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Effects of essential hypertension on short latency human somatosensory-evoked potentials

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Abstract

Reduced perception of somatosensory stimulation in patients with essential hypertension may be due to deficits in the ascending somatosensory pathway. Function in the ascending somatosensory pathway was assessed by measuring N9, N13 and N20 somatosensory-evoked potentials in 14 unmedicated essential hypertensives and 22 normotensives. N9 amplitudes were smaller and N13 amplitudes marginally smaller in hypertensives than normotensives. N9 amplitudes were inversely associated with blood pressure. N20 amplitudes and N9, N13 and N20 latencies did not differ between groups. In addition, plexus-cord, cord-cortex and plexus-cortex conduction times were not different between groups. These data suggest that hypertension affects the peripheral nervous system by reducing the number of active sensory nerve fibres without affecting myelination. However, hypertension does not seem to affect the afferent somatosensory pathway within the brain.

Descriptors: Arterial hypertension; Essential hypertension; Median nerve; Somatosensory evoked potentials

Introduction

There is evidence that essential hypertension is characterized by reduced sensitivity to peripheral stimulation (Ghione, 1996; Waldstein, Manuck, Ryan, & Muldoon, 1991). Studies have demonstrated that essential hypertensives have reduced perception of pain (Ghione, 1996), higher sensory detection thresholds for electrical stimulation of tooth pulp (Ghione et al., 1985; Ghione, Rosa, Mezzasalma, & Panattoni, 1988; Rosa, Ghione, Panattoni, Mezzasalma, & Giuliano, 1986; Zamir & Shuber, 1980) as well as electrocutaneous stimulation of the hand (Edwards, Ring, McIntyre, Winer, & Martin, 2008; Rosa, Vignocchi, Panattoni, Rossi, & Ghione, 1994), and leg (Ring et al., 2008), compared to normotensives. It is possible that sensory deficits may be due to alterations in the afferent sensory pathways. Indeed, among patients with diabetes mellitus, hypertension is associated with the progression of neuropathy (Tesfaye et al., 2005) and microvascular disease (Forrest, Maser, Pambianco, Becker, & Orchard, 1997). Evidence supports an association between hypertension and neuropathy in diabetics, however, the influence of essential hypertension on nerve function in the absence of diabetes is not yet established.

Hypertension is a risk factor for peripheral vascular disease (Makin, Lip, Silverman, & Beevers, 2001). Peripheral vascular disease is associated with structural alterations in the microcirculation leading to reductions in the number of arterioles or capillaries in the vascular beds of target organs (Mourad & Laville, 2006). The vascular system supplying the peripheral nervous system, which incorporates the vasa nervorum, lacks autoregulatory capabilities (Smith, Kobrine, & Rizzoli, 1977). This absence of autoregulation makes the peripheral nerves vulnerable to hypoxia when their blood supply is compromised (Low & Tuck, 1984; Olsson, 1972). Thus,

hypertensives, characterised by increased vascular resistance, are more vulnerable to ischaemia and hypoxia of the peripheral nerves.

Animal studies demonstrate that the vascular supply to the peripheral nerves is impaired in the spontaneously hypertensive rat (Sabbatini, Bellagamba, Vega, & Amenta, 2001; Sabbatini, Vega, & Amenta, 1996). These impairments were improved by antihypertensive treatment (Sabbatini et al., 2001). Morphological changes and decreased nerve conduction velocity have also been documented in the aortic depressor nerve (Fazan, Fazan, Salgado, & Barreira, 1999) (Fazan, Salgado, & Barreira, 2001) and sciatic nerve (Tomassoni, Traini, Vitaoli, & Amenta, 2004) of spontaneously hypertensive rats. Importantly, these morphological changes were not present when blood pressure was maintained at normotensive levels by pharmacological treatment with a vasodilator (Tomassoni et al., 2004).

In patients with essential hypertension, the evidence for peripheral neuropathy is less consistent. Reduced motor nerve conduction velocities have been reported in the upper extremities of hypertensives compared to normotensives; conduction velocities were inversely related to diastolic blood pressure (Viskoper, Chaco, & Aviram, 1971). However, two subsequent studies found normal sensory and motor nerve conduction velocities in the upper and lower limbs of hypertensive patients (Bridgman, Bidgood, & Hoole, 1973; Halar, Stewart, Venkatesh, & Chrissian, 1978). These conflicting findings might be explained by methodological inconsistencies. Factors that can influence nerve function were not always controlled; Viskoper et al. (1971) did not measure limb temperature and pharmacological antihypertensive treatment was not controlled in these studies (Bridgman et al., 1973; Halar et al., 1978; Viskoper et al., 1971). A recent study which controlled for both medication and limb temperature found that sensory action potential amplitudes were reduced in

