg)= 119±5	-N=6 -Normotensives -Age (yrs)= 25±1 -Weight (kg)= 66±4 -BMI (kg/m^2)= 23.7±0.1 -Finger MAP (mmHg)= 96±3	Records performed on peroneal nerve posterior to the fibular head	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)
Grassi et al., 1997 (12) Grassi et al., 2002 (23)	Interventional	-Untreated mild or moderate essential hypertensive males -History and physical or laboratory evidence of CV disease or major target organ damage, such as congestive heart failure, coronary or cerebrovascular disease, peripheral artery disease, renal insufficiency or LVH, major non-CV diseases	-N=9 -Age (yrs)= 34.1±3.3 -Weight (kg)= 78.6±2.1 -SBP (mmHg)= 142.5±2.4 -DBP (mmHg)= 98.0±2.5 -Finger SBP (mmHg)= 140.5±2.5 -Finger DBP (mmHg)= 95.5±2.1 -HR (b/min)= 64.4±2.3 -Respiration rate (breaths/min)= 19.8±1.4	-	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats) PRA (ng/mL/h) Plasma aldosterone (pg/mL)
Grassi et al., 1998 (13)	Interventional	-Moderate (≥95 DBP ≤105 mmHg) and	-N=14 -Moderate hypertensives	-N=15 -Normotensives	Records performed on	Burst rate (bursts/min)

		more severe (DBP>105 mmHg) essential hypertensive subjects -History and/or evidence of smoking, excessive alcohol consumption, coronary heart disease, congestive heart failure, cerebrovascular disease, renal insufficiency or DM	-Age (yrs)= 51.8±2.4 -BMI (kg/m^2)= 26.7±0.6 -SBP (mmHg)= 140.1±3.5 -DBP (mmHg)= 97.2±3.9 -Finger SBP (mmHg)= 136.7±3.0 -Finger DBP (mmHg)= 94.5±1.7 -HR (b/min)= 71.1±2.0 -LVMI (g/m^2)= 122.4±4.4 -N=14 -More severe hypertensives -Age (yrs)= 52.6±2.1 -BMI (kg/m^2)= 25.4±0.4 -SBP (mmHg)= 149.9±4.8 -DBP (mmHg)= 107.2±4.1 -Finger SBP (mmHg)= 147.1±4.6 -Finger DBP (mmHg)=104.8±3.0 -HR (b/min)= 69.1±1.4 -LVMI (g/m^2)= 139.9±5.7	-Age (yrs)= 49.5±3.6 -BMI (kg/m^2)= 24.8±0.6 -SBP (mmHg)= 135.2±4.1 -DBP (mmHg)= 83.1±3.0 -Finger SBP (mmHg)=133.1±3.7 -Finger DBP (mmHg)= 80.7±2.7 -HR (b/min)= 69.2±2.5 -LVMI (g/m^2)= 114.7±3.7	peroneal nerve posterior to the fibular head of supine subjects		
						Burst incidence (bursts/100 heart beats)	
Grassi et al., 1998 (14)	Observational	-Mild essential hypertensive subjects (≥90 DBP ≤109 mmHg) -History and/or clinical evidence of hypertension-related complications or major end organ damage	-N=10 -Age (yrs)= 47.8±4.6 -BMI (kg/m^2)= 26.1±1.3 -SBP (mmHg)= 141.3±3.3 -DBP (mmHg)= 99.1±3.0 -Finger SBP (mmHg)= 138.9±3.2 -Finger DBP (mmHg)= 96.8±1.9 -HR (b/min)= 71.1±3.5 -Respiration rate (breaths/min)= 19.3±1.4	-N=10 -Healthy lean normotensives -Age (yrs)= 38.1±4.0 -BMI (kg/m^2)= 25.3±1.1 -SBP (mmHg)= 134.0±3.1 -DBP (mmHg)= 80.5±2.6 -Finger SBP (mmHg)= 132.5±3.5 -Finger DBP (mmHg)= 79.4±2.9 -HR (b/min)= 72.3±3.2 -Respiration rate (breaths/min)= 18.9±1.3	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min)	
						Burst incidence (bursts/100 heart beats)	
Grassi et al., 1998 (16)	Observational	-Mild to moderate essential hypertensive subjects -History of excessive alcohol consumption, CV disease, renal insufficiency or DM	-N=113 -Men (%)= 81.6 -Age (yrs)= 51.1±7.6 -BMI (kg/m^2)= 24.4±2.8 -Finger MAP (mmHg)= 109.7±10.1 -LVEF (%)=63.2±9.7	-N=38 -Healthy Normotensive -Men (%)= 91.2 -Age (yrs)= 48.2±12.1 -BMI (kg/m^2)= 24.1±3.8 -Finger MAP (mmHg)= 91.5±10.4 -LVEF (%)= 66.4±7.5	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min)	
						Plasma Norepinephrine (pg/mL)	
						HR (b/min)	
Grassi et al., 1998 (15)	Interventional	-Untreated mild or moderate essential hypertensive subjects (≥95 DBP ≤105 mmHg) -History or physical or laboratory evidence of	-N=9 -Men (%)= 100 -Age (yrs)= 47.9±2.5 -SBP (mmHg)= 139.7±3.0 -DBP (mmHg)= 96.5±2.7 -Finger MAP (mmHg)=108.9±2.8 -HR (b/min)= 66.7±2.9	-	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst incidence (bursts/100 heart beats)	
						Plasma Norepinephrine (pg/mL)	

		CV disease or major target-organ damage, such as congestive heart failure, coronary insufficiency, stroke, peripheral artery disease, renal insufficiency or echocardiographic LVH and no major concomitant non-CV diseases.				PRA (ng/mL/h)
Greenwood et al., 1999 (17)	Observational	-Stage I (BP≤159/99 mmHg) and stage II/III (BP≥160/100 and ≥180/110 mmHg, respectively) uncomplicated essential hypertensive Caucasian subjects -Secondary hypertension, arrhythmia or chronic disease	-N=19 -Stage I hypertensives -Men (%)= 58 -Age (yrs)= 43±2.8 -Weight (Kg)= 80±3.8 -BMI (kg/m^2)= 27±1.0 -Finger SBP (mmHg)= 148±1.5 -Finger DBP (mmHg)= 92±1.2 -Finger MAP (mmHg)= 111±0.8 -Finger HR (b/min)= 72±2.2 -N=21 -Stage II/III hypertensives -Men (%)= 47.6 -Age (yrs)= 45±2.3 -Weight (Kg)= 80±4.0 -BMI (kg/m^2)= 28±1.0 -Finger SBP (mmHg)= 171±4.6 -Finger DBP (mmHg)= 108±2.6 -Finger MAP (mmHg)= 129±2.6 -Finger HR (b/min)= 73±1.8	-N=17 -Normotensives -Men (%)= 41.2 -Age (yrs)= 37±2.0 -Weight (Kg)= 72±2.7 -BMI (kg/m^2)= 26±0.7 -Finger SBP (mmHg)= 117±1.9 -Finger DBP (mmHg)= 75±1.3 -Finger MAP (mmHg)= 89±1.2 -Finger HR (b/min)= 66±2.0	Records performed on peroneal nerve posterior to the fibular head of semi-supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)
Miyajima et al., 1999 (18)	Interventional	-Stage I or II (WHO classification) uncomplicated essential hypertensive subjects with elevated PRA (>1.0 ng/mL/h) -Secondary hypertension	-N=28 -Men (%)= 64.3 -Age (yrs)= 43±2.0 -SBP (mmHg)= 162.3±4.2 -DBP (mmHg)= 98.1±2.8 -HR (b/min)= 69.1±1.8	-N=20 -Normotensives	Records performed on tibial nerve	Burst rate (bursts/min) Plasma Noradrenaline (nmol/L)
Grassi et al., 2000 (19)	Interventional	-Elderly essential hypertensive subjects -Secondary hypertension, DM, BMI >25, history or physical or laboratory evidence of congestive heart failure, cerebrovascular disease, coronary heart disease or other major CV or non-CV diseases, major renal damage and history of excessive alcohol consumption	-N=10 -Systo-diastolic (DBP>90 mmHg) hypertensives -Men (%)= 80 -Age (yrs)= 67.2±1.5 -BMI (kg/m^2)= 24.8±0.8 -SBP (mmHg)= 167.4±3.8 -DBP (mmHg)= 100.5±1.9 -HR (b/min)= 66.3±2.7 -Respiration rate (breaths/min)= 20.1±1.6 -LVEF (%)= 60.8±2.9 -LVMI (g/m^2)= 128.4±4.1 -N=10 -Isolated systolic (SBP≥160, DBP <90 mmHg) hypertensives -Men (%)= 80 -Age (yrs)= 66.9±1.7 -BMI (kg/m^2)= 25.1±0.7 -SBP (mmHg)= 179.3±3.3 -DBP (mmHg)= 86.8±2.7 -HR (b/min)= 69.2±3.2 -Respiration rate (breaths/min)= 19.9±1.7 -LVEF (%)= 61.1±2.6 -LVMI (g/m^2)= 129.1±4.2	-N=11 -Normotensives -Men (%)= 72.7 -Age (yrs)= 68.1±1.6 -BMI (kg/m^2)= 24.1±0.7 -SBP (mmHg)= 130.4±4.2 -DBP (mmHg)= 83.5±3.0 -HR (b/min)= 69.3±3.4 -Respiration rate (breaths/min)= 19.6±1.5 -LVEF (%)= 62.4±2.5 -LVMI (g/m^2)= 109.3±3.5	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)

