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Hypertension and daytime hypotension found on ambulatory blood pressure is associated with fatigue following stroke and TIA

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Summary

Background: Fatigue affects up to 68% of subjects following stroke. In non-stroke patients, associations are reported between chronic fatigue and both hypertension and hypotension. We hypothesized that, in patients with stroke or transient ischaemic attack (TIA), an association may exist between fatigue and abnormal blood pressure (BP) detected on ambulatory monitoring.

Methods: Subjects recruited from a secondary prevention clinic underwent 24-h ambulatory BP monitoring and completed a questionnaire including the Fatigue Severity Scale (FSS).

Results: One hundred subjects were included (51% female, mean age 69 years). Mean FSS was 3.6 and 42 has a FSS >4 indicative of significant fatigue. Mean daytime BP for all subjects was 134/74 (SD 16/11 mmHg). There was no significant difference in mean BP between patients with and those without significant fatigue. Patients with stroke suffered

worse fatigue than those with TIA (mean FSS 3.8 vs. 3.0, $P=0.03$). Twenty-four subjects were hypertensive (mean 24-h BP >145/90 mmHg), 26 had a lowest daytime diastolic BP (DBP) <50 mmHg and 4 had both. Fifty-four subjects were normotensive and these had a significantly lower mean FSS than either those with hypertension (mean FSS 3.2 vs. 4.2, $P=0.02$, t -test) or those with low DBP (mean FSS 3.2 vs. 4.2, $P=0.01$, t -test). Hypertensive subjects were more likely to be significantly fatigued [χ^2 3.8, $P=0.05$, OR 3.1 (1.1–8.3)] as were subjects with low daytime DBP [χ^2 8.4, $P=0.004$, OR 4.2 (1.5–11.1)].

Conclusion: In subjects who have suffered a stroke or TIA, fatigue is associated with measures of both hypertension and hypotension on ambulatory monitoring. Patients with stroke suffered worse fatigue than those with TIA.

Fatigue is a common symptom following stroke. It affects between 30% and 68% of patients suffering stroke^{1,2} and is classed by 40% as amongst their worst symptoms.³ Despite this, there are few proven associations and no effective treatments.¹ There is however substantial evidence of an association

between various forms of hypotension and idiopathic forms of chronic fatigue,^{4,5} fatigue has been found associated with lower blood pressure (BP) in larger population studies⁶ and is a reported side effect of a number of antihypertensive medications.⁷ Unlike most symptoms associated with stroke

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which are maximal at or near the time of the event, fatigue severity may increase in the months following stroke.¹ Institution of antihypertensive therapy following stroke may be one possible cause of this.

Hypertension is less often reported associated with fatigue although there is some evidence that hypertensive subjects suffer more fatigue-related symptoms.⁸ There is however good evidence^{9,10} of the effectiveness of antihypertensive therapy in secondary prevention of cerebrovascular disease, and there is now increased emphasis on reducing BP in patients who have suffered stroke and transient ischaemic attack (TIA) with recent guidelines advocating lowering BP in 'normotensive' patients.¹¹ In light of the high prevalence of fatigue and hypertension in stroke patients and the emphasis on BP lowering to reduce risk of recurrent events, we hypothesized that there may be an association between post-stroke fatigue and abnormalities in BP, so we performed a study to determine if an association existed between hypertensive or hypotensive BP changes on 24-h ambulatory BP monitoring performed as part of assessment for secondary prevention and a fatigue score performed at the same time.

An association has been noted between depression and fatigue in stroke patients. After a planned midpoint review of the study, we agreed that this relation should be considered and a substudy was commenced to examine this relation in our population.

Methods

Written ethical approval for the study was obtained from the local St James's Hospital/AMNCH joint ethics committee. Subjects were recruited from patients attending a secondary prevention clinic for patients with cerebrovascular disease between 1 and 6 months following stroke or TIA. They gave informed consent prior to study recruitment. Independent (modified Rankin scale ≤ 2) patients of any age or gender were eligible for inclusion in the study.

Exclusion criteria were presence of significant cognitive impairment, inability to tolerate 24-h ambulatory BP monitoring performed using the chosen devices and inability to complete the fatigue assessment measures. Demographic data were collected for each patient in addition to information on co-morbid conditions, details of antihypertensive medication use and a brief questionnaire regarding symptoms of hypotension, especially orthostatic symptoms was completed. The second 50 subjects recruited also underwent a depression assessment to

determine if a relation existed between depression fatigue and BP.

