Increased diastolic blood pressure is associated with MRI biomarkers of dementia-related brain pathology in normative ageing

Abstract

Background

Hypertension is a risk for brain ageing, but the mechanisms underlying this effect remain unclear. MRI detected biomarkers of brain ageing include white matter hyperintensities (WMH); a marker of cerebrovascular disease, and hippocampal volume, a marker of Alzheimer's disease pathology.

Objective

To examine relationships between blood pressure (BP) components and brain pathology in older adults.

Subjects

227 members of the Aberdeen 1936 Birth Cohort between ages 64y and 68y.

Methods

BP was assessed biennially between 64 to 68y and brain MRI performed at 68y. The risk factors of interest were diastolic and systolic BP and their visit-to-visit variability. Outcomes were white matter hyperintensity abundance, and hippocampal volume. Regression models, controlling for confounding factors, examined their relationships.

Results

Higher diastolic BP predicted increased WMH (β=.13, p = .044) and smaller hippocampi (β=-.25, p=.006). In contrast, increased systolic BP predicted larger hippocampi (β=.22, p=.013). Variability of diastolic BP predicted lower hippocampal volume (β=-.15, p=.033). These relationships were independent of confounding life-course risk factors. Anti-hypertensive medication did not modify these relationships, but was independently associated with increased WMH (β=.17, p=.011).

Conclusions

Increased diastolic BP is associated with biomarkers of both cerebrovascular and Alzheimer's diseases, whereas the role of systolic BP is less clear, with evidence for a protective effect on hippocampal volume. These differing relationships emphasises the importance of considering individual BP components with regards to brain ageing and pathology. Interventions targeting diastolic hypertension and its chronic variability may provide new strategies able to slow the accumulation of these harmful pathologies.

Introduction

Hypertension is common in older age [1] and is linked to MRI markers of brain degeneration that accompany ageing and dementia. Cerebrovascular disease is visible on MRI scans as hyper-intense regions named white matter hyperintensities (WMH). Although first detected within the white matter, WMH have been shown to be present throughout the brain [2]. WMH are associated with reduced cognitive performance and dementia [3, 4], and are more prevalent in older adults with hypertension than normotensive controls [5]. We have shown that the negative influence of hypertension on cognition was entirely explained by the WMH burden in normal ageing [5]. Some evidence suggests the relationship between blood pressure (BP) and cognition in the elderly is non-linear with hypotension associated with faster decline in older adults with cognitive impairment; [6] nevertheless, the association between hypotension and brain pathology remains unknown.

A relationship between hypertension and dementias, including Alzheimer's disease and vascular dementia, is widely accepted [7], although evidence in support of treatment of hypertension to prevent dementia is somewhat conflicting [8, 9]. The relationships between BP, cognition and brain ageing are not straight-forward with a systematic review finding reports of positive, negative, U shaped, J shaped and quadratic relationships between BP and cognitive function. Furthermore, it has been demonstrated that diastolic (dBP) and systolic blood pressure (sBP) can have independent relationships with cognition [7].

Reduced hippocampal volume is a marker of hippocampal atrophy and is a useful indication of Alzheimer's pathology [10]. The LADIS study found no association between BP and medial temporal lobe volume (including the hippocampus) in an ageing cohort [11], whereas, the Honolulu ageing project found that both diastolic and systolic midlife hypertension were associated with reduced hippocampal size in late life [12].

BP variability has been implicated as an independent vascular risk factor [13]. Patients with vascular dementia have greater sBP variability (over 24h) than controls [14]. In patients with Alzheimer's disease, greater visit-to-visit sBP variability predicted cognitive decline [15].

Although it is plausible that the relationship between hypertension and brain pathologies is causal, alternative hypotheses exist. Early life socioeconomic circumstance is

related to late-life hippocampal volume and WMH abundance [16, 17]. Furthermore, it has been found that prenatal stress can increase the risk of adult hypertension [18]. Therefore, hypertension and brain deterioration could share a common cause. A further potential factor that could influence these relationships is the use of anti-hypertensive treatments, that could mask hypertension related brain deterioration, or successfully ameliorate their effects.