Grassi et al., 2000 (20)	Interventional	-Lean essential hypertensive subjects -Secondary hypertension, DM, family history of hypertension, history, physical or laboratory evidence of congestive heart failure, coronary heart disease or other major CV disease, history of major organ damage (serum creatinine >1.5 mg/dL, proteinuria or LVEF <50%) and history of smoking and/or excessive alcohol consumption	-N=13 -Men (%)= 84.6 -Age (yrs)= 38.5±1.8 -BMI (kg/m^2)= 24±0.8 -Weight (Kg)= 79±1.7 -SBP (mmHg)= 154.2±3.0 -DBP (mmHg)= 97.1±3.1 -Finger SBP (mmHg)=150.4±2.4 -Finger DBP (mmHg)=95.6±2.7 -HR (b/min)= 71.5±2.1 -Respiration rate (breaths/min)= 21.8±0.9	-N=14 -Lean normotensives -Men (%)= 78.6 -Age (yrs)= 33.5±2.2 -BMI (kg/m^2)= 22.8±0.7 -Weight (Kg)= 77.3±2.1 -SBP (mmHg)= 127.3±2.5 -DBP (mmHg)= 75.5±2.0 -Finger SBP (mmHg)= 124.4±2.1 -Finger DBP (mmHg)= 74.1±1.7 -HR (b/min)= 69.9±2.0 -Respiration rate (breaths/min)= 21.2±0.8	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats) Plasma Norepinephrine (nmol/L)	
Greenwood et al., 2000 (21)	Interventional	-Untreated essential hypertensive Caucasian subjects -Secondary hypertension, arrhythmia or chronic disease	-N=12 -Age (yrs)= 57±2.4 -Weight (Kg)= 81±3.8 -BMI (kg/m^2)= 28±0.9 -MAP (mmHg)= 136±2.5 -SBP (mmHg)= 192±7.3 -DBP (mmHg)= 108±2.2 -HR (b/min)= 69±3.9	-	Records performed on peroneal nerve posterior to the fibular head of semi-supine subjects	-	
Greenwood et al., 2001 (22)	Observational	-Moderate to severe (stages II/III [JNC]-VI classification) essential hypertensive Caucasian subjects -Secondary hypertension, arrhythmia or chronic disease	-N=14 -Hypertensives with LVH -Men (%)= 42.9 -Age (yrs)= 55±2.4 -Weight (Kg)= 84±3.3 -BMI (kg/m^2)= 30±1.3 -Finger SBP (mmHg)= 174±6.6 -Finger DBP (mmHg)= 101±2.6 -Finger MAP (mmHg)= 125±3.2 -HR (b/min)= 67±2.1 -PWT (mm)= 13±0.8 -Estimated LVM (g)= 301 ±26.6 -LVMI (g/m^2)= 155±13	-N=14 -Hypertensives without LVH -Men (%)= 64.3 -Age (yrs)= 53±1.8 -Weight (Kg)= 84±4.0 -BMI (kg/m^2)= 30±1.0 -Finger SBP (mmHg)= 173±4.5 -Finger DBP (mmHg)= 107±4.1 -Finger MAP (mmHg)= 128±3.4 -HR (b/min)= 74±2.6 -PWT (mm)= 10±0.3 -Estimated LVM (g)= 215±19 -LVMI (g/m^2)= 113±10.9	Records performed on peroneal nerve posterior to the fibular head of semi-supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats) IVST (mm) End-diastolic volumes (mL)	
Grassi et al., 2002 (24)	Observational	-Mild essential hypertensive subjects with isolated PVCs (with coupling intervals between 50% and 80% of baseline R-R intervals) displayed by ECG-Holter monitoring	-N=14 -Age (yrs)= 53.8±2.6 -BMI (kg/m^2)= 23.9±0.4 -SBP (mmHg)= 149.3±2.6 -DBP (mmHg)= 98.0±2.5 -Finger SBP (mmHg)=147.1±2.5 -Finger DBP (mmHg)=96.4±2.6 -HR (b/min)= 71.8±2.1 -LVEF (%)= 66.4±2.4 -LVEDD (mm)= 50.8±2.6	-N=16 -Healthy subjects in Lown class<II -Age (yrs)= 54.9±2.4 -BMI (kg/m^2)= 23.4±0.4 -SBP (mmHg)= 138.2±2.5 -DBP (mmHg)= 84.3±2.4 -Finger SBP (mmHg)=135.9±2.4 -Finger DBP (mmHg)=82.2±2.5 -HR (b/min)= 72.4±1.9	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min)	

		-Historical, physical, or laboratory evidence of valvular heart disease, history of smoking and/or excessive alcohol consumption, history of recent (≤12 months) myocardial infarction and evidence, during Holter monitoring, of tachyarrhythmias, plurifocal PVCs, monofocal PVCs with coupling intervals <50% or >80% of baseline R-R interval, or monofocal PVCs with a rate >30/hour (Lown class ≥II)	-Respiration rate (breaths/min)= 18.4±0.8	-LVEF (%)= 68.8±2.1 -LVEDD (mm)= 50.1±2.7 -Respiration rate (breaths/min)= 18.8±0.6		Burst incidence (bursts/100 heart beats)
Smith et al., 2002 (25)	Observational	-Newly diagnosed and untreated essential hypertensive Caucasian subjects -Secondary hypertension, LVH, arrhythmia or chronic disease	-N=12 -Men (%)= 50 -Age (yrs)= 47±3.2 -Weight (Kg)= 78±4.0 -BMI (kg/m^2)= 27±0.9 -SBP (mmHg)= 155±3.4 -DBP (mmHg)= 93±1.4 -MAP (mmHg)= 114±1.3 -HR (b/min)= 66±1.7 -PW thickness (mm)= 9.6±0.2 -IVS thickness (mm)= 9.2±0.4 -LVID (mm)= 47.8±0.6 -LVM (g)= 180±3.4 -LVMI (g/m^2)= 93±2.5 -Daytime SBP (mmHg)=144±2.1 -Daytime DBP (mmHg)=87±1.8 -Daytime MAP (mmHg)= 106±1.5 -Daytime HR (b/min)= 79±2.0 -Night-time SBP (mmHg)=121±3.8 -Night-time DBP (mmHg)= 75±2.2 -Night-time MAP (mmHg)= 90±2.5 -Night-time HR (b/min)= 72±3.0	-N=12 -Normotensives -Men (%)= 50 -Age (yrs)= 46±3.9 -Weight (Kg)= 81±3.4 -BMI (kg/m^2)= 28±0.8 -SBP (mmHg)= 129±1.7 -DBP (mmHg)= 82±2.1 -MAP (mmHg)= 98±2.2 -HR (b/min)= 64±2.7 -PW thickness (mm)= 8.3±0.7 -IVS thickness (mm)= 8.7±0.3 -LVID (mm)= 48.3±1.2 -LVM (g)= 159±9.5 -LVMI (g/m^2)= 76±5.0 -Daytime SBP (mmHg)=121±1.3 -Daytime DBP (mmHg)=76±1.5 -Daytime MAP (mmHg)= 91±1.1 -Daytime HR (b/min)= 81±0.6 -Night-time SBP (mmHg)= 99±1.2 -Night-time DBP (mmHg)= 66±0.3 -Night-time MAP (mmHg)= 77±0.6 -Night-time HR (b/min)= 66±2.9	Records performed on peroneal nerve	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)
Hugget et al., 2003 (26)	Observational	-Essential hypertensive white subjects -Secondary hypertension, cardiac dysrhythmias, LVH, vascular disease, microalbuminuria or chronic disease, including peripheral or autonomic neuropathy	-N=17 -Men (%)= 58.8 -Age (yrs)= 57±2.2 -Weight (Kg)= 84±2.8 -BMI (kg/m^2)= 30±1.0 -SBP (mmHg)= 141±3.1 -DBP (mmHg)= 83±2.1 -MAP (mmHg)= 103±2.3 -HR (b/min)= 63±2.1 -Fasting glucose (mmol/L)= 5.5±0.2 -Fasting insulin (µU/mL)= 7.2±1.8 -HOMA$_{IR}$ (units)= 1.9±0.6	-N=17 -Normotensives -Men (%)= 53 -Age (yrs)= 56±1.9 -Weight (Kg)= 81±2.9 -BMI (kg/m^2)= 28±0.9 -SBP (mmHg)= 132±1.9 -DBP (mmHg)= 82±0.8 -MAP (mmHg)= 99±1.0 -HR (b/min)= 67±1.2 -Fasting glucose (mmol/L)= 5.0±0.2 -Fasting insulin (µU/mL)= 6.0±1.3 -HOMA$_{IR}$ (units)= 1.4±0.3	Records performed on peroneal nerve posterior to the fibular head of semi-supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)
Schlaich et al., 2003 (27) Schlaich et al., 2004 (31)	Interventional	-Essential hypertensive subjects -Accelerated hypertension, clinical coronary heart disease, heart failure, history of stroke, renal insufficiency or DM	-N=15 -Hypertensives with LVH -Men (%)= 73.3 -Age (yrs)= 47±12 -BMI (kg/m^2)= 28.1±7.0 -Intra-arterial SBP (mmHg)= 165.2±13.5 -Intra-arterial DBP (mmHg)= 82.5±9.1 -HR (b/min)= 70.2±8.5 -Total cholesterol (mmol/L)= 5.09±1.08 -LDL cholesterol (mmol/L)=	-N=10 -Normotensives -Men (%)= 80 -Age (yrs)= 41±14 -BMI (kg/m^2)= 23.1±3.8 -Intra-arterial SBP (mmHg)= 129.0±11.1 -Intra-arterial DBP (mmHg)= 68.8±7.3 -HR (b/min)= 68.6±6.0 -Total cholesterol (mmol/L)= 4.78±0.73 -LDL cholesterol (mmol/L)=	Records performed on peroneal nerve of semi-supine subjects	Burst rate (bursts/min)