BP monitoring

Subjects underwent ambulatory BP monitoring using British Hypertension Society Validated Ambulatory Blood Pressure Monitors^{12,13} (A& D TM-2430- A& D Instruments Ltd, Oxfordshire, UK and Meditech ABPM-04 - PMS Instruments Ltd, Berkshire, UK). A cuff of appropriate size for the arm circumference was fitted to the non-dominant arm and the procedure for measurement explained. Participants were instructed that the monitor arm be kept stationary during the 1–2 min period required to obtain readings and that the monitor would automatically repeat measurement where the initial attempt was unsuccessful. A test reading was taken for each participant at time of fitting. The monitor was programmed to obtain readings every 30 min during daytime (7 am to 11 pm) and every 60 min at night (11 pm to 7 am). Each participant was provided with a diary sheet to record activities during the period of study. The times of retiring to, and rising from, bed were recorded, as were the times of meals and medications. Monitors were removed after 24 h and data downloaded using proprietary software. The daytime and night-time periods were defined in a time-dependent manner. Minimum, maximum and mean with standard deviation values were expressed for systolic BP (SBP), diastolic BP (DBP), mean arterial pressure and differences between mean and minimum BP readings calculated. Those studies with 10 or more daytime readings were deemed adequate for daytime analysis. Night-time analysis required at least 5 night-time readings. Where data was considered inadequate on a first 24-h study, the study was repeated.

Patients with a mean 24 h SBP >145 mmHg or DBP >90 mmHg were considered hypertensive for the purposes of the study. On review of the patient data in the course of the study, a significant proportion of patients were unexpectedly noted to suffer marked dips in DBP during their BP recordings. This subgroup of subjects were identified for analysis in the course of the study with hypotensive episodes defined as a drop of DBP to <50 mmHg at any point in the day. This level was chosen because the SHEP and Syst-Eur studies showed that pressure above 50 mmHg was not associated with increased cardiovascular morbidity but sustained hypotension below this level may be.^{14,15} BP under this level is also likely to be below the level at which autoregulatory mechanisms can maintain cerebral

perfusion. The remainder of the subjects were classified as normotensive.

Measurement of fatigue

All subjects completed the Fatigue Severity Scale (FSS)¹⁶ prior to discussion of their BP results. The FSS is a 9-item scale designed to evaluate fatigue in a variety of conditions and has been widely used to assess post-stroke fatigue. Each of the nine items is scored from 1 to 7 in terms of severity and the overall result divided by 9 to give an overall result. A total score of >4 is used to indicate significant fatigue.¹⁶

Measurement of depression

After a planned review at the midway point of the study, it was agreed that future subjects should complete the Hospital Anxiety Depression (HAD) Scale given the previous reported associations between depression, BP and fatigue. In accordance with usual practice, scores >7 in either the HAD-anxiety (HAD-A) or depression (HAD-D) subscales were considered potentially significant.¹⁷

Statistical analysis

Statistical analyses were performed using SPSS version 14.0 (SPSS Inc, Chicago, IL, USA). Student's *t*-tests were performed to compare mean values between groups. Pearson's correlation coefficients were used to calculate continuous parametrically distributed variables.

The primary outcome measure was the difference in minimum SBP between those with significant fatigue and those without. Assuming 50% of patients suffered significant fatigue, the study was powered at 70% to detect a difference in mean SBP of 10 mmHg between groups.

Results

One hundred and seven subjects were initially recruited to create a study group of 100 subjects, all independent for activities of daily living. Two subjects were unable to understand the FSS Likert scale and one declined to complete it. Four patients were unable to tolerate 24-h ambulatory BP monitoring. One hundred remaining subjects (Table 1) (51% female, mean age 69 years) were recruited to the study and completed Fatigue Severity Scores.

Mean FSS was 3.6 and 42 subjects (42%) had significant fatigue, defined as an FSS >4 . There was no association between age or gender and fatigue (Table 2). Patients with stroke suffered worse fatigue

Table 1 Summary patient data ($n=100$)