Here we test the hypothesis that BP components and variability have heterogenous relationships with WMH and hippocampal volume. We analysed the data from Aberdeen Birth Cohort of 1936 for whom extensive life course data are available.

Methods

Participants and sampling

In 2000 we recruited 497 participants of the 1947 Scottish Mental Survey, aged 64 years, into the Aberdeen Birth Cohort of 1936. In 2004, 244 participants entered a brain MRI sub-study. MRI data suitable for inclusion were obtained from 227 (WMH) and 225 (hippocampal volume). The Grampian Research Ethics Committee approved the study and informed written consent was obtained from all participants.

Brain MRI acquisition and analysis

Brain MRI examinations were carried out (1.5T NVi GE system, Milwaukee, Wi) using T2 axial (TR/TE 4900/81.4, slice thickness 5mm, space 1.2mm), fluid attenuation inversion recovery axial (FLAIR) (TR/TE 9002/1.33, TI 2200, slice thickness 5 mm, space 1.2 mm) and 3D T1 weighted (TR/TE 20/6ms, flip angle 35^{o}, slice thickness 1.6mm, matrix 256x192, in-plane resolution 1x1mm) sequences [5]. T2 and FLAIR images were analysed by a neuroradiologist, using Scheltens's scale which assesses brain WMH [19]. Whole brain WMH score was calculated and due to a non-normal distribution was was log transformed for subsequent analyses. The T1W images were processed on a PC running Scientific LINUX (version 5.5). The volumetric segmentation of hippocampus and total intracranial volume (TICV) were performed using FreeSurfer (version 4.5.0) (http://surfer.nmr.mgh.harvard.edu). The sum of hippocampal volumes, corrected for TICV, was used for all subsequent analyses.

BP components

BP was assessed biennially on three occasions (waves 1, 2 and 3: w1, w2, w3) between 2000 and 2004. Measurements were taken, after five minutes seated in a warm quiet room, by a trained nurse using an Omicron BP monitor using an appropriately sized cuff. At each measurement wave sBP and dBP were measured three times and their means recorded. The overall mean of the three waves for sBP and dBP were then calculated. From these mean values, the inter-session coefficients of variability (CV; ratio of standard deviation to mean, expressed as percentage) of sBP and dBP were calculated (sBPvar, dBPvar respectively).

Antihypertensive treatment

At each wave, participants were asked to list all medications. These records were examined for anti-hypertensive (AH) medications. Data were collated and coded as “0”, no AH treatment; and “1”, AH treatment at one or more waves.

Childhood occupational social circumstance

For childhood occupational social circumstance (cOSC), paternal occupational grade at participant age 11 was coded according to the UK's Office of Population Statistics classification: 1, managerial; 2, professional; 3, lesser professional; 4, secretarial; 5, skilled manual; 6, semi-skilled; 7, lesser semi-skilled; 8, unskilled , and 9, lesser unskilled. This gives higher status occupations a lower score [20]. Those with cOSC grades 1-4, and 5-9 were recoded as high (‘2’) and low (‘1’) cOSC respectively. For clarity in interpretation of regression analyses, higher status occupations were assigned the larger code. Dichotomous recoding was performed based on evidence that the influence of cOSC on brain pathology is non-linear, with a step change increase in risk between skilled the manual and secretarial grades [16, 17].

Statistical Analysis

To examine BP component changes over the 3 waves of measurement, repeated measures ANOVA with Tukey’s range post hoc test and a test for linear trend were performed.

Multiple regression was performed with log transformed WMH score and total hippocampal volume, corrected for cranial volume, as dependent variables. Missing values (<5%) were replaced with the sample mean. Linearity was investigated by comparing a linear to a quadratic response in hierarchical regression models for all BP variables, and examining change statistics between linear and quadratic models. There was no significant evidence of non-linear relationships in any model. Exploratory analyses found age at MRI correlated with WMH and hippocampal volume and found gender differences in hippocampal volumes, therefore, these confounding variables were added to all relevant models.