			3.22±0.92 -HDL cholesterol (mmol/L)= 1.19±0.27 -Left atrial diameter (cm)= 3.64±0.34 -PWT (mm)= 11.2±1.3 -SWT (mm)= 12.0±1.2 -LVID (cm)= 5.19±0.44 -Estimated LVM (g)= 238±39 -LVMI (g/m^2)= 138±17 -N=11 -Hypertensives without LVH -Men (%)= 72.7 -Age (yrs)= 42±11 -BMI (kg/m^2)= 27.5±6.2 -Intra-arterial SBP (mmHg)= 161.9±8.8 -Intra-arterial DBP (mmHg)= 84.5±8.9 -HR (b/min)= 69.9±7.4 -Total cholesterol (mmol/L)= 5.30±0.68 -LDL cholesterol (mmol/L)= 3.29±0.74 -HDL cholesterol (mmol/L)= 1.35±0.39 -Left atrial diameter (cm)= 3.59±0.26 -PWT (mm)= 9.4±1.1 -SWT (mm)= 9.8±1.2 -LVID (cm)= 5.01±0.41 -Estimated LVM (g)= 176±47 -LVMI (g/m^2)= 106±11	2.99±0.54 -HDL cholesterol (mmol/L)= 1.27±0.34 -Left atrial diameter (cm)= 3.52±0.23 -PWT (mm)= 8.9±0.1 -SWT (mm)= 9.3±1.3 -LVID (cm)= 4.57±0.40 -Estimated LVM (g)= 139±28 -LVMI (g/m^2)= 87±15		Burst incidence (bursts/100 heart beats) Arterial plasma Norepinephrine (pg/mL) Coronary sinus plasma Norepinephrine (pg/mL) Total systemic Norepinephrine spillover (ng/min) Cardiac Norepinephrine spillover (ng/min) Renal Norepinephrine spillover (ng/min)

Smith et al., 2004 (32)	Observational	-Newly diagnosed and untreated essential hypertensive (stages I-III [JNC]-VI classification) white subjects with or without LVH -Secondary hypertension, arrhythmia or chronic disease	-N=12 -Stage I hypertensives -Men (%)= 50 -Age (yrs)= 47±3.1 -BMI (kg/m^2)= 29±0.9 -Weight (Kg)=80±2.9 -SBP (mmHg)= 151±1.2 -DBP (mmHg)= 93±1.8 -MAP (mmHg)= 112±1.2 -HR (b/min)= 66±2.7 -Daytime SBP (mmHg)=147±1.2 -Daytime DBP (mmHg)=89±1.7 -Daytime MAP (mmHg)= 107±1.2 -Daytime HR (b/min)= 82±1.4 -Night-time SBP (mmHg)=131±1.4 -Night-time DBP (mmHg)= 80±1.7 -Night-time MAP (mmHg)= 97±1.5 -Night-time HR (b/min)= 74±2.7 -N=14 -Stage II/III hypertensives -Men (%)= 64.3 -Age (yrs)= 46±3.0 -BMI (kg/m^2)= 28±1.3 -Weight (Kg)=80±2.5 -SBP (mmHg)= 171±3.6 -DBP (mmHg)= 106±1.4 -MAP (mmHg)= 128±1.7 -HR (b/min)= 69±3.1 -Daytime SBP (mmHg)=156±2.7 -Daytime DBP (mmHg)=101±2.6 -Daytime MAP (mmHg)= 119±2.7 -Daytime HR (b/min)= 81±4.6 -Night-time SBP (mmHg)=144±3.3 -Night-time DBP (mmHg)= 85±4.7 -Night-time MAP (mmHg)= 105±2.8 -Night-time HR (b/min)= 67±3.9 -N=12 -Hypertensives with LVH -Men (%)= 50 -Age (yrs)= 48±3.0 -BMI (kg/m^2)= 28±1.0 -Weight (Kg)=80±3.7 -SBP (mmHg)= 176±5.0 -DBP (mmHg)= 106±4.3 -MAP (mmHg)= 129±4.3 -HR (b/min)= 63±2.2 -Daytime SBP (mmHg)=158±8.2 -Daytime DBP (mmHg)=99±4.0 -Daytime MAP (mmHg)= 119±5.2 -Daytime HR (b/min)= 81±3.6 -Night-time SBP (mmHg)=142±9.3 -Night-time DBP (mmHg)= 84±3.5 -Night-time MAP (mmHg)= 103±6.8 -Night-time HR (b/min)= 70±4.4	-N=13 -Normotensives -Men (%)= 46.2 -Age (yrs)= 45±3.5 -BMI (kg/m^2)= 27±0.8 -Weight (Kg)=78±2.2 -SBP (mmHg)= 126±1.6 -DBP (mmHg)= 77±1.9 -MAP (mmHg)= 93±1.8 -HR (b/min)= 68±3.2 -Daytime SBP (mmHg)= 118±09 -Daytime DBP (mmHg)= 74±1.5 -Daytime MAP (mmHg)= 89±0.9 -Daytime HR (b/min)= 75±4.0 -Night-time SBP (mmHg)=96±2.0 -Night-time DBP (mmHg)= 63±2.8 -Night-time MAP (mmHg)= 79±0.8 -Night-time HR (b/min)= 70±4.9	Records performed on peroneal nerve of semi-supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)	

Smith et al., 2004 (33)	Observational	-Untreated and uncomplicated essential hypertensive (stages I-III [JNC]-VI classification) white subjects with and without NVC of the rostral ventrolateral medulla -Complicated or secondary hypertension, LVH, arrhythmia or chronic disease	-N=26 -Stage I hypertensives -Men (%)= 46.2 -Age (yrs)= 49±2.1 -BMI (kg/m2)= 27±0.8 -Weight (Kg)= 79±2.9 -SBP (mmHg)= 149±1.1 -DBP (mmHg)= 95±0.8 -MAP (mmHg)= 113±0.9 -HR (b/min)= 67±1.9 -N=19 -Stage II/III hypertensives -Men (%)= 63.2 -Age (yrs)= 52±2.7 -BMI (kg/m^2)= 28±1.1 -Weight (Kg)= 83±3.7 -SBP (mmHg)= 170±3.2 -DBP (mmHg)= 101±1.3 -MAP (mmHg)= 124±1.5 -HR (b/min)= 74±2.6	-N=24 -Normotensives -Men (%)= 45.8 -Age (yrs)= 46±2.5 -BMI (kg/m^2)= 26±0.8 -Weight (Kg)= 76±2.5 -SBP (mmHg)= 125±1.0 -DBP (mmHg)= 80±0.8 -MAP (mmHg)= 95±1.0 -HR (b/min)= 65±1.9	Records performed on peroneal nerve of semi-supine subjects	Burst incidence (bursts/100 heart beats)	
Lambert and Schlaich, 2004 (30)	Interventional	-Young and older essential hypertensive (BP>140/90) subjects with and without family history of hypertension -History of major illness, CV disease other than hypertension and drug medication just before study entry	-N=13 -Old hypertensives -Men (%)= 70 -Age (yrs)= 53±1.0 -BMI (kg/m^2)= 28±2.0 -Finger SBP (mmHg)= 155±3.0 -Finger DBP (mmHg)= 82±4.0 -HR (b/min)= 59±2.0 -N=8 -Young hypertensives with family history of HT -Men (%)= 87.5 -Age (yrs)= 28±3.0 -BMI (kg/m^2)= 25±2.0 -Finger SBP (mmHg)= 154±9.0 -Finger DBP (mmHg)= 83±9.0 -HR (b/min)= 68±4.0	-N=8 -Old normotensives -Men (%)= 50 -Age (yrs)= 52±2.0 -BMI (kg/m^2)= 25±2.0 -Finger SBP (mmHg)= 135±4.0 -Finger DBP (mmHg)= 75±2.0 -HR (b/min)= 68±2.0 -N=14 -Young normotensives with family history of HT -Men (%)= 85.7 -Age (yrs)= 25±2.0 -BMI (kg/m^2)= 25±1.0 -Finger SBP (mmHg)= 129±4.0 -Finger DBP (mmHg)= 67±3.0 -HR (b/min)= 67±2.0 -N=11 -Young normotensives without family history of HT -Men (%)= 90.9 -Age (yrs)= 27±2.0 -BMI (kg/m^2)= 23±1.0 -Finger SBP (mmHg)= 118±4.0 -Finger DBP (mmHg)= 63±3.0 -HR (b/min)= 69±2.0	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)	