patients with unmedicated essential hypertension compared to normotensives (Edwards et al., 2008). This study also reported similar sensory and motor nerve conduction velocities for hypertensives and normotensives (Edwards et al., 2008). These findings suggest that hypertension may be associated with axonal degeneration but not demyelination. This study also reported that hypertensives had reduced sensitivity to electrocutaneous stimulation compared to normotensives, and interestingly, sensory detection thresholds were inversely related to sensory action potential amplitudes. These findings suggest that the sensory-perceptual deficits found in hypertensives may be due, at least in part, to subclinical peripheral neuropathy. Considered as a whole, evidence from both animal and human studies indicates that hypertension may constitute a risk factor for peripheral neuropathy.

To date, investigation into the effect of unmedicated essential hypertension on the afferent sensory pathway has been confined to the peripheral nervous system. However, it is possible that alterations in the ascending somatosensory pathway may also occur within the central nervous system. Indeed, evidence indicates that hypertension has a detrimental effect on cerebral perfusion. For instance, autoregulation of cerebral blood flow is altered in hypertension (Heistad & Kontos, 1983). In order to maintain normal cerebral blood flow at high perfusion pressures the cerebral blood vessels tonically constrict to maintain increased cerebrovascular resistance (Chillon & Baumbach, 1997; Paulson, Strandgaard, & Edvinsson, 1990), leading to vascular hypertrophy and remodelling (Heistad & Baumbach, 1992). In hypertensives, structural changes and impaired endothelium-mediated dilatation lead to a decreased maximal vasodilator capacity, impairing autoregulatory vasodilatation during hypotension and predisposing hypertensives to cerebral ischemia (Baumbach & Heistad, 1988; Faraci & Heistad, 1998; Heistad & Baumbach, 1992; Maeda et al.,

1994; Tamaki, Nakai, Yokota, & Ogata, 1995). As neural activity in the brain creates a metabolic demand that induces an enhanced blood flow to active tissue (Raichle, Grubb, Gado, Eichling, & Ter-Pogossian, 1976), a decreased maximal vasodilator capacity may also affect functional hyperemia. Indeed, a recent memory study found that cerebral blood flow response was reduced in the posterior parietal and thalamic areas of hypertensives compared to normotensives (Jennings et al., 2005). The reduced cerebral blood flow response to active neural areas was related to lower memory performance. Preliminary evidence also suggests that cerebral blood flow may be reduced in hypertensives patients at rest (Fujishima, Ibayashi, Fujii, & Mori, 1995; Nobili et al., 1993). In addition, hypertension can also promote atherosclerosis in large cerebral arteries and lipohyalinosis in penetrating arterioles (Dickinson, 2001; Faraci, Baumbach, & Heistad, 1990), thus increasing susceptibility to vascular occlusions and further compromising cerebral perfusion (Girouard & Iadecola, 2006). Overall, the literature indicates that individuals with hypertensive blood pressure are more vulnerable to cerebral hypoperfusion and ischemia.

The current study investigated the hypothesis that the ascending somatosensory pathway is detrimentally affected by hypertension. Short latency somatosensory-evoked potentials are electrical potentials generated at peripheral, spinal, subcortical and cortical levels of the nervous system within the first 60 ms after electrical stimulation of peripheral nerves (Mauguiere et al., 1999). They reflect conduction of the afferent volley primarily along the heavily myelinated dorsal columns, through the medial lemniscal pathways, to the primary somatosensory cortex (Lee & Seyal, 1998). Short latency somatosensory-evoked potentials correlate with function in somatosensory pathways (Fukutake, Kuwabara, Kaneko, Kojima, & Hattori, 1998; Leocani, Martinelli, Natali-Sora, Rovaris, & Comi, 2003) and are used

to identify clinically silent lesions to diagnose demyelinating conditions such as multiple sclerosis (Gronseth & Ashman, 2000). Partial support for the hypothesis that afferent somatosensory system may be affected by hypertension comes from a previous study that reported decreased amplitude short and middle latency somatosensory evoked potentials in juvenile hypertensives but not middle-aged hypertensives compared to normotensive controls (Varsik, Buranova, Balaz, & Duris, 2002). Critically, the study by Varsik et al. (2002) was performed in medicated hypertensives with normalised blood pressure, therefore, the effect of blood pressure *per se* is hard to determine. The current study is the first to compare peripheral, spinal and cortical short latency somatosensory-evoked potentials, elicited by median nerve stimulation, in patients with unmedicated essential hypertension and healthy normotensive individuals. As such, the study examined the effect of hypertension on conduction within the sensory afferent pathway as well as activation of the primary somatosensory cortex in order to determine the presence of sensory abnormalities within the ascending somatosensory pathways of unmedicated essential hypertensives. As white matter disease is prevalent in long-standing hypertension (Phillips & Whisnant, 1992) and cognitive deficits are more pronounced in younger hypertensives (Waldstein, 1995) the current study was conducted in a group of relatively young, newly diagnosed hypertensive patients without symptoms cerebrovascular disease in order to examine the effect of hypertension on somatosensory function in younger hypertensives before white matter disease becomes prevalent.