Sources of Funding

This work was supported by Alzheimer's Research Trust (now Alzheimer's Research UK) and the University of Aberdeen Development Trust.

Results

Study population

This sample comprised 227 participants (male 48%, mean age at w1 = 64.5y, SD = 0.81y). dBP and sBP at age 64y did not differ between the study sample and the members of ABC1936 not included.

BP characteristics & anti hypertensives (AH)

101 (45%) of participants reported taking AH medication on at least one study wave. Three wave means (SD) of sBP and dBP were 139.9 (1.52) mmHg and 79.5 (0.93) mmHg respectively. Although no significant differences were found between waves, a significant negative slope for mean dBP was detected. BP variables were significantly elevated in the AH group (Table 1).

Relationships between BP components and WMH

Table 2 shows the relationships between BP and WMH including confounding variables and AH treatment. Age was positively associated with WMH in models 1,3 and 4. In relevant models, increased dBP, but not sBP, predicted greater WMH (Models 1 and 2). sBP and dBP variability were not associated with WMH (Model 2). Model 3 adds cOSC, and finds a trend for higher cOSC to predict reduced WMH. Adding AH treatment in Model 4 finds that AH treatment was significantly, independently, associated with greater WMH, and that higher status cOSC was associated with lower WMH.

Relationship between BP components and hippocampal volume

Table 3 details regression models that examined the relationships between BP components and hippocampal volume. All models demonstrate that higher dBP but lower sBP were associated with reduced hippocampal volume (Models 5-8). Model 6 shows that increased dBPvar was independently associated with reduced hippocampal volume, whereas sBPvar was not.

Model 7 adds the putative hippocampal volume modifying factor cOSC, and did not find a relationship with hippocampal volume. AH treatment was not associated with hippocampal volume (Model 8) in adjusted models.

Discussion

Overview of findings

In this study, we explore the chronic effects of BP components on brain imaging biomarkers of cerebral small vessel disease and Alzheimer's pathology in a normal ageing cohort. We find that increased diastolic BP is significantly associated with increased WMH burden and reduced hippocampal volume. We also find that increased visit-to-visit variability in diastolic BP is independently associated with reduced hippocampal volume.

BP components and brain hyperintensities

We demonstrate that elevated dBP is an independent predictor of greater brain WMH, a marker of small vessel disease. Relatively few studies have examined diastolic versus systolic BP effects on WMH. Aribisala and colleagues found that both systolic and diastolic pressure predicted WMH density [21], whereas prospective studies have found systolic BP to more strongly predict WMH progression [22]. Recent clinical trials in an older cohort (80y) have successfully reduced sBP but without a resultant reduction in WMH accumulation [23], suggesting that WMH progression is insensitive to sBP changes in later life.

Although BP variability has been hypothesised as an independent influence on cardiovascular diseases including stroke, CVD and early death [13], little is known about its relationship with WMH. A prospective study found that increased midlife sBP variability is a risk factor for WMH in late-life [24], others have found WMH progression to be unaffected by BP variability [25]. We found no association between BP variability and WMH, adding to the evidence that BP variability does not promote WMH.

BP components and hippocampal volume

The relationship between BP and dementia, in particular Alzheimer's disease, is not straightforward [7]. Several large-scale prospective studies found that mid-life hypertension increased the risk of future dementia [26] and medial temporal lobe atrophy in later life [12]. Other studies, however, found low systolic BP to be associated with dementia [27].