Burns et al., 2004 (28)	Interventional	-Untreated essential hypertensive subjects -Secondary hypertension, LVH, peripheral vascular disease, arrhythmia or chronic disease	-N=14 -Men (%)= 78.6 -Age (yrs)= 51±3.2 -Weight (kg)= 94±4.0 -BMI (kg/m^2)= 32±1.1 -SBP (mmHg)= 162±6.0 -DBP (mmHg)= 97±2.4 -MAP (mmHg)= 117±3.3 -HR (b/min)= 68±2.6	-	Records performed on peroneal nerve of semi-supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)	
Huggett et al., 2004 (29)	Observational	-Essential hypertensive white subjects -Secondary hypertension, familial dyslipidemia, DM, cardiac dysrhythmias, peripheral vascular disease and chronic disease	-N=16 -Men (%)= 56.3 -Age (yrs)= 54±2.3 -BMI (kg/m^2)= 30±0.9 -Waist/hip ratio= 0.94±0.01 -WC (cm)= 99±2.0 -SBP (mmHg)= 130±2.1 -DBP (mmHg)= 75±1.6 -MAP (mmHg)= 94±1.4 -HR (b/min)= 67±1.4 -Fasting glucose (mmol/L)= 5.4±0.1 -Fasting insulin (µU/mL)= 9.4±2.2 -HOMA$_{IR}$ (units)= 2.3±0.6 -Total cholesterol (mmol/L)= 5.1±0.1 -LDL cholesterol (mmol/L)= 3.1±0.1 -HDL cholesterol (mmol/L)= 1.3±0.03 -Triglycerides (mmol/L)= 1.5±0.05	-N=18 -Normotensives -Men (%)= 55.6 -Age (yrs)= 51±2.0 -BMI (kg/m^2)= 32±1.1 -Waist/hip ratio= 0.91±0.02 -WC (cm)= 98±2.2 -SBP (mmHg)= 129±1.7 -DBP (mmHg)= 78±1.6 -MAP (mmHg)= 95±1.3 -HR (b/min)= 65±1.4 -Fasting glucose (mmol/L)= 5.2±0.1 -Fasting insulin (µU/mL)= 8.8±1.0 -HOMA$_{IR}$ (units)= 2.0±0.2 -Total cholesterol (mmol/L)= 5.2±0.2 -LDL cholesterol (mmol/L)= 3.0±0.1 -HDL cholesterol (mmol/L)= 1.4±0.04 -Triglycerides (mmol/L)= 1.4±0.08	Records performed on peroneal nerve posterior to the fibular head of semi-supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)	
Burns et al., 2007 (34)	Observational	-Uncomplicated and untreated essential hypertensive white subjects -Secondary hypertension, peripheral vascular disease, renal insufficiency, DM, arrhythmias or other chronic disease	-N=25 -Hypertensives with LVH -Men (%)= 68 -Age (yrs)= 52±2.2 -Weight (Kg)= 85±3.0 -BMI (kg/m^2)= 28±0.8 -SBP (mmHg)= 170±4.7 -DBP (mmHg)= 98±2.5 -MAP (mmHg)= 121±3.0 -HR (b/min)= 68±1.8 -LVM (g)= 182±8.6 -LVMI (g/m^2)= 91±3.4 -N=24 -Hypertensives without LVH -Men (%)= 58.3 -Age (yrs)= 52±1.5 -Weight (Kg)= 81±2.8 -BMI (kg/m^2)= 29±0.9 -SBP (mmHg)= 161±2.4 -DBP (mmHg)= 97±4.0 -MAP (mmHg)= 118±1.7 -HR (b/min)= 72±1.9 -LVM (g)= 131±6.1 -LVMI (g/m^2)= 67±2.1	-N=24 -Normotensives -Men (%)= 45.8 -Age (yrs)= 49±2.5 -Weight (Kg)= 77±2.4 -BMI (kg/m^2)= 27±0.7 -SBP (mmHg)= 127±2.5 -DBP (mmHg)= 79±1.4 -MAP (mmHg)= 95±1.7 -HR (b/min)= 64±1.8 -LVM (g)= 107±5.8 -LVMI (g/m^2)= 57±2.2	Records performed on peroneal nerve posterior to the fibular head of semi-supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)	
Lambert et	Observational	-Normal-weight	-N=10	-N=11	Records	Burst rate	

al., 2007 (37)		essential hypertensive subjects -DM, secondary hypertension, obstructive sleep apnea, renal, liver, or thyroid disease and a history of myocardial infarction or stroke	-Men (%)= 80 -Age (yrs)= 44±4 -BMI (kg/m^2)= 25±0.8 -SBP (mmHg)= 157±3 -DBP (mmHg)= 84±4 -HR (b/min)= 64±3	-Normotensives -Men (%)= 54.5 -Age (yrs)= 37±3 -BMI (kg/m^2)= 23±0.6 -SBP (mmHg)= 120±3 -DBP (mmHg)= 67±2 -HR (b/min)= 67±2	performed on peroneal nerve posterior to the fibular head of supine subjects	(bursts/min) Burst incidence (bursts/100 heart beats) Total MSNA frequency (U/min) Total MSNA incidence (U/100 heart beats)	
Grassi et al., 2007 (35)	Interventional	-"In-office" and "out-of-office" middle-aged, non-obese, essential hypertensive subjects -History of smoking, excessive alcohol consumption, CV and non-CV disease including DM, use of antihypertensive and other CV or metabolic drugs, LVH, alterations in renal function, microalbuminuria or ultrasonographic carotid artery thickening or plaques; history or symptoms of sleep apnea syndrome, history of regular exercise habit or involvement in physical training programs	-N=20 -Men (%)= 70 -Age (yrs)= 54.6±2.0 -BMI (kg/m^2)= 27.6±0.4 -WC (cm)= 98.4±3.2 -24h SBP (mmHg)= 136.8±2.1 -24h DBP (mmHg)= 84.3±1.8 -24h HR (b/min)= 70.5±1.8 -Clinic SBP (mmHg)= 159.1±2.0 -Clinic DBP (mmHg)= 95.7±1.9 -Clinic HR (b/min)= 72.2±1.9 -Finger SBP (mmHg)=157.5±2.2 -Finger DBP (mmHg)= 94.2±2.1 -LVMI (g/m^2)= 103.8±4.5 -Plasma glucose (mmol/L)= 5.1±0.5 -Plasma insulin (µU/mL)= 8.9±0.7 -HOMA index (a.u.)= 2.0±0.2	-N=20 -Normotensives -Men (%)= 65 -Age (yrs)= 53.4±2.2 -BMI (kg/m^2)= 24.7±0.5 -WC (cm)= 94.8±2.7 -24h SBP (mmHg)= 117.5±2.2 -24h DBP (mmHg)= 72±1.5 -24h HR (b/min)= 66.9±2.0 -Clinic SBP (mmHg)= 122.3±2.8 -Clinic DBP (mmHg)= 78.6±2.1 -Clinic HR (b/min)= 68.4±2.1 -Finger SBP (mmHg)=120.1±2.9 -Finger DBP (mmHg)= 76.2±2.3 -LVMI (g/m^2)= 82.4±4.9 -Plasma glucose (mmol/L)= 4.9±0.4 -Plasma insulin (µU/mL)= 7.6±0.7 -HOMA index (a.u.)= 1.52±0.2	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats) Plasma Norepinephrine (pg/mL)	
Hogarth et al., 2007 (36)	Observational	-Untreated and uncomplicated essential hypertensive Caucasian subjects -Secondary hypertension, LVH, peripheral vascular disease, arrhythmia, neuropathy or chronic disease	-N=18 -Female hypertensives -Age (yrs)= 51±2.4 -BMI (kg/m^2)= 29±1.2 -WC (cm)= 91±2.7 -SBP(mmHg)= 162±3.1 -DBP (mmHg)= 94±2.2 -MAP (mmHg)= 117±2.0 -HR (b/min)= 70±2.1 -N=18 -Male hypertensives -Age (yrs)= 51±1.7 -BMI (kg/m^2)= 27±0.6 -WC (cm)= 89±2.7 -SBP(mmHg)= 158±3.7 -DBP (mmHg)= 96±2.9 -MAP (mmHg)= 117±2.8 -HR (b/min)= 66±2.0	-N=18 - Female Normotensives -Age (yrs)= 50±2.5 -BMI (kg/m^2)= 27±1.1 -WC (cm)= 95±1.4 -SBP(mmHg)= 132±1.8 -DBP (mmHg)= 82±0.7 -MAP (mmHg)= 99±0.9 -HR (b/min)= 67±2.5 -N=18 -Male normotensives -Age (yrs)= 51±2.4 -BMI (kg/m^2)= 27±0.7 -WC (cm)= 97±1.8 -SBP(mmHg)= 131±1.2 -DBP (mmHg)= 82±1.0 -MAP (mmHg)= 98±1.3 -HR (b/min)= 66±2.4	Records performed on peroneal nerve of semi-supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)	

Grassi et al., 2008 (38)	Observational	-Untreated mild-to-moderate essential hypertensive subjects -Overweight or obese, history of smoking, excessive alcohol consumption or major CV or non-CV disease, including DM. Use of antihypertensive and other CV or metabolic drugs, LVH, alteration in renal function or evidence of carotid artery thickening or plaques, secondary hypertension, history of regular exercise habit or involvement in physical training programmes	-N=14 -Men (%)= 71.4 -Age (yrs)= 46.1±3.3	-	Records performed on peroneal nerve posterior to the fibular head of supine subjects	-	
Grassi et al., 2008 (39)	Interventional	-Untreated middle-aged essential hypertensive subjects -BMI>30 kg/m^2, history of smoking, excessive alcohol consumption and major CV or non-CV disease, including DM, use of antihypertensive and other CV or metabolic drugs, evidence of LVH, alteration in renal function or evidence of carotid artery thickening or plaques, secondary hypertension, history, symptoms or clinical evidence of sleep apnea syndrome	-N=34 -Hypertensive dippers -Men (%)= 79.4 -Age (yrs)= 47.5±2.0 -BMI (kg/m^2)= 26.1±0.3 -WC (cm)= 97.3±2.4 -Clinic SBP (mmHg)= 161.1±2.6 -Clinic DBP (mmHg)= 97.5±2.1 -Clinic HR (b/min)= 73.6±1.9 -24h SBP (mmHg)= 140.7±2.4 -24h DBP (mmHg)= 85.4±1.6 -24h HR (b/min)= 70.8±1.6 -Plasma glucose (mmol/L)= 5.1±0.5 -Plasma insulin (µU/mL)= 9.1±0.5 -HOMA index (a.u.)= 2.11±0.2 -Serum creatinine (mg/dL)= 0.95±0.01 -Cr clearance (mL/min)= 97.3±4.5 -Total cholesterol (mg/dL)= 210.5±4.3 -HDL cholesterol (mg/dL)= 54.3±0.9	-N=17 -Normotensive dippers -Men (%)= 76.5 -Age (yrs)= 46.9±2.3 -BMI (kg/m^2)= 24.3±0.3 -WC (cm)= 93.9±2.4 -Clinic SBP (mmHg)= 121.6±2.9 -Clinic DBP (mmHg)= 79.4±2.2 -Clinic HR (b/min)= 69.4±2.0 -24h SBP (mmHg)= 117.8±2.1 -24h DBP (mmHg)= 73.2±1.9 -24h HR (b/min)= 67.5±2.2 -Plasma glucose (mmol/L)= 4.8±0.5 -Plasma insulin (µU/mL)= 7.4±0.7 -HOMA index (a.u.)= 1.59±0.2 -Serum creatinine (mg/dL)= 0.91±0.03 -Cr clearance (mL/min)= 96.2±5.1 -Total cholesterol (mg/dL)= 202.2±4.5 -HDL cholesterol (mg/dL)= 56.5±1.1	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats) Plasma Norepinephrine (pg/mL)	
Hogarth et al., 2008 (40)	Observational	-Untreated and uncomplicated, middle-aged or older essential hypertensive Caucasian subjects -Secondary hypertension, LVH, peripheral vascular disease, arrhythmia, neuropathy or chronic disease	-N=21 -Postmenopausal female-EHT -Age (yrs)= 58±6.6 -BMI (kg/m^2)= 27±4.8 -WC (cm)= 92±9.2 -SBP(mmHg)= 174±19.9 -DBP (mmHg)= 97±10.1 -MAP (mmHg)= 123±12.0 -HR (b/min)= 71±8.5 -N=21 -Male hypertensives -Age (yrs)= 58±6.2 -BMI (kg/m^2)= 28±4.1 -WC (cm)= 96±7.5 -SBP(mmHg)= 173±25.7 -DBP (mmHg)= 100±10.8 -MAP (mmHg)= 124±14.2 -HR (b/min)= 65±7.5	-N=21 -Postmenopausal female-NT -Age (yrs)= 57±8.1 -BMI (kg/m^2)= 27±3.2 -WC (cm)= 91±10.1 -SBP(mmHg)= 134±10.1 -DBP (mmHg)= 80±7.1 -MAP (mmHg)= 98±7.4 -HR (b/min)= 66±7.5 -N=21 -Male normotensives -Age (yrs)= 59±6.4 -BMI (kg/m^2)= 27±3.6 -WC (cm)= 94±13.7 -SBP(mmHg)= 134±7.6 -DBP (mmHg)= 82±4.6 -MAP (mmHg)= 100±4.3 -HR (b/min)= 66±12.5	Records performed on peroneal nerve of semi-supine subjects	Burst incidence (bursts/100 heart beats)	