Method

Participants

Fourteen patients with essential hypertension and 22 healthy normotensive individuals participated. These participants were a sub-sample of individuals who took part in an earlier study (Edwards et al., 2008) who were invited back to the laboratory for further testing. Table 1 shows the characteristics of the hypertensive and normotensive groups. Patients with newly diagnosed essential hypertension were recruited from the hypertension clinic at University Hospital, Birmingham, UK, and were tested prior to the initiation of pharmacological treatment. Normotensive volunteers were recruited from the general population of Birmingham, UK, and screened in the same way as the hypertensive group. Participants were instructed to refrain from caffeine, alcohol, and vigorous exercise for 2 hours prior to testing. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee. Volunteers gave written consent to participate.

Screening

Exclusion Criteria. In an initial screening session, each participant's medical status and eligibility were determined. All patients had a detailed medical history and clinical examination performed by the consultant in charge of the Hypertension Clinic. Screening tests included renal and liver function tests, lipid profile, blood glucose and thyroid function tests. All patients had an electrocardiogram and 24-hour monitoring of their blood pressure. On the basis of medical history, physical examination and blood tests participants were excluded for the following: age younger than 18 years or older than 50 years, current use of prescription medication (excluding contraceptives), any chronic disease or any condition predisposing to carpal tunnel syndrome or peripheral neuropathy including diabetes mellitus (either pre-existing or diagnosed on blood sugar sample), high alcohol intake (>28 units (1

unit = 284 ml of beer, 125 ml of wine, or 25 ml of spirits) of alcohol per week in men, >21 units of alcohol per week in women), thyroid disease, chronic liver disease, cerebrovascular disease, peripheral vascular disease, rheumatoid or osteoarthritis, obesity, acromegaly or gout, symptoms of numbness, tingling, itching or abnormal sensations, neuromuscular disease, peripheral nerve injury, hereditary/genetic neuropathy, neck or back surgery, cancer or chemotherapy, history of myocardial infarction, symptoms of angina or major psychiatric disorder (e.g., depression, schizophrenia). If clinically indicated the patients in the hypertensive group had appropriate investigations to exclude secondary causes of hypertension. For example, if there was evidence of hypokalaemia patients had renin:aldosterone levels to exclude hyperaldosteronism. If there was evidence of renal impairment with raised serum creatinine, and/or reduced eGFR and/or proteinuria, patients were investigated for renal artery stenosis, glomerulonephritis, or pyelonephritis. Finally, if clinically indicated patients had urinary screening tests for pheochromocytoma. Patients with evidence of secondary hypertension were excluded from the study.

Blood Pressure Status. British Hypertension Society guidelines were used to establish blood pressure status (Williams et al., 2004). Each participant's blood pressure was measured at the non-dominant upper arm for 24 hours using an ambulatory blood pressure monitor (Model 90217, SpaceLabs Medical). Participants were instructed to go about their usual activities during the monitoring period. Blood pressure readings were obtained every 30 minutes between the hours of 7:00 am and 11:00 pm, and every 60 minutes between 11:00 pm and 7:00 am. Mean daytime systolic and diastolic blood pressures were calculated from all readings taken between 7:00 am and 11:00 pm. Patients with a systolic blood pressure of ≥ 160 mmHg or a diastolic blood

pressure of ≥ 100 mmHg at referral, and confirmed at clinic and on ambulatory blood pressure monitoring (mean daytime pressure) were diagnosed as hypertensive; this category comprised 71% of patients. Patients with a systolic blood pressure of 140–159 mmHg and/or a diastolic blood pressure of 90–99 mmHg at referral, clinic, and on ambulatory blood pressure monitor, were diagnosed as hypertensive if their 10 year cardiovascular risk was $>20\%$ and/or there was evidence of left ventricular hypertrophy on a 12 lead electrocardiograph or echocardiograph, or there was other evidence of end organ damage. The cardiovascular risk profile was calculated using the Joint British Societies Cardiac Risk Assessor computer program (Williams et al., 2004). Participants were classified as being normotensive if they had a clinic systolic blood pressure of < 140 mmHg and a clinic diastolic blood pressure of < 90 mmHg, confirmed on ambulatory blood pressure monitoring, and $<20\%$ cardiovascular risk in the next 10 years. In addition, laboratory blood pressure was measured during the screening session using an oscillometric sphygmomanometer (Dinamap, Critikon) and a brachial cuff attached to the participant's upper left arm.