We find that increased dBP predicts reduced total hippocampal volume, whereas sBP is associated with greater hippocampal volume when other BP components are included. It is interesting to note that the apparent protective effect of sBP on the

hippocampus is only detectable when the negative association between dBP and hippocampal volume is accounted for in the model. This supports the evidence that relationship between BP and brain health is more complex than previously thought. One possible mechanism underlying this finding is that increased dBP is a risk factor or marker of early Alzheimer's pathology in this ageing sample, whereas increased sBP protects hippocampal volume from the deleterious effects of dBP through the maintenance of blood supply [28]. Classifications of older people into binary groups of hypertensives versus non-hypertensives may obscure important markers of brain ageing risk informed by considering independent BP components.

Visit-to-visit BP variability has been proposed as a risk for Alzheimer's disease progression, with visit-to-visit sBP variability associated with cognitive decline in Alzheimer's patients.[15] Furthermore, dBP and sBP variability has been associated with increased risk of incident dementia [29], We found that in our dementia free cohort, diastolic variability is associated with lower hippocampal volume independently of mean BP. This finding suggests that dBP variability may increase risk of Alzheimer's disease, or accelerate the development of pre-existing pathologies.

Whilst we cannot confirm higher dBP and its variability are risk factors for rather than consequences of brain pathology, it is plausible and also more likely that brain damage is caused by BP fluctuations disrupting the microvascular structure of the hippocampus, and other brain tissues [12].

Antihypertensive (AH) medication

We found greater WMH in the AH group was independent of the influence of dBP. It is highly likely AH treatment is an indication of chronic, more severe pre-treatment hypertension, and increased pathology was a consequence of this earlier exposure to hypertension. It is possible, however, that AH treatment may be a direct risk for WMH. Indeed, Hogh et al reported WMH progression associated with AH treatment, but not hypertension itself, in older age [30].

Childhood Occupational Social Circumstances

It is plausible that poor early life socioeconomic circumstances may increase the risk of late life pathology through hypertension. As previously shown, [17] we find an independent association between lower cOSC and increased WMH, possibly an indication of early life

programming of WMH risk in later life. We found no association between cOSC and hippocampal volume, in contrast to our previously finding [16]**.** This previous investigation of cOSC and late life hippocampal volume did not include hypertension as a mediating mechanism. This suggests that cOSC may influence hippocampal atrophy indirectly, through early life programming of late-life blood pressure dysfunction.

Strengths of this Study

We measured BP at three time points over 4 years giving a reliable and robust measurement of chronic BP exposure. The study population is a normal ageing cohort, free from dementia at recruitment, and a relevant study population for investigating hypertension. Uniquely, members of ABC1936 share many of the same life-course factors which can impact on later life and we additionally adjusted for age within this narrow age range sample. Furthermore, we accounted for other variables hypothesised to influence brain ageing. The use of MRI for the quantification of brain pathology allows sensitive and validated measures of hippocampal volume and WMH [2].

Limitations

Although causal relationships cannot be assumed, it is unlikely brain pathologies would determine BP in a dementia-free sample. This study did not correct for all potential cardiovascular risk factors for brain pathology, and therefore it is not known if these elements interact or modify the BP and brain pathology findings presented here. The use of the Scheltens's WMH visual rating scale can be criticised for vulnerability to inter-rater variability and ceiling effects, however it has been well validated and compares well with automated methods. The healthy volunteer effect causes ABC1936 to be relatively advantaged compared to the general population. This selection bias would be likely to underestimate the strength of these findings in the general population.

Conclusions

Our findings provide insight into the complex and differing relationships between BP components and brain pathology, and may explain the heterogeneous relationships between BP and cognition reported in previous studies. Treating systolic hypertension may have the consequence of accelerating hippocampal atrophy, whereas treating diastolic hypertension, and reducing its long–term variability could ameliorate hippocampal atrophy and cerebrovascular disease, both risk factors for dementia: Given this potential dual action,

targeting diastolic hypertension should be a primary goal for reducing neurodegeneration in older age.

Acknowledgements

We gratefully acknowledge the contribution of participants of the Aberdeen 1936 Birth cohort who have willingly given their time to participate.

Conflicts of Interest

None.