Grassi et al., 2009 (42)	Interventional	-Untreated Middle-aged male essential hypertensive subjects with cardiac sinus rhythm -Secondary hypertension, BMI>26 kg/m^2, evidence of LVH, history of smoking, excessive alcohol consumption, and major CV or metabolic diseases, including metabolic syndrome and DM, use of antihypertensive or metabolic drugs, symptoms or evidence of obstructive sleep apnea, renal function alteration, history of regular exercise habit or involvement in physical training programs	-N=20 -Hypertensives without LVDD -Age (yrs)= 46.3±2.4 -BMI (kg/m^2)= 24.2±0.8 -Clinic SBP (mmHg)= 158.8±2.8 -Clinic DBP (mmHg)= 96.7±2.2 -24h SBP (mmHg)= 138.1±2.4 -24h DBP (mmHg)= 86.3±2.2 -Finger SBP (mmHg)= 156.4±2.7 -Finger DBP (mmHg)= 95.2±2.4 -HR (b/min)= 70.5±2.3 -LVEF (%)=67.5±1.1 -LVEDD (mm)= 47.7±0.8 -LVMI (g/m^2)= 110.0±4.5 -N=17 -Hypertensives with LVDD -Age (yrs)= 47.7±2.9 -BMI (kg/m^2)= 24.8±0.9 -Clinic SBP (mmHg)= 160.5±2.9 -Clinic DBP (mmHg)= 97.8±2.5 -24h SBP (mmHg)= 142.9±2.6 -24h DBP (mmHg)= 87.4±2.2 -Finger SBP (mmHg)= 158.2±2.4 -Finger DBP (mmHg)= 96.0±2.4 -HR (b/min)= 71.5±2.2 -LVEF (%)=66.2±1.3 -LVEDD (mm)= 47.5±0.9 -LVMI (g/m^2)= 115.3±4.6	-N=20 -Normotensives -Age (yrs)= 45.2±1.7 -BMI (kg/m^2)= 24.0±0.6 -Clinic SBP (mmHg)= 120.2±2.7 -Clinic DBP (mmHg)= 78.5±1.9 -24h SBP (mmHg)= 116.7±2.2 -24h DBP (mmHg)= 72.9±1.6 -Finger SBP (mmHg)= 118.0±2.5 -Finger DBP (mmHg)= 76.8±2.2 -HR (b/min)= 68.5±2.0 -LVEF (%)=65.7±0.9 -LVEDD (mm)= 47.2±0.7 -LVMI (g/m^2)= 86.3±4.8	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats) Plasma Norepinephrine (pg/mL)	
Siński et al., 2009 (43)	Interventional	-Mild to moderate essential hypertensive male subjects with hypercholesterolaemia -Secondary hypertension and DM	-N=10 -Age (yrs)= 43.2±12.5 -BMI (kg/m^2)= 28.2±4.2 -Finger SBP(mmHg)=145.1±10.3 -Finger DBP(mmHg)= 89.3±10.6 -HR (b/min)= 76.1±6.4 -Total cholesterol (mg/dL)= 252.6±22.6 -LDL cholesterol (mg/dL)= 160.8±21.0 -HDL cholesterol (mg/dL)= 46.5±11.2	-N=8 -Healthy subjects -Age (yrs)= 37.1±7.0 -BMI (kg/m^2)= 27.5±5.0 -Finger SBP(mmHg)=124.1±11.1 -Finger DBP (mmHg)= 78.1±8.9 -HR (b/min)= 71.6±8.7 -Total cholesterol (mg/dL)= 179.8±20.7 -LDL cholesterol (mg/dL)= 105.1±26.5 -HDL cholesterol (mg/dL)= 49±9.2	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)	
Frank et al 2009 (41)	Interventional	-Severe essential hypertensive subjects with NVC -Secondary	-N=14 -Men (%)= 28.6 -Age (yrs)= 46±9.5 -BMI (kg/m^2)= 29.7±4.7 -SBP (mmHg)= 179±30.8	-	Records performed on peroneal nerve posterior to	Burst rate (bursts/min)	

		hypertension, end-organ damage, LVH, arteriosclerosis of the peripheral arteries	-DBP (mmHg)= 101±21.4		the fibular head of supine subjects		
Hering et al., 2010 (44)	Observational	-Never-treated, uncomplicated essential hypertensive smokers	-N=30 -Hypertensive smokers -Cigarette/day (n)=10-20 -Smoking vintage (yrs)= 2 -Men (%)= 73.3 -Age (yrs)= 38±4 -BMI (kg/m^2)= 27±1 -Office SBP (mmHg)= 151±4 -Office DBP (mmHg)= 88±3 -Office HR (b/min)= 70±2 -Daytime SBP (mmHg)= 145±2 -Daytime DBP (mmHg)= 90±2 -Daytime HR (b/min)= 87±2 -Night-time SBP (mmHg)=125±2 -Night-time DBP (mmHg)=75±2 -Night-time HR (b/min)= 73±2	-N=38 -Hypertensive non-smokers -Men (%)= 79 -Age (yrs)= 42±3 -BMI (kg/m^2)= 27±1 -Office SBP (mmHg)= 156±5 -Office DBP (mmHg)= 92±4 -Office HR (b/min)= 67±2 -Daytime SBP (mmHg)= 140±3 -Daytime DBP (mmHg)=89±2 -Daytime HR (b/min)= 77±2 -Night-time SBP (mmHg)=127±2 -Night-time DBP (mmHg)=77±2 -Night-time HR (b/min)= 66±2	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)	
Kontak et al., 2010 (45)	Interventional	-Stage I essential hypertensive subjects -History of heart disease, DM or CKD or evidence of target organ damage such as LVH	-N=20 -Men (%)= 70 -Age (yrs)= 47±2 -BMI (kg/m^2)= 31.9±2 -SBP(mmHg)= 150±4 -DBP (mmHg)= 90±2 -HR (b/min)= 65±2	-N=18 -Normotensives -Men (%)= 72.2 -Age (yrs)= 45±2 -BMI (kg/m^2)= 30±1 -SBP(mmHg)= 119±2 -DBP (mmHg)= 76±2 -HR (b/min)= 61±2	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats) Direct renin (pg/mL) Plasma aldosterone (ng/dL)	
Maqbool et al., 2010 (46)	Observational	-Untreated essential hypertensive white subjects -Secondary hypertension, peripheral vascular disease, renal insufficiency, DM, cardiac arrhythmias or other chronic disease	-N=87 -Men (%)= 52.9 -Age (yrs)= 53±1 -BMI (kg/m^2)= 28±0.4 -Waist-to-hip ratio= 0.92±0.01 -SBP (mmHg)= 167±1.7 -DBP (mmHg)= 99±1.2 -MAP (mmHg)= 121±1.2 -HR (b/min)= 70±1	-N=85 -Normotensives -Men (%)= 53 -Age (yrs)= 40±1.2 -BMI (kg/m^2)= 26±0.5 -Waist-to-hip ratio= 0.87±0.01 -SBP (mmHg)= 122±1.1 -DBP (mmHg)= 78±0.8 -MAP (mmHg)= 92±0.8 -HR (b/min)= 64±1.1	Records performed on peroneal nerve of semi-supine subjects	Burst incidence (bursts/100 heart beats)	
Fatouleh and Macefield, 2011 (48)	Observational	-Long-standing essential hypertensive subjects	-N=13 -Men (%)= 77 -Age (yrs)= 58±2 -SBP (mmHg)= 152±4 -DBP (mmHg)= 88±2 -MAP (mmHg)= 110±2 -HR (b/min)= 63±5	-N=10 -Healthy normotensives -Men (%)= 50 -Age (yrs)= 50±3 -SBP(mmHg)= 130±6 -DBP (mmHg)= 75±4 -MAP (mmHg)= 90±6 -HR (b/min)= 60±3	Records performed on peroneal nerve posterior to the fibular head of semi-recumbent subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)	
Hogarth et al., 2011 (49)	Observational	-Pre- and post-menopausal, untreated and uncomplicated essential hypertensive Caucasian women -Secondary	-N=19 -Pre-menopausal-EHT -Age (yrs)= 39±1.9 -Weight (kg)= 76±3.0 -BMI (kg/m^2)= 27±1.1 -SBP (mmHg)= 158±2.9 -DBP (mmHg)= 95±1.4	-N=19 -Pre-menopausal-NT -Age (yrs)= 38±1.4 -Weight (kg)= 71±3.7 -BMI (kg/m^2)= 26±1.5 -SBP (mmHg)= 122±2.4 -DBP (mmHg)= 76±1.3	Records performed on peroneal nerve of semi-supine subjects	Burst incidence (bursts/100 heart beats)	