Apparatus and Measurements

Median nerve stimulation (single 100 μ s square wave pulse) was delivered electrocutaneously using a constant current stimulator (DS7A, Digitimer) via a surface electrode secured to the wrist of the dominant hand (handedness was determined by self-report). The bipolar stimulating electrode (XLTEK) comprised a bar with two saline soaked felt contacts, 2.5 cm centre-to-centre, secured with Velcro at the proximal wrist crease, between the central palmaris longus tendon the flexor capri radialis tendon, with the cathode proximal to the anode.

Short latency somatosensory-evoked potentials were recorded and measured in accordance with the guidelines of the International Federation of Clinical Physiology (Mauguiere et al., 1999). The short latency somatosensory-evoked potentials were recorded orthodromically using 10 mm diameter Ag-AgCl disk electrodes (Unimed). N9 recording electrodes were placed bilaterally at Erb's point, located at the supraclavicular fossa. Erb's point ipsilateral to stimulation was defined as the active recording electrode which was referred to contralateral Erb's (EPi – EPc). The N13 active recording electrode was placed in the posterior neck region at the 6th cervical vertebra (Cv6) with reference electrode on the skin of the supra-glottal region on the midline (AC). Finally, N20 was measured on the scalp using the 10-20 international system of EEG electrode placement. The active N20 electrode was positioned parietally and contralateral to stimulation, 7 cm lateral to midline and 5 cm posterior to Cz. The N20 reference electrode was placed at Fz. A ground electrode was positioned at Cz. Skin impedance was < 5 K Ω . Recording electrodes were fixed in place using conductive paste (Ten20, D.O.Weaver & Co.). A computer programmed in Spike2 (CED) and a Power1401 (CED) presented trigger pulses for stimulus presentation and response averaging. Responses were recorded and averaged online with a Neuromax system (Model 1004, XLTEK) with a sampling rate of 60kHz and an analysis period of 50 ms post-stimulation. The somatosensory-evoked potential signal was bandpass filtered (10-3000 Hz) with gain of 5 μ V/division sensitivity and a 5 ms/division time base. Signals with amplitudes surpassing 50 μ V were automatically rejected.

Procedure

A qualified clinical neurophysiologist applied the electrodes and recorded and scored the short latency somatosensory-evoked potentials at the Neurophysiology Outpatients Department, University Hospital Birmingham, UK. The neurophysiologist was blinded to the blood pressure status of each participant. The participant sat in a comfortable chair with dominant hand held in a relaxed position with palm upwards and forearm supinated. Following instrumentation and instruction (10 min), the stimulus intensity required to adequately elicit the somatosensory-evoked potentials was determined (5 min). The stimulation intensity required to produce a motor twitch (motor threshold) in the abductor pollicis brevis was determined using an ascending method of limits. The stimulation intensity was then set at three times motor threshold. At this stimulation intensity all short latency somatosensory-evoked potentials components reach maximal amplitude (Mauguiere et al, 1999).

Each participant's short latency somatosensory-evoked potentials were then recorded (50 min). Four runs, each containing 500 averaged sweeps, were obtained. During each run, the computer program delivered electrocutaneous stimuli to the dominant wrist at the predetermined intensity for 500 trials. The interstimulus interval was 800 ms. N9, N13 and N20 waveforms were averaged online. Figure 1 shows an example run containing 500 averaged waveforms recorded from a normotensive participant. Muscle artefact was kept to a minimum by encouraging the patient to remain quiet and relaxed. Each run was separated by a 5 minute rest. Skin surface temperature at the dominant hand and arm was maintained between 31 - 35 °C. Temperature measurements were taken before each assessment using a laser thermometer (610LC, Maplin). When skin temperature dropped below 31 °C the arm was heated using a wheat bag (Physio Med Services). At the end of the procedure the

participant's arm length was measured from stimulating cathode to ipsilateral Erb's point electrode.