Mean age in years (SD)	69 (11.3)
Female	51%
Mean Fatigue Severity Score (SD)	3.6 (1.7)
Stroke	69%
Diabetes	11%
Weight in kilograms (SD)	75 (12)
GFR (Cockcroft-Gault) ml/s	76 (28)
History of ischaemic heart disease	18%
Previous syncope or pre-syncope	24%
Previous orthostatic symptoms	51%
Mean 24 h SBP in mmHg (SD)	134 (16)
Mean 24 h DBP in mmHg (SD)	71 (11)
Mean daytime minimum SBP in mmHg (SD)	109 (20)
Mean daytime minimum DBP in mmHg (SD)	62 (15)
Mean night-time minimum SBP in mmHg (SD)	106 (18)
Mean night-time minimum DBP in mmHg (SD)	55 (13)
BP variability: mean standard deviation of SBP (SD)	18.5 (4.9)
BP medications: none	30
1	29
2	25
3	11
4	5

than those with TIA (mean FSS 3.8 vs. 3.0, SD 1.4, $P=0.03$) but there were no significant differences in BP recordings between stroke and TIA patients (mean SBP 133 vs. 134, $P=0.8$). Twenty-four subjects acknowledged past symptoms of syncope or pre-syncope and 51 had occasional symptoms of light headedness on standing up.

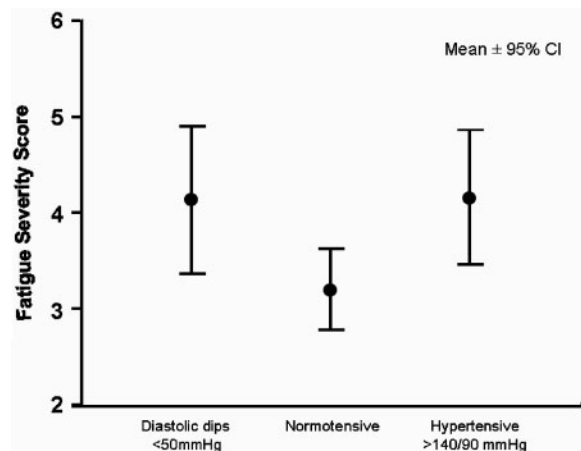
Mean 24 h BP for all subjects was 134/71 (SD 16/11 mmHg). There was no significant difference in 24 h mean systolic pressure, the primary outcome measure or in mean diastolic pressure, lowest day or night-time SBP or DBP between patients with significant fatigue and those without (Table 2). Seventy percent of subjects were on at least one antihypertensive medication. Subjects with significant fatigue were more likely to be taking BP medications (81% vs. 62%, χ^2 4.14, $P=0.04$).

Twenty-four subjects were found to be hypertensive using the threshold of $>145/90$ mmHg and 26 dipped their daytime DBP below the 50 mmHg threshold. Four subjects were both hypertensive and dipped BP leaving 54 subjects in the normotensive group (Table 2).

Using a lower $>140/85$ threshold, 35 patients were hypertensive, 6 of whom also dipped their

Table 2 Comparison of fatigued and non-fatigued subjects

	Fatigued (FSS >4)	Non-fatigued (FSS <4)	P
n	42	58	
Mean age in years (SD)	67.4	70.0	0.14
Female (%)	24 (57)	27 (47)	0.3
Stroke	35 (83)	34 (59)	0.008
Diabetes	6 (14)	5 (9)	0.9
Mean 24 h SBP in mmHg (SD)	136 (18)	133 (15)	0.4
Mean 24 h DBP in mmHg (SD)	73 (11)	70 (10)	0.3
Mean daytime minimum SBP in mmHg (SD)	108 (22)	110 (20)	0.8
Mean daytime minimum DBP in mmHg (SD)	60 (16)	63 (14)	0.4
Mean night-time minimum SBP in mmHg (SD)	108 (20)	104 (15)	0.3
Mean night-time minimum DBP in mmHg (SD)	55 (12)	54 (13)	0.7
Taking antihypertensive medications (%)	34 (81%)	36 (62%)	0.04

**Figure 1.** Mean fatigue severity scores of normotensive patients, those with episodes of daytime DBP <50 mmHg and hypertensive patients (BP 145/90 mmHg).

DBP below 50 mmHg. Normotensive subjects had a significantly lower mean FSS than either those with low daytime DBP (Mean FSS 3.2 vs. 4.2, $P=0.01$, t -test) or those with hypertension (mean BP >145/90 mmHg: mean FSS 3.2 vs. 4.2, $P=0.02$, t -test, mean BP >140/85 mmHg: mean FSS 3.1 vs. 4.0 $P=0.01$) (Figure 1). No association was found between low nocturnal DBP ($r=0.145$, $P=0.16$ Pearson's rho) and fatigue or between BP variability as expressed by the standard deviation of mean BP readings ($r=0.52$, $P=0.7$, Pearson's rho). Mean FSS for the six subjects with both hypertension >140/85 and diastolic dips was 5.1 although numbers were too small for useful statistical analysis. Subjects with dips in daytime DBP <50 mmHg were more likely to have significant fatigue defined as a FSS >4 [61% vs. 28%, χ^2 8.4, $P=0.004$, OR 4.2 (1.5–11.1)] as were hypertensive subjects [54% vs. 28%, χ^2 3.8, $P=0.05$, OR 3.1 (1.1–8.3)] (Table 3).