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Table 1. BP, BP components and brain MRI pathology biomarkers in participants with and without anti-hypertensive medication. Sample includes 119 men and 108 women of Aberdeen Birth Cohort 1936 aged 64y.

	Prescribed Anti-Hypertensive Medication						
	No			Yes			t-test
	Mean	SEM	N	Mean	SEM	N	p-value
sBP (mmHg)	136.8	1.3	124	143.7	1.6	99	0.001
dBP (mmHg)	78.3	0.7	124	81.1	0.7	99	0.005
sBPvar (%)	5.7	0.3	124	8.2	0.5	99	<0.001
dBPvar (%)	6.0	0.3	124	7.1	0.4	99	0.033
WMH	14.7	0.8	126	18.5	1.0	101	0.004
Total Hippo (%)	0.55	0.01	124	0.53	0.00	101	0.037

sBP, systolic blood pressure; dBP, diastolic blood pressure; sBPvar, systolic blood pressure variability; dBPvar, diastolic blood pressure variability; WMH, white matter hyperintensities; Total Hippo (%), total hippocampal volume as a proportion of intracranial volume; SEM, standard error of the mean.

Table 2: Results of regression models examining the effect of blood pressure and related variables on total WMH score (N=227).

Model 1 (BP)			Model 2 (+variability)			Model 3 (+risk factors)			Model 4 (+AH)		
Variable	Statistic		Variable	Statistic		Variable	Statistic		Variable	Statistic	
	Std Beta	p-value		Std Beta	p-value		Std Beta	p-value		Std Beta	p-value
Age	0.13	0.048	Age	0.13	0.053	Age	0.13	0.043	Age	0.13	0.049
dBP	0.21	0.036	dBP	0.19	0.046	dBP	0.17	0.012	dBP	0.13	0.044
sBP	-0.04	0.747	sBP	-0.03	0.772	cOSC	-0.12	0.070	cOSC	-0.13	0.048
			dBPvar	-0.04	0.645				AH	0.17	0.011
			sBPvar	0.05	0.494						
R2	0.050			0.052			0.063			0.90	
Adjusted R2	0.037			0.030			0.051			0.074	

Missing values (<5% of total n) are replaced with sample mean. sBP, systolic blood pressure; dBP, diastolic blood pressure; sBPvar, systolic blood pressure variability; dBPvar, diastolic blood pressure variability; WMH, white matter hyperintensities. AH, use of antihypertensive medication; cOSC, childhood occupational social class.

Table 3: Results of regression models examining the relationship between BP and hippocampal volume (N=227)

Model 5 (BP)			Model 6 (+variability)			Model 7 (+risk factors)			Model 8 (+AH)		
Variable	Statistic		Variable	Statistic		Variable	Statistic		Variable	Statistic	
	Std Beta	p-value		Std Beta	p-value		Std Beta	p-value		Std Beta	p-value
Gender	0.40	<0.001	Gender	0.38	<0.001	Gender	0.39	<0.001	Gender	0.38	<0.001
Age	-0.07	0.261	Age	-0.09	0.138	Age	-0.09	0.133	Age	-0.09	0.152
dBP	-0.19	0.029	dBP	-0.25	0.006	dBP	-0.24	0.007	dBP	-0.25	0.007
sBP	0.17	0.046	sBP	0.22	0.013	sBP	0.22	0.013	sBP	0.24	0.009
			dBPvar	-0.15	0.033	dBPvar	-0.17	0.008	dBPvar	-0.16	0.014
			sBPvar	-0.04	0.600	cOSC	0.05	0.395	AH	-0.09	0.163
R^2	0.199			0.226			0.227			0.232	
Adjusted R^2	0.184			0.205			0.206			0.211	

Missing values (<5% of total n) are replaced with sample mean. sBP, systolic blood pressure; dBP, diastolic blood pressure; sBPvar, systolic blood pressure variability; dBPvar, diastolic blood pressure variability; AH, use of antihypertensive medication; cOSC, childhood occupational social class.