Data Reduction and Analyses

Three blood pressure recordings taken over a 5 minute period were averaged to yield laboratory blood pressures. The somatosensory-evoked potentials were recorded and measured in accordance with the guidelines of the International Federation of Clinical Physiology (Mauguiere et al., 1999). The Erb's point potential (N9) is a negative peak at a latency of 9 ms, which arises from the brachial plexus trunk. The N13 cervical potential is a negative potential with approximately a 13 ms latency generated by a compound segmental post-synaptic potential triggered in the dorsal horn gray matter by an afferent volley in fast conducting myelinated fibres. The N20 cortical potential is a negative potential with about a 20 ms post-stimulation latency generated from the primary somatosensory cortex in the posterior wall of the central fissure. N9, N13 and N20 peak latencies (ms) were measured from their peaks, whereas the amplitude (μV) of the N9, N13 and N20 potentials was measured from their peaks to the succeeding positive deflection. Median nerve conduction velocity (m/s), for the sensory action potential was calculated by dividing the arm length by the N9 latency. Three conduction times were calculated based on somatosensory-evoked potential latencies: plexus-cord (N13-N9); cord-cortex (N20-N13); plexus-cortex (N20-N9).

Separate 2 Group (hypertensive, normotensive) analyses of covariance (ANCOVAs) were performed on N9 amplitude and latencies. Age and stimulation-to-recording distance were entered as covariates because of their known effects on peripheral nerve sensory action potentials (Bolton & Carter, 1980; Horowitz & Krarup, 1992).

Separate 2 Group (hypertensive, normotensive) analyses of covariance (ANCOVAs)

were performed on N13 and N20 latencies and amplitudes. Age and arm length were entered as covariates in this analysis because these factors can affect short latency somatosensory-evoked potentials (Mauguiere et al., 1999). Correlational analyses indicated that although arm length (i.e., distance from wrist to N9 recording site) was not significantly correlated with short somatosensory-evoked potential amplitudes (r 's $\leq .11$, p 's $\geq .52$), it was positively related to N9 ($r = .64$, $p = .000$), N13 ($r = .56$, $p = .000$) and N20 ($r = .55$, $p = .001$) latencies. Separate 2 Group (hypertensive, normotensive) analyses of variance (ANOVAs) were performed on plexus-cord, cord-cortex and plexus-cortex conduction times. Age and arm length were not entered as covariates because these factors do not influence interpeak intervals (Mauguiere et al., 1999). A significance level of .05 was adopted. Differences in the reported degrees of freedom reflect occasional missing data. In addition to reporting significance levels, we have reported eta-squared (η^2), the effect size. The strength of association (i.e., effect size) between a factor and a dependent variable in ANOVA is indicated by η^2 , which is equal to R-squared (Tabachnick & Fidell, 2001) and represents the proportion of total variation in the dependent variable attributable to the factor. Accordingly, values of .02, .13, and .26 for η^2 represent small, medium, and large effect sizes, respectively (Cohen, 1992). The data were analysed using SPSS 15.0.

Results

Group Characteristics

Group blood pressures and demographics are presented in Table 1. Chi-square analysis revealed no significant group differences for sex, $\chi^2 (1) = 1.22$, $p = .27$, between the hypertensive group (9 men, 5 women) and the normotensive group (10 men, 12 women). Similarly, smoking status, $\chi^2 (1) = 0.23$, $p = .63$, did not differ

between the hypertensive group (12 non-smokers, 2 smokers) and the normotensive group (20 non-smokers, 2 smokers). A series of 2 Group (hypertensive, normotensive) ANOVAs were performed on the continuous variables (see Table 1). These analyses confirmed that, compared to the normotensive group, the hypertensive group exhibited higher blood pressures. The groups did not differ in terms of age, height, body mass index and alcohol consumption.

Separate 2 Group (hypertensive, normotensive) ANOVAs were performed on variables that have previously been shown to affect peripheral nerve function measures, including limb temperature, room temperature, stimulation-to-recording distance, and intensity of supramaximal electrocutaneous stimulation. In all instances, there was no difference between groups.

Hypertension and N9

Separate 2 Group (hypertensive, normotensive) ANCOVAs were performed on the latency and amplitude of the N9, covarying for age and distance between stimulation and recording site. As shown in Table 2, these analyses revealed significant group differences in N9 amplitudes¹ but not latencies. Hypertensives had significantly smaller N9 amplitudes than normotensives (see Figure 2). The effect size for this group difference in N9 amplitudes was medium-to-large (Cohen, 1992). Further, the group differences in N9 amplitude survived additional covariate adjustment for BMI.