Seventy subjects were prescribed antihypertensive therapy and 33 subjects were found to be hypertensive (mean 24 h BP >140/90 mmHg) on ABPM. Subjects on antihypertensive therapy were more likely to have significant fatigue (FSS >4) [49% vs. 27%, χ^2 4.14, $P=0.042$, OR 2.6 (1.02–6.6)]. When currently hypertensive (BP >140/90 mmHg) subjects were removed from the population this difference was more marked [49% vs. 17%, χ^2 6.7, $P=0.009$, OR 4.8 (1.3–16.3)]. There was no difference in fatigue levels between hypertensive and non-hypertensive patients on antihypertensive medication (49% vs. 51%, $P=0.82$), but untreated hypertensives tended to more significant fatigue than normotensive subjects on no antihypertensive treatment ($P=0.1$, Fisher's exact) but numbers in the untreated group were very small. There was no significant correlation between number of antihypertensive agents and FSS ($r=0.135$, $P=0.18$).

Depression and fatigue

In the subset of 50 subjects who completed HAD scores 19 (38%) subjects had a HAD-A subscale >7 and 7 (14%) had a HAD-D subscale >7 indicative of potentially significant depression. Twenty-one subjects (42%) had one or other HAD scale >7. FSS correlated significantly with both the HAD-A ($r=0.37$, $P=0.009$, Pearson rho) and HAD-D ($r=0.42$, $P=0.002$) scales. Ten of the 19 (53%) subjects with a HAD-A >7 and 4 of the 7 (57%) with a HAD-D >7 had significant fatigue (FSS >4). However, 7 of 30 (23%) non-depressed subjects (HAD-A and HAD-D ≤7) also had significant fatigue (FSS >4) and 10 of 32 subjects (31%) without significant fatigue had significant depression scores.

Table 3 Comparison of patients with hypertension and daytime DBP dips vs. normotensive patients

	Normotensive	Daytime DBP <50 mmHg	Hypertensive (mean 24 h BP >145/90 mmHg)
N	54	26	24
Mean age in years (SD)	68 (12)	69 (12) <i>P</i> =0.9	70 (9) <i>P</i> =0.4
Male (%)	28 (51)	11 (42) <i>P</i> =0.4	11 (46) <i>P</i> =0.6
Mean fatigue severity score (SD)	3.2 (1.6)	4.2 (1.7) <i>P</i> =0.01	4.2 (1.7) <i>P</i> =0.02
Orthostatic symptoms (%)	27 (50)	11 (42)	14 (58)

Discussion

In the population studied, of patients who have recently suffered a stroke or TIA, fatigue is associated with measures of both hypertension and daytime low BP recorded on ambulatory BP monitoring. Patients receiving antihypertensive medication were more fatigued than those who were not but fatigue severity did not correlate with number of drugs taken and untreated hypertensive patients were not less fatigued than those on therapy. Although all patients studied were independent for activities of daily living, subjects with stroke suffered significantly more fatigue than those with TIA. Severity of fatigue correlated with both anxiety and depression subscores of the HAD scale, but more than half of subjects with either significant fatigue or depression did not suffer the other symptom to a significant degree.

There were some limitations to the study as the subjects were recruited from patients attending a dedicated secondary prevention clinic for people with cerebrovascular disease; the great majority of these are mobile and self-caring. We did not include patients with more significant disability (modified Rankin Scale >2) because of the difficulty in distinguishing symptoms due to fatigue and those due to physical impairment or disability. Accordingly, the population studied is quite selected not only in terms of disability but also in terms of age, as older patients tend to suffer more severe disability following stroke. The mean age of patients (69 years) was a lower than the Irish national average age of onset (73 years). We feel, however, that this selection is unlikely to have affected the study's primary finding that fatigue is associated with daytime low BP as this measure is likely to be relatively independent of age and disability and it is of note that despite an age range in the study of

38–90 years no correlation was found between age and fatigue.