		hypertension, LVH, peripheral vascular disease, metabolic syndrome, arrhythmia, neuropathy or chronic disease	-MAP (mmHg)= 111±5.5 -HR (b/min)= 69±2.5 -N=19 -Post-menopausal-EHT -Age (yrs)= 58±1.7 -Weight (kg)= 71±2.4 -BMI (kg/m^2)= 28±1.1 -SBP (mmHg)= 166±4.4 -DBP (mmHg)= 95±2.4 -MAP (mmHg)= 119±2.9 -HR (b/min)= 70±1.8	-MAP (mmHg)= 91±1.5 -HR (b/min)= 65±2.0 -N=19 -Post-menopausal-NT -Age (yrs)= 56±1.2 -Weight (kg)= 71±2.1 -BMI (kg/m^2)= 26±0.7 -SBP (mmHg)= 129±1.8 -DBP (mmHg)= 80±0.9 -MAP (mmHg)= 97±1.0 -HR (b/min)= 65±1.0			
Bruno et al., 2011 (47)	Interventional	-Never-treated mild essential hypertensive subjects with SBP/DBP range (140-159/90-99) -Secondary hypertension, history or evidence of overt CV disease, target organ damage or major non-CV diseases. Smoking and daily intake of ≥3 alcoholic beverages just before the experimental session	-N=15 -Men (%)= 73.3 -Age (yrs)= 45.8±6.8 -BMI (kg/m^2)= 23.8±4.1 -Finger SBP(mmHg)=150.9±11.7 -Finger DBP (mmHg)= 90.6±8.6 -Finger HR (b/min)= 71.1±8.8 -Total cholesterol (mmol/L)= 5.1±0.9 -HDL cholesterol (mmol/L)= 1.2±0.4 -LDL cholesterol (mmol/L)= 3.0±0.6 -Blood glucose (mmol/L)= 5.2±0.2 -Plasma creatinine (µmol/L) =80.0±13.1	-N=12 -Normotensives -Men (%)= 75 -Age (yrs)= 43.5±5.6 -BMI (kg/m^2)= 22.2±3.5 -Finger SBP (mmHg)= 130.1±7.1 -Finger DBP (mmHg)= 82±7.9 -Finger HR (bpm)= 68.7±7.0 -Total cholesterol (mmol/L)= 5.0±0.6 -HDL cholesterol (mmol/L)= 1.3±0.5 -LDL cholesterol (mmol/L)= 2.8±0.7 -Blood glucose (mmol/L)= 4.9±0.4 -Plasma creatinine (µmol/L) =78.3±9.1	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min)	
						Burst incidence (bursts/100 heart beats)	
						Plasma Norepinephrine (nmol/L)	
						Plasma Epinephrine (pmol/L)	
Bruno et al., 2012 (50)	RCT	-Never-treated essential hypertensive subjects (office SBP/DBP≥140/90) -Secondary hypertension, history of CV disease, DM, alcohol consumption >50g/d, smoking and use of mineral or vitamin supplements just before the experimental session, major non-CV comorbidities	-N=32 -Men (%)= 80 -Age (yrs)= 47.1±8.0 -BMI (kg/m^2)= 26.4±3.3 -Finger SBP(mmHg)=144.8±13.4 -Finger DBP(mmHg)= 91.9±10.5 -HR (b/min)= 66.2±9.5 -Total cholesterol (mmol/L)= 5.6±1.2 -HDL cholesterol (mmol/L)= 1.4±0.3 -LDL cholesterol (mmol/L)= 3.2±0.9 -Triglycerides (mmol/L)= 1.4±0.6 -Blood glucose (mmol/L)= 5.1±0.6 -Serum creatinine (µmol/L)= 82.8±18.0	-N=20 -Normotensives -Men (%)= 68.8 -Age (yrs)= 45.7±7.0 -BMI (kg/m^2)= 27±3.6 -Finger SBP (mmHg)= 123.5±9.1 -Finger DBP (mmHg)= 76.5±9.5 -HR (b/min)= 65.3±10.3 -Total cholesterol (mmol/L)= 5.5±1.0 -HDL cholesterol (mmol/L)= 1.3±0.4 -LDL cholesterol (mmol/L)= 3.2±1.3 -Triglycerides (mmol/L)= 1.4±0.5 -Blood glucose (mmol/L)= 5.2±0.4 -Serum creatinine (µmol/L)= 80.0±12.2	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min)	
						Burst incidence (bursts/100 heart beats)	
						Plasma Norepinephrine (nmol/L)	
Hering et al., 2013 (51)	RCT	-Untreated, newly diagnosed essential hypertensive men (140≤SBP≤160 and DBP≤95 mmHg) -Secondary	-N=10 -Age (yrs)= 37.0±4.0 -BMI (kg/m^2)= 26.0±0.9 -Waist-to-hip ratio= 0.9±0.01 -Finger SBP (mmHg)= 151±9 -HR (b/min)= 63±4 -Respiratory rate	-	Records performed on peroneal nerve posterior to the fibular head of supine	Burst rate (bursts/min)	

		hypertension	(breaths/min)=12.7±1.9		subjects		
Inomata et al., 2014 (53)	RCT	-Uncontrolled, nonsmoking essential hypertensive subjects without DM or CKD -Secondary hypertension, HbA1c >6.5%, eGFR<60 mL/min/1.73m^2, symptomatic heart failure and acute CV disease	-N=14 -Men (%)= 64.3 -Age (yrs)= 63.1±10.4 -BMI (kg/m^2)= 24.7±1.7 -SBP (mmHg)= 152±6 -DBP (mmHg)= 89±5 -HR(b/min)= 67±7.3 -LVEF (%)= 66.9±6.6 -LVEDD (mm)= 46±4.1 -LVESD (mm)= 28.9±4 -eGFR (mL/min/1.73m^2)= 79.2±15 -Fasting blood glucose (mg/dL)= 97.6±6.4	-	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min)	
						Burst incidence (bursts/100 heart beats)	
						Plasma Adrenaline (ng/mL)	
						Plasma Noradrenaline (ng/mL)	
Grassi et al., 2014 (52)	Observational	-Treated essential hypertensive subjects -Secondary hypertension, congestive heart failure, atrial fibrillation or other major cardiac arrhythmias, history of coronary or cerebrovascular disease, clinical or laboratory evidence of valvular heart disease and history of smoking or excessive alcohol consumption, moderate or severe sleep apnea, renal insufficiency, DM	-N=35 -Men (%)= 77.1 -Age (yrs)= 57.8±2.0 -BMI (kg/m^2)= 24.8±0.3 -Waist-to-hip ratio= 0.76±0.01 -Finger SBP (mmHg)= 135.5±1.2 -Finger DBP (mmHg)= 83.6±0.9 -eGFR (mL/min/1.73m^2)= 80.0±2.5 -LVEF (%)= 61.5±1.2 -LVMI (g/m^2)= 108.2±4.0 -Respiration rate (breaths/min)= 18.3±0.5	-N=19 -Normotensives -Men (%)=73.7 -Age (yrs)= 57.5±2.3 -BMI (kg/m^2)= 24.7±0.6 -Waist-to-hip ratio= 0.77±0.01 -Finger SBP (mmHg)= 132.1±1.3 -Finger DBP (mmHg)= 82.1±0.9 -eGFR (mL/min/1.73m^2)= 84.4±2.8 -LVEF (%)= 61.2±1.0 -LVMI (g/m^2)= 84.4±4.4 -Respiration rate (breaths/min)= 18.1±0.4	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min)	
						Burst incidence (bursts/100 heart beats)	
						Plasma aldosterone (ng/dL)	
						HOMA (a.u.)	
						Office and Beat-to beat BP (mmHg)	
						Ambulatory BP (mmHg)	
						Office, ambulatory and beat-to-beat HR (b/min)	

Data are mean±SEM unless otherwise specified; NS: no significant.

ACEI: angiotensin converting enzyme inhibitor, ANF: atrial natriuretic factor, ARBs: angiotensin II receptor blockers, BMI: body mass index, BP: blood pressure, CCBs: calcium channel blockers, CKD: chronic kidney disease, CPT: cold pressor test, Cr: creatinine, CV: cardiovascular, DBP: diastolic blood pressure, DM: diabetes mellitus, ECG: electrocardiogram, eGFR: estimated glomerular filtration rate, EHT: essential hypertensive, HbA1c: glycated hemoglobin, HDL: high density lipoprotein, HOMA: homeostatic model assessment, HR: heart rate, HT: hypertension, IHG: isometric handgrip, IVST: interventricular septal thickness, JNC: Joint National Committee, LDL: low density lipoprotein, LVDD: left ventricle diastolic dysfunction, LVEDD: left ventricle end diastolic diameter, LVEF: left ventricle ejection fraction, LVESD: left ventricle end systolic diameter, LVH: left ventricular hypertrophy, LVID: left ventricle internal diameter, LVM: left ventricular mass, LVMI: left ventricular mass index, MAP: mean arterial pressure, MRI: magnetic resonance imaging, MSNA: muscle sympathetic nerve activity, NE: norepinephrine, NT: normotensive, NVC: neurovascular compression, PRA: plasma renin activity, PVCs: provoked premature ventricular contractions, PWT: posterior wall thickness, RCT: randomized controlled trial, SBP: systolic blood pressure, SWT: septal wall thickness, WC: waist circumference, WHO: World Health Organization

S 3. Summary of main characteristics and findings of the studies on borderline, and offspring, hypertensive subjects