Continuous Blood Pressure and N9 amplitudes

As well as examining the influence of blood pressure status on N9 amplitudes by comparing groups of normotensive and hypertensive participants, it is also possible to treat blood pressure as a continuous rather than a dichotomous variable. Accordingly,

multiple regression analyses were performed to determine the association between N9 amplitudes and blood pressure while accounting for the possible moderating influence of putative confounders, age and stimulation-to-recording distance. Four hierarchical regression analyses were conducted. Age and distance between stimulation and recording sites were entered together in the first step. Each of the four blood pressure measures (daytime ambulatory systolic blood pressure, daytime ambulatory diastolic blood pressure, laboratory systolic blood pressure or laboratory diastolic blood pressure) were entered separately in the second step (i.e., only one blood pressure variable was entered in any one analysis). As Figure 3 illustrates, N9 amplitudes were negatively associated with daytime ambulatory systolic blood pressure ($B = -0.06$, 95% CI for $B = -0.10$ to -0.02 , $\beta = -.44$, $t = -2.91$, $\Delta R^2 = .19$, $p = .007$), daytime ambulatory diastolic blood pressure ($B = -0.06$, 95% CI for $B = -0.12$ to 0.00 , $\beta = -.36$, $t = -2.17$, $\Delta R^2 = .12$, $p = .04$), laboratory systolic blood pressure ($B = -0.06$, 95% CI for $B = -0.09$ to -0.02 , $\beta = -.49$, $t = -3.34$, $\Delta R^2 = .23$, $p = .002$), and laboratory diastolic blood pressure ($B = -0.06$, 95% CI for $B = -0.10$ to -0.01 , $\beta = -.38$, $t = -2.42$, $\Delta R^2 = .14$, $p = .02$)².

Hypertension and N13

Separate 2 Group (hypertensive, normotensive) ANCOVAs were performed on the latency and amplitude of the N13, adjusting for age and arm length. As shown in Table 2, these analyses revealed a trend for N13 amplitudes but not latencies.

Continuous Blood Pressure and N13 amplitudes

Multiple regression analyses (see above) revealed that N13 amplitudes were not significantly associated with any of the four blood pressure measures.

Hypertension and N20

Separate 2 Group (hypertensive, normotensive) ANCOVAs, adjusting for age and arm length, were performed on the amplitude and latency of the N20. As shown in Table 2, analyses revealed no group differences in N20 amplitudes or latencies.

Peripheral Nerve Conduction Velocities, Conduction Times and Hypertension

A 2 Group (hypertensive, normotensive) ANCOVA, with age as covariate, performed on the sensory median nerve conduction velocities revealed no group differences. In addition, separate 2 Group (hypertensive, normotensive) ANOVAs, performed on plexus-cord, cord-cortex and plexus-cortex conduction times also revealed no group differences in conduction speeds.

Discussion

The current study examined peripheral (i.e., N9), spinal (i.e., N13) and cortical (i.e., N20) short latency somatosensory-evoked potentials, elicited by median nerve stimulation, in young patients with unmedicated essential hypertension with no history of peripheral neuropathy and associated symptoms. The major finding of this study was that the peripheral portion of the ascending somatosensory pathway was affected by hypertension. N9 amplitudes, generated by peripheral sensory nerve fibres at the brachial plexus (Lee & Seyal, 1998), were 37% smaller in hypertensives than normotensives. This finding is compatible with our previous study which reported reduced amplitude sensory action potentials in the median nerve at the index finger after stimulation at the wrist and elbow in hypertensives compared to normotensives (Edwards et al., 2008). The present study also found that N9 amplitudes decreased as

continuous blood pressure levels increased. Thus, the current study provides additional evidence for blood pressure-related alterations in peripheral nerve function. As the amplitude of a sensory action potential reflects the number of large diameter myelinated fibres synchronously depolarised in the vicinity of the active recording electrode (Buchthal & Rosenfalck, 1966), a reduction may indicate axonal loss (Gilliatt, 1978). The observation that peripheral nerve conduction velocities were not different between hypertensives and normotensives in the current study concurs with the null findings of most previous studies (Bridgman et al., 1973; Edwards et al., 2008; Halar et al., 1978). Taken together with previous studies, the present finding of unaltered peripheral sensory nerve conduction velocities but reduced amplitude sensory nerve action potentials in our sub-sample of unmedicated hypertensives suggests that hypertension may cause axonal loss without affecting the myelination of peripheral afferents. It is worth noting that the mean N9 amplitude value for the hypertensive group was within the normal range (Tanosaki, Ozaki, Shimamura, Baba, & Matsunaga, 1999) and, therefore, was not clinically abnormal. Despite being within the normative range, these subtle subclinical differences may still be of clinical importance; indicating blood pressure-related functional changes in the peripheral nervous system and suggesting a role of the peripheral nervous system in the pathophysiology of essential hypertension.

