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Title:

Cerebrovascular reactivity and dynamic autoregulation in ischaemic subcortical white matter disease

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Abstract

Background:

It has been suggested that impaired cerebral autoregulation and vasodilatory capacity may play a role in the pathogenesis of the leukoaraiosis seen in small vessel disease. Adequate perfusion of the deep white matter of the brain depends on the relationships between blood pressure (BP), cerebral vasoreactivity and autoregulation.

Methods:

24-hour ambulatory BP measurement, quantitative volumetric MRI analysis of white matter lesion (WML) volume and transcranial Doppler ultrasound assessments of CO₂ reactivity in response to hypercapnia and dynamic cerebral autoregulatory index (ARI) were undertaken in 64 patients with cerebral small vessel disease.

Results:

Subjects had mean 24-hour BP 133/76 mmHg (SD 13/9), median WML volume 7169 (IQR 20497) mm³, mean CO₂ reactivity 83.6 (SD 37.4) % and mean ARI 5.6 (SD 1.4) (range 0-9). In multivariate models, after adjusting for age, gender, vascular risk profile and WML volume, ARI correlated with 24-hour mean BP levels (R^2 : 0.127, t : 2.440, $p=0.019$) and CO₂ reactivity correlated with duration of hypertension (R^2 : 0.085, t : -2.244, $p=0.029$). In individuals with hypertension for more than 10 years, ARI also correlated with nocturnal BP dipping ($r=0.806$, $p=0.002$). ARI and CO₂

reactivity were unaffected by WML volumes and ARI and CO₂ reactivity were unrelated.

Conclusion:

Cerebral autoregulation and CO₂ reactivity are two distinct processes which are not related to WML volume but are related to BP levels and duration of hypertension respectively. Greater nocturnal dipping was associated with higher ARI values, suggesting preservation of autoregulation in patients with increased vulnerability to reduced cerebral perfusion.

Introduction

With the current emphasis on lowering BP to slow down progression of cerebrovascular disease,¹ a better understanding of cerebral vasoreactivity and autoregulation in patients with small vessel disease becomes very important. Whilst studies initially suggested that cerebral vasoreactivity was impaired in patients with small vessel disease,²⁻⁴ investigations that have excluded individuals with carotid artery stenoses or acute ischaemic events, that may have acted as confounding variables, have provided conflicting results.⁵⁻⁹ Limited evidence also exists on the relationships between small vessel disease and cerebral autoregulation. Cerebral autoregulation has been shown to be impaired in individuals with extensive leukoaraiosis on brain imaging,¹⁰⁻¹² but there is a lack of data on the integrity of cerebral autoregulation in patients with small vessel disease and no concomitant large vessel disease.

Recent studies have emphasised the importance of physiological variations in BP in the prediction of cerebral blood flow (CBF) and cerebrovascular disease, particularly with reference to nocturnal BP fall.¹³⁻¹⁴ The integrity of cerebral vasoreactivity and autoregulation is crucial to maintaining a constant CBF in the face of such BP fluctuations. Cerebral autoregulation can be static i.e. adjustments in response to prolonged BP changes or dynamic i.e. ability to maintain CBF in the face of BP changes occurring over a matter of seconds. Dynamic cerebral autoregulation is more vulnerable to impairment because of the complex neural, metabolic, myogenic and possible endothelium-related mechanisms involved.^{6, 15} The objective of this study was to assess vasoreactivity, vascular reserve and dynamic cerebral autoregulation in

response to physiological variations in BP in patients with early evidence of cerebral small vessel disease using ambulatory 24-hour BP measurement, quantitative volumetric MRI analysis of cerebral small vessel disease and transcranial Doppler ultrasound (TCD) assessments of CO₂ reactivity and dynamic cerebral autoregulation.

Methods

Subjects

The study was undertaken in 64 subjects over the age of 50 years with evidence of small vessel (lacunar infarction, leukoaraiosis) but not large vessel cerebrovascular disease on MR neuroimaging. Subjects were recruited prospectively (January 2003 – June 2005) from a hypertension clinic in a teaching hospital where all patients underwent MR brain imaging as an investigation of target organ damage. All patients were on antihypertensive treatment at the time of the study. Participants were included in the study if they fulfilled the following criteria: (1) treated BP in the normotensive range (because of the known associations between impaired cerebral autoregulation and high or low BP); (2) no clinical history of a cerebrovascular disturbance (such as stroke, TIA or syncope) in the previous 3 months which may affect the integrity of cerebral autoregulation; (3) no clinical history of intermittent claudication or other symptoms of peripheral vascular disease (precluding autoregulatory assessments using thigh cuff inflation/deflation); (4) no cerebral large artery stenosis (>50%); (5) no intracranial pathology other than cerebral small vessel disease on brain imaging; (6) no contraindication to MRI such as prosthetic heart valves, pacemakers, cochlear implants or claustrophobia.

A detailed history was taken and a physical examination was performed in all individuals. Data were collected on demography, anthropometry and education, vascular risk profile including hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking and alcohol consumption. Hypertension was further characterised by its duration since diagnosis and drug treatment. Duplex ultrasound studies were performed to rule out significant (>50%) carotid artery stenosis or abnormal blood flows in the carotid, vertebral or intracranial large arteries. The