BP monitoring was performed according to standard protocols with measures being taken every 30 min during daytime and 60 min at night. Subjects could trigger extra measure if they felt symptomatic, but rarely did so. Clearly, episodes of daytime hypotension could have been missed in some subjects due to the relative infrequency of automatic measures. However, the study was designed to determine if fatigue correlated with routinely recorded measures of BP and it was decided that more frequent recording was inappropriate given this.

The FSS, initially developed for patients with systemic lupus erythematosus,¹⁶ has been used in multiple conditions associated with fatigue including multiple sclerosis^{18,19} and stroke.^{20,21} Whilst the majority of subjects found the scale easy to use, two were unable to understand the concept of a Likert scale and had to be excluded. Other authors have recently suggested the FSS has limitations in patients with physical disability,²² which was another factor that influenced our decision to exclude significantly disabled patients. Naess and colleagues²³ demonstrated that fatigue is more common in patients with stroke than in healthy controls. They also found that fatigue may be related to level disability more than size of cerebral lesion, a finding supported by other authors^{24,25} and that fatigue adversely affects quality of life²⁵ in young stroke survivors. Our findings are consistent with this in that stroke patients suffered more fatigue than those with TIAs despite being similar in age and mean BP characteristics. Whilst all patients recruited to the trial were independent for personal activities of daily living and had a modified Rankin scale of 2 or less, some of the stroke patients had minor levels of residual impairment and disability and this may explain the

difference in level of fatigue found with subjects with TIA.

Since the publication of the PROGRESS trial in 2001,¹⁰ increased emphasis has been given to BP lowering in patients with stroke and TIA. The finding from PROGRESS that even normotensive stroke patients benefit significantly from antihypertensive therapy has led to recommendations that BP lowering should be considered even in patients with 'normal' BP and that the level of BP lowering sought in these patients should be more profound than in the past.¹¹ It is therefore reassuring that our study showed an association between presence of hypertension and fatigue in stroke patients. Whilst an association between fatigue and hypotension is well reported both in chronic fatigue syndrome⁵ and in population studies,⁶ the association with hypertension is less well recognized. Erickson and colleagues⁸ reported an increase prevalence of 'weariness' on the Symptom Distress Checklist reported in 437 subjects attending general medicine and hypertension clinics. The cause of the association between hypertension and fatigue is unclear. Most of those subjects who were hypertensive in the study were on antihypertensive medications already and these were being titrated up in the clinic. Fatigue is reported as a potential adverse reaction to many antihypertensive medications, including β -adrenoreceptor antagonists, calcium channel antagonists and thiazide diuretics, drugs that differ significantly in both structure and mechanism of action. Our finding that fatigue is commoner in patients taking antihypertensives but not related to the number of drugs taken may suggest that the association results from the drugs effect on BP rather than the agents themselves.

The finding that fatigue is related to low dips in minimum daytime BP raises questions as to what these minimum values represent. The most likely explanation is that these subjects are suffering episodes of orthostatic hypotension. Although there was no association found with orthostatic symptoms in our population, orthostatic hypotension in older people is commonly asymptomatic.²⁶ Although the association with low BP is a novel finding in patients with post-stroke fatigue, a number of authors have reported associations between autonomic dysfunction and orthostatic intolerance and the chronic fatigue syndrome,^{5,6} although the extent and relevance of this association are controversial.²⁷

The depression substudy was performed as low mood and anxiety have previously been well described as associated with post-stroke fatigue.¹⁻³ We included a depression substudy at the mid-point of our study after discussion between investigators

and review of ethics approval. Our study findings support the conclusions of DeGroot and colleagues¹ that whilst the two conditions correlate they are not synonymous. More than half of our subjects (17 of 29) with either of the symptoms of fatigue or depression were not affected by the other symptom. Distinguishing between fatigue and depression using scales is fraught as fatigue is acknowledged by many as a somatic symptom of depressive disease and questions regarding one symptom may be influenced by the presence of the other e.g. the HAD scale includes statements, such as 'I feel as if I am slowed down' and 'I still enjoy the things I used to enjoy' which clearly may be affected by underlying fatigue whereas the FSS has the statement 'My motivation is lower when I am fatigued' which could be affected by the presence of depression.

This study is relatively small and further studies are necessary to clarify the association between fatigue and BP post-stroke, including studies formally looking at BP response to orthostasis and head up tilt in fatigued and non-fatigued patients, the effect of initiation of antihypertensive therapy on post-stroke fatigue and whether adjustment of therapy to avoid diastolic dips will reduce fatigue levels. In the meantime however this study reinforces the importance of good BP control following stroke and TIA.

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