Importantly, the current study, to our knowledge, is the first to investigate the possible influence of unmedicated hypertension on the ascending somatosensory fibres of the central nervous system, and activation of the primary somatosensory cortex. The current study measured N13, reflecting postsynaptic activity triggered in the dorsal horn gray matter of the cervical spinal cord, and N20, representing the earliest cortical response generated from the primary somatosensory cortex in the

posterior wall of the central fissure (Mauguiere et al., 1999). That the amplitude of evoked potentials generated from dorsal cervical spine (i.e., N13) was marginally affected by blood pressure status (i.e. small-to-medium effect size), whereas the amplitude of the evoked potentials generated in the primary somatosensory cortex (i.e., N20) was unaffected by blood pressure suggests that blood pressure in relatively young, newly diagnosed and unmedicated hypertensive patients may also affect transmission and processing of sensory information within the spinal cord but not the brain. Thus, our hypothesis that the ascending somatosensory pathway may be detrimentally affected by unmedicated hypertension in a relatively young and newly diagnosed group of patients with, arguably, a shorter duration of exposure to elevated blood pressure was partially supported, as deficits were detected in the peripheral nervous system and spinal cord but not the brain.

The mechanism underlying any hypertension-related axonal degeneration in the peripheral nervous system has yet to be established. However, the lack of autoregulatory capabilities in the peripheral nerve vascular system (Smith et al., 1977), means that the peripheral nerves need adequate vascularisation to prevent ischaemia and hypoxia (Low & Tuck, 1984; Olsson, 1972). As such, structural and functional alterations in the peripheral microcirculation associated with hypertension (Mourad & Laville, 2006) could cause nerve hypoxia leading to axonal neuropathy. Indeed, blood flow in the brain is maintained by autoregulation. Although individuals with chronic hypertension may be prone to cerebral hypoperfusion (Baumbach & Heistad, 1988; Faraci & Heistad, 1998; Fujishima et al., 1995; Heistad & Baumbach, 1992; Maeda et al., 1994; Nobili et al., 1993; Tamaki et al., 1995), the current findings suggest that hypertension-related impairment of cerebral perfusion may not be enough to impair brain activity in the primary somatosensory cortex associated

with activation of the afferent somatosensory system, at least in relatively young hypertensive patients.

Although the results with regard to hypertension and peripheral nerve function agree with previous studies, there are some limitations that should be noted. It is commonly accepted that N9, evoked by stimulation of the median nerve at the wrist, is generated by peripheral sensory nerve fibres at the brachial plexus (Lee & Seyal, 1998), however, it must be pointed out that there may be some contribution to the N9 potential by antidromically stimulated motor fibres. However, as a recent study involving the same participants reported deficits in sensory but not motor action potential amplitudes (Edwards et al., 2008), we are confident that the differences in N9 amplitudes reported in hypertensives in the current study reflect deficits in sensory fibres. Another limitation of the current study was that only upper limb short latency somatosensory-evoked potentials were tested. Future studies would do well to test lower limb short latency somatosensory-evoked potentials in order to confirm the present study's findings. In addition, axonal degeneration is often characterised by 'dying-back' in the most distal segments of the nerve (Greenfield, 1954), and therefore, examination of lower limb nerves may be better placed to demonstrate the presence of mild hypertension-related axonal neuropathy. The current study only tested somatosensory-evoked potentials in the dominant arm, and therefore, future studies should compare function in both dominant and non-dominant arms. If hypertension is causing the reported N9 amplitude differences then it would be anticipated that these differences would be present in both sides of the median nerve. In addition, the current study tested function in the ascending somatosensory pathway related to activity in the large myelinated afferents which convey sensation from mechanoreceptors and was not designed to assess function in smaller A-delta and C

fibres, which might explain deficits in pain perception which characterise hypertension (Ghione, 1996). It is recommended that future studies perform a battery of sensory tests to examine the effect of hypertension on thinly myelinated and unmyelinated afferents to investigate the hypothesis that hypertensive hypoalgesia may be due to deficits in peripheral nerve function. Overall, definitive conclusions about hypertension-related peripheral nerve function cannot be drawn from these preliminary findings, which should be interpreted with caution until larger scale studies have been conducted.

In sum, the finding of smaller N9 sensory action potential amplitudes in hypertensives compared to normotensives suggests that hypertensives may suffer from a mild subclinical form of axonal neuropathy. Sensory action potential amplitudes were found to be inversely related to arterial blood pressure suggesting that blood pressure exerts a graded influence on peripheral nerve function. These data suggest that sensory-perceptual deficits found in hypertensives may be, at least in part, due to mild subclinical peripheral neuropathy. These findings support the hypothesis that hypertension may be a risk factor for peripheral neuropathy.