Study, year (ref)	Study design	-Inclusion criteria -Exclusion criteria	Population characteristics	Control group	MSNA technique	Variables
Yamada et al., 1988 (54)	Interventional	-Male borderline hypertensive and normotensive offspring	-N=11 -Borderline hypertensive offspring of HT parents -Age (yrs)= 22±0.3 -SBP (mmHg)= 148±3 -DBP (mmHg)= 89±3 -HR (b/min)= 78±2	-N=10 -Normotensive offspring of HT parents -Age (yrs)= 21.7±0.3 -SBP (mmHg)= 128±2 -DBP (mmHg)= 80±2 -HR (b/min)= 66±2 -N=12 -Control normotensives -Age (yrs)= 21.4±0.5 -SBP (mmHg)= 128±2 -DBP (mmHg)= 78±2 -HR (b/min)= 68±2	Records performed on tibial nerve at the popliteal fossa in supine subjects	Burst rate (bursts/min)
						Burst incidence (bursts/100 heart beats)
Anderson et al., 1989 (55)	RCT	-Male borderline hypertensive subjects	-N=12 -Borderline hypertensives -Age (yrs)= 24.6±0.9 -Weight (Kg)= 87±3 -SBP (mmHg)= 133±1 -DBP (mmHg)= 81±1	-N=15 -Normotensives -Age (yrs)= 24.5±0.5 -Weight (Kg)= 77±2 -SBP (mmHg)= 121±1 -DBP (mmHg)= 73±1	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min)
Floras et al., 1989, 1991 (56, 57)	Interventional	-Young, male borderline hypertensive subjects	-N=9 -Borderline hypertensives -Age (yrs)= 25±3 -SBP (mmHg)= 136±12 -DBP (mmHg)= 82±12 -HR (b/min)= 70±9	-N=10 -Normotensives -Age (yrs)= 28±5 -SBP (mmHg)= 118±11 -DBP (mmHg)= 72±6 -HR (b/min)= 56±9	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min)
						Burst incidence (bursts/100 heart beats)
						Plasma Noradrenaline (nmol/L)
Matsukawa et al., 1991 (58)	Interventional	-Male borderline hypertensive subjects	-N=9 -Borderline hypertensive offspring of HT parents -Age (yrs)= 22±1 -Weight (Kg)= 70±3 -SBP (mmHg)= 127±3 -DBP (mmHg)= 83±2 -MAP (mmHg)= 98±2 -HR (b/min)= 72±4	-N=11 -Control normotensives -Age (yrs)= 21±1 -Weight (Kg)= 64±3 -SBP (mmHg)= 116±2 -DBP (mmHg)= 71±1 -MAP (mmHg)= 86±1 -HR (b/min)= 63±1	Records performed on tibial nerve at the popliteal fossa in supine subjects	Burst rate (bursts/min)
						Plasma Norepinephrine (pg/mL)
						Plasma Epinephrine (pg/mL)
Noll et al., 1996 (59)	RCT	-Normotensive offspring of hypertensive parents	-N=10 -Normotensive offspring of HT parents -Age (yrs)= 27±3 -Waist hip ratio= 0.84±0.01 -BMI (kg/m^2)= 22.4±0.6	-N=8 -Control normotensives -Age (yrs)= 27±4 -Waist hip ratio= 0.80±0.01 -BMI (kg/m^2)= 21.8±0.6 -SBP (mmHg)= 125±4	Records performed on peroneal nerve posterior to the fibular	Burst rate (bursts/min)

			-SBP (mmHg)= 126±3 -DBP (mmHg)= 85±2 -HR (b/min)= 72±3	-DBP (mmHg)= 81±3 -HR (b/min)= 75±2	head of supine subjects		
						Plasma Norepinephrine (pg/mL)	
Hausberg et al., 1998 (60)	Interventional	-Young, lean, healthy normotensive offspring of hypertensive parents	-N=17 -Normotensive offspring of HT parents -Age (yrs)= 33±0.4 -Male (%)= 53 -BMI (kg/m^2)= 24.9±0.8 -Weight (Kg)=73±3 -SBP (mmHg)= 115±3 -DBP (mmHg)= 71±2 -MAP (mmHg)= 86±3 -HR (b/min)= 61±2 -Fasting plasma glucose (mg/dL)= 85±2 -Fasting plasma insulin (µU/mL)= 13±2	-N=17 -Control normotensives -Age (yrs)= 32±0.5 -Male (%)= 53 -BMI (kg/m^2)= 24.5±1.1 -Weight (Kg)= 75±5 -SBP (mmHg)= 113±3 -DBP (mmHg)= 71±2 -MAP (mmHg)= 85±3 -HR (b/min)= 62±2 -Fasting plasma glucose (mg/dL)= 86±1 -Fasting plasma insulin (µU/mL)= 13±2	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min)	
Schobel et al., 1998, 1998 (61, 62)	Interventional	-Young, lean, male borderline hypertensive subjects	-N=20 -Borderline hypertensives -Age (yrs)= 24±2 -BMI (kg/m^2)= 24.2±3 -Weight (Kg)=80±8 -Finger MAP (mmHg)= 113±9 -HR (b/min)= 74±8	-N=21 -Normotensives -Age (yrs)= 25±3 -BMI (kg/m^2)= 23.3±2.4 -Weight (Kg)=78±10 -Finger MAP (mmHg)= 89±9 -HR (b/min)= 62±8	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min)	
						Burst incidence (bursts/100 heart beats)	
						Plasma Norepinephrine (pg/mL)	
						Plasma Epinephrine (pg/mL)	
Greenwood et al., 1999 (17)	Observational	-Subjects with high-normal BP (SBP/DBP 130–139/85–89 mmHg)	-N=17 -High normal -Men (%)= 47 -Age (yrs)= 44±2.5 -Weight (Kg)= 78±3.7 -BMI (kg/m^2)= 27±1 -Finger SBP (mmHg)= 134±1.1 -Finger DBP (mmHg)= 86±1.0 -Finger MAP (mmHg)= 102±0.7 -Finger HR (b/min)= 67±2.6	-N=17 -Normotensives -Men (%)= 41.2 -Age (yrs)= 37±2.0 -Weight (Kg)= 72±2.7 -BMI (kg/m^2)= 26±0.7 -Finger SBP (mmHg)= 117±1.9 -Finger DBP (mmHg)= 75±1.3 -Finger MAP (mmHg)= 89±1.2 -Finger HR (b/min)= 66±2.0	Records performed on peroneal nerve posterior to the fibular head of semi-supine subjects	Burst rate (bursts/min)	
						Burst incidence (bursts/100 heart beats)	
Smith et al., 2004 (32)	Observational	-Untreated borderline hypertensive and subjects with high-normal BP	-N=13 -Borderline hypertensives -Men (%)= 38.5 -Age (yrs)= 48±3.7 -BMI (kg/m2)= 28±1.3 -Weight (Kg)=79±4.1 -SBP (mmHg)= 144±1.9 -DBP (mmHg)= 90±1.2 -MAP (mmHg)= 108±1.3 -HR (b/min)= 69±2.6 -Daytime SBP (mmHg)= 136±1.5 -Daytime DBP (mmHg)= 83±0.7 -Daytime MAP(mmHg)=101±0.6 -Daytime HR (b/min)= 80±2.8 -Night-time SBP	-N=13 -Normotensives -Men (%)= 46.2 -Age (yrs)= 45±3.5 -BMI (kg/m2)= 27±0.8 -Weight (Kg)=78±2.2 -SBP (mmHg)= 126±1.6 -DBP (mmHg)= 77±1.9 -MAP (mmHg)= 93±1.8 -HR (b/min)= 68±3.2 -Daytime SBP (mmHg)= 118±0.9 -Daytime DBP (mmHg)= 74±1.5 -Daytime MAP (mmHg)= 89±0.9 -Daytime HR (b/min)= 75±4.0 -Night-time SBP	Records performed on peroneal nerve of semi-supine subjects	Burst rate (bursts/min)	

			(mmHg)=107±3.8 -Night-time DBP (mmHg)= 69±2.9 -Night-time MAP (mmHg)= 82±3.0 -Night-time HR (b/min)= 66±3.0 -N=14 -High normal -Men (%)= 42.8 -Age (yrs)= 46±3.0 -BMI (kg/m2)= 27±0.8 -Weight (Kg)=77±3.7 -SBP (mmHg)= 132±1.2 -DBP (mmHg)= 83±0.8 -MAP (mmHg)= 99±0.9 -HR (b/min)= 69±2.6 -Daytime SBP (mmHg)= 122±2.0 -Daytime DBP (mmHg)= 76±1.5 -Daytime MAP (mmHg)= 91±0.3 -Daytime HR (b/min)= 81±0.3 -Night-time SBP (mmHg)=102±1.3 -Night-time DBP (mmHg)= 68±1.7 -Night-time MAP (mmHg)= 79±0.6 -Night-time HR (b/min)= 69±1.9	(mmHg)=96±2.0 -Night-time DBP (mmHg)= 63±2.8 -Night-time MAP (mmHg)= 79±0.8 -Night-time HR (b/min)= 70±4.9		Burst incidence (bursts/100 heart beats)
Smith et al., 2004 (33)	Observational	-High-normal BP subjects with and without NVC of the rostral ventrolateral medulla	-N=14 -High normal -Men (%)= 57.1 -Age (yrs)= 49±2.7 -BMI (kg/m2)= 27±0.8 -Weight (Kg)= 82±3.7 -SBP (mmHg)= 136±1.0 -DBP (mmHg)= 85±1.2 -MAP (mmHg)= 102±0.9 -HR (b/min)= 66±3.0	-N=24 -Normotensives -Men (%)= 45.8 -Age (yrs)= 46±2.5 -BMI (kg/m2)= 26±0.8 -Weight (Kg)= 76±2.5 -SBP (mmHg)= 125±1.0 -DBP (mmHg)= 80±0.8 -MAP (mmHg)= 95±1.0 -HR (b/min)= 65±1.9	Records performed on peroneal nerve of semi-supine subjects	Burst incidence (bursts/100 heart beats)
Lambert and Schlaich, 2004 (30)	Interventional	-Young normotensive subjects with and without family history of hypertension	-N=14 -Young normotensives with family history of HT -Men (%)= 85.7 -Age (yrs)= 25±2.0 -BMI (kg/m2)= 25±1.0 -Finger SBP (mmHg)= 129±4.0 -Finger DBP (mmHg)= 67±3.0 -HR (b/min)= 67±2.0	-N=11 -Young normotensives without family history of HT -Men (%)= 90.9 -Age (yrs)= 27±2.0 -BMI (kg/m2)= 23±1.0 -Finger SBP (mmHg)= 118±4.0 -Finger DBP (mmHg)= 63±3.0 -HR (b/min)= 69±2.0	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)
Grassi et al., 2007 (35)	Interventional	-Middle-aged subjects with masked hypertension	-N=18 -Masked hypertension -Men (%)= 72.2 -Age (yrs)= 54.4±2.1 -BMI (kg/m^2)= 27.8±0.5 -WC (cm)= 98.5±3.1 -24h SBP (mmHg)= 130.1±2.5 -24h DBP (mmHg)= 82.1±2.1 -24h HR (b/min)= 69.1±2.1 -Clinic SBP (mmHg)= 128.1±2.3 -Clinic DBP (mmHg)= 82.8±2.0 -Clinic HR (b/min)= 70.1±2.0 -Finger SBP (mmHg)= 126.0±2.4 -Finger DBP (mmHg)= 80.9±2.1 -LVMI (g/m^2)= 99.8±4.9 -Plasma glucose (mmol/L)= 5.8±0.6 -Plasma insulin (µU/mL)= 9.7±0.9 -HOMA index (a.u.)= 2.45±0.3	-N=20 -Normotensives -Men (%)= 65 -Age (yrs)= 53.4±2.2 -BMI (kg/m^2)= 24.7±0.5 -WC (cm)= 94.8±2.7 -24h SBP (mmHg)= 117.5±2.2 -24h DBP (mmHg)= 72±1.5 -24h HR (b/min)= 66.9±2.0 -Clinic SBP (mmHg)= 122.3±2.8 -Clinic DBP (mmHg)= 78.6±2.1 -Clinic HR (b/min)= 68.4±2.1 -Finger SBP (mmHg)=120.1±2.9 -Finger DBP (mmHg)= 76.2±2.3 -LVMI (g/m^2)= 82.4±4.9 -Plasma glucose (mmol/L)= 4.9±0.4 -Plasma insulin (µU/mL)= 7.6±0.7 -HOMA index (a.u.)= 1.52±0.2	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats) Plasma Norepinephrine (pg/mL)

Seravalle et al., 2015 (63)	Interventional	-Untreated borderline hypertensive subjects (SBP/DBP 130–139/85–89 mmHg) -History of smoking or excessive alcohol consumption, coronary heart disease, congestive heart failure, cerebrovascular disease, renal insufficiency, obesity, DM, metabolic syndrome, obstructive sleep apnea, respiratory diseases	-N=38 -High-normal BP subjects -Age (yrs)= 39.3±2.2 -Male (%)= 81.6 -Weight (Kg)= 75.1±2.8 -BMI (kg/m^2)= 25.8±05 -Waist hip ratio=0.78±0.01 -Plasma glucose (mmol/L)= 4.18±0.4 -Plasma insulin (mU/mL)= 8.5±0.3 -HOMA Index (a.u.)= 1.62±0.1 -Total cholesterol (mg/dL)= 196.5±9.5 -HDL-cholesterol (mg/dL)= 57.2±4.0 -eGFR (mL/min/1.73m^2)= 83.1±3.3 -Resp. rate (breaths/min)= 16.0±1.1 -LVEF (%)=70.2±0.8 -LVMI (g/m^2)= 88.3±1.2	-N=24 -Optimal BP subjects -Age (yrs)= 37.1±2.5 -Male (%)= 79.2 -Weight (Kg)= -BMI (kg/m^2)= -Waist hip ratio= -Plasma glucose (mmol/L)= -Plasma insulin (mU/mL)= -HOMA Index (a.u.)= -Total cholesterol (mg/dL)= -HDL-cholesterol (mg/dL)= -eGFR (mL/min/1.73m^2)= -Resp. rate (breaths/min)= -LVEF (%)= -LVMI (g/m^2)= -N=27 -Normal BP subjects -Age (yrs)= 36.9±2.2 -Male (%)= 85.2 -Weight (Kg)= 71.4±2.2 -BMI (kg/m^2)= 23.9±0.7 -Waist hip ratio= 0.76±0.01 -Plasma glucose (mmol/L)= 4.04±0.3 -Plasma insulin (mU/mL)= 8.0±0.4 -HOMA Index (a.u.)= 0.94±0.1 -Total cholesterol (mg/dL)= 188±10.4 -HDL-cholesterol (mg/dL)= 56.1±5.6 -eGFR (mL/min/1.73m^2)= 82.7±4.3 -Resp. rate (breaths/min)= 16.1±1.3 -LVEF (%)=69.4±0.9 -LVMI (g/m^2)= 86.1±1.1	Records performed on peroneal nerve posterior to the fibular head of supine subjects	Burst rate (bursts/min) Burst incidence (bursts/100 heart beats)	

Data are mean±SEM unless otherwise specified, NS: no significant.

BMI: body mass index, BP: blood pressure, DBP: diastolic blood pressure, DM: diabetes mellitus, eGFR: estimated glomerular filtration rate, EHT: essential hypertensive, HDL: high density lipoprotein, HOMA: homeostatic model assessment, HR: heart rate, HT: hypertensive/hypertension, LVEF: left ventricle ejection fraction, LVMI: left ventricular mass index, MAP: mean arterial pressure, MSNA: muscle sympathetic nerve activity, NE: norepinephrine, NVC: neurovascular compression, RCT: randomized controlled trial, SBP: systolic blood pressure, WC: waist circumference.

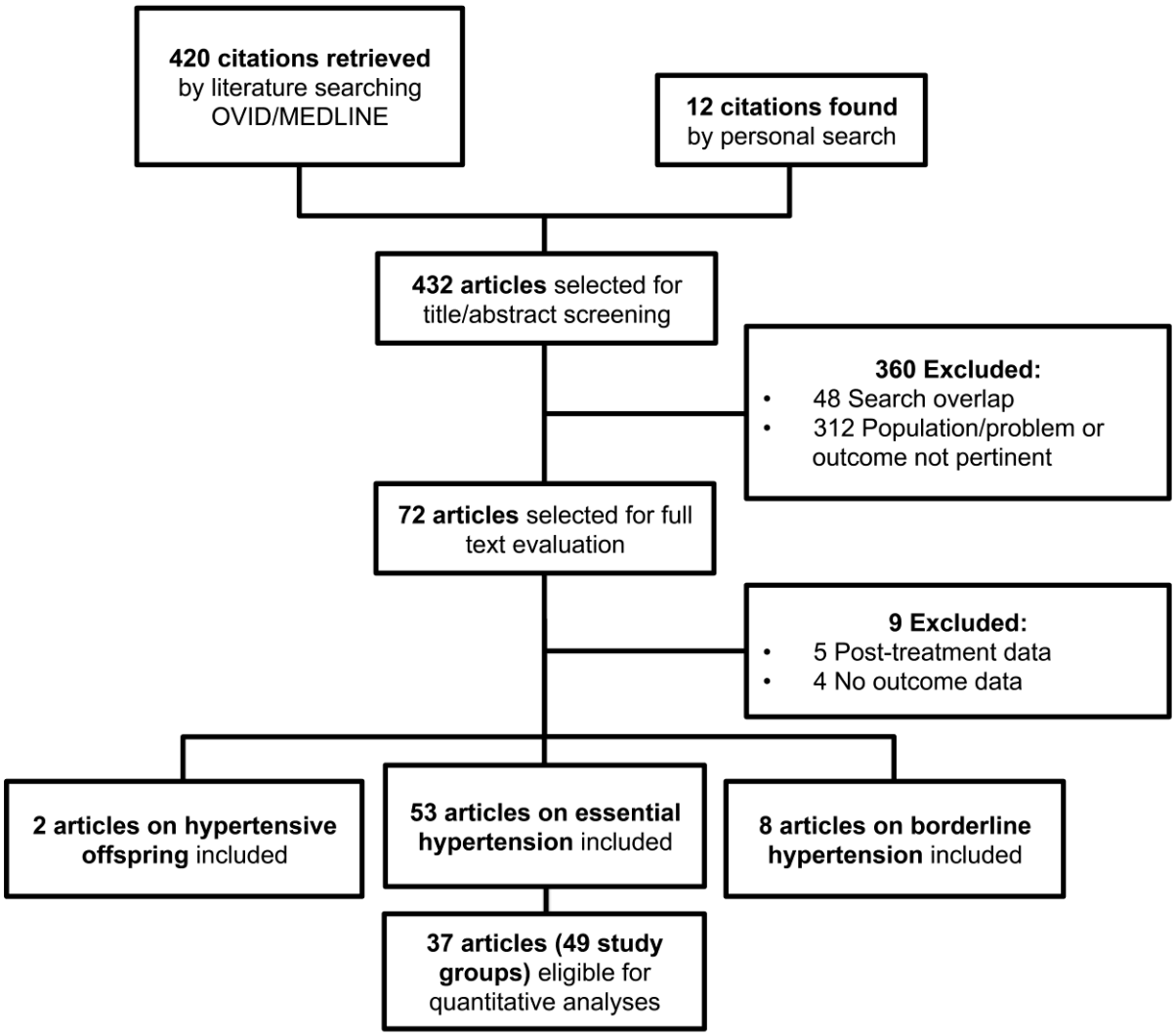

Figure S 1 -The flow diagram of the studies selection process