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Foot Notes

1. A 2 Group \times 2 Sex ANCOVA, with group and sex as between-subjects factors, on N9 amplitude, with age and stimulation to recording distance as covariates, confirmed the significant main effect for Group, $F(1,30) = 6.01, p = .02, \eta^2 = .17$.
2. Hierarchical regression analyses, with sex, age, and stimulation-recording distance entered in step one, confirmed that N9 amplitudes were negatively associated with daytime ambulatory systolic blood pressure ($B = -0.05, \beta = -.37, p = .02$) and laboratory systolic blood pressure ($B = -0.05, \beta = -.42, p = .01$). Moreover, N9 amplitudes were marginally associated with daytime ambulatory diastolic blood pressure ($B = -0.05, \beta = -.29, p = .08$) and laboratory diastolic blood pressure ($B = -0.04, \beta = -.29, p = .10$).

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Table 1. *Mean (Standard Deviation) Characteristics of the Hypertensive and Normotensive Groups as well as the Degrees of Freedom, F-values and Statistical Significance Level of the Group Effects and Associated Effect Size*

Variable	Hypertensive	Normotensive	df	F	p	η^2
Ambulatory (Daytime)						
Systolic blood pressure (mmHg)	148.1 (6.9)	119.2 (9.98)	1, 34	89.93	<.001	.73
Diastolic blood pressure (mmHg)	97.5 (7.5)	77.5 (6.7)	1, 34	69.38	<.001	.67
Laboratory						
Systolic blood pressure (mmHg)	144.7 (12.3)	117.8 (14.8)	1, 34	32.27	<.001	.49
Diastolic blood pressure (mmHg)	95.0 (10.4)	72.3 (8.8)	1, 34	49.54	<.001	.59
Body mass index (kg/m ²)	26.7 (3.6)	25.4 (3.8)	1, 34	1.28	.27	.04
Height (m)	1.73 (0.09)	1.73 (0.10)	1, 34	0.01	.92	.00
Age (years)	40.0 (6.0)	37.1 (6.4)	1, 34	2.38	.13	.07
Alcohol intake (units/week)	8.8 (8.7)	8.1 (8.8)	1, 34	0.03	.86	.00

Table 2. *Mean (Standard Deviation) Unadjusted Amplitudes and Latencies for N9, N13 and N20 plus Median Nerve Conduction Velocity, Relative Conduction Times and Stimulation Intensities of the Hypertensive and Normotensive Groups as well as the Degrees of Freedom, F-values and Statistical Significance Level of the Group Effects and Associated Effect Size*

Variable	Hypertensive	Normotensive	df	F	p	η^2
Stimulation Intensity (mA)	12.00 (2.66)	12.79 (3.76)	1,34	0.46	.50	.01
N9						
Amplitude (μ V)	3.60 (1.26)	5.71 (2.24)	1,32	7.97	.008	.20
Latency (ms)	10.21 (0.78)	10.36 (0.76)	1,32	0.99	.33	.03
N13						
Amplitude (μ V)	1.01 (0.36)	1.38 (0.53)	1,32	3.09	.09	.09
Latency (ms)	13.33 (0.99)	13.57 (0.98)	1,32	1.44	.24	.04
N20						
Amplitude (μ V)	4.38 (2.35)	3.87 (2.20)	1,32	1.19	.28	.04
Latency (ms)	19.23 (1.26)	19.35 (0.95)	1,32	0.51	.48	.02
Sensory nerve conduction velocity (m/s)	61.46 (3.77)	61.27 (3.63)	1,33	0.57	.46	.02
Plexus-cord conduction time (ms)	3.12 (0.62)	3.21 (0.46)	1,34	0.24	.63	.01
Cord-cortex conduction time (ms)	5.90 (0.81)	5.78 (0.77)	1,34	0.21	.65	.01
Plexus-cortex conduction time (ms)	9.02 (0.70)	8.99 (0.61)	1,34	0.03	.87	.00

Figure Captions

Figure 1. Example Run Containing 500 Averaged N9, N13 and N20 Short Latency Somatosensory-Evoked Potential Components Obtained from a Normotensive Participant. Note: 5 μ V/division sensitivity, 5 ms/division time base.

Figure 2. Mean (Standard Error) N9 Amplitudes Elicited by Median Nerve Stimulation at the Wrist in Healthy Normotensives and Unmedicated Essential Hypertensives.

Figure 3. Scatter Plots with Regression Lines Illustrating the Relationship between N9 Amplitude and Systolic Ambulatory Blood Pressure (panel a), Ambulatory Diastolic Blood Pressure (panel b), Laboratory Systolic Blood Pressure (panel c), and Laboratory Diastolic Blood Pressure (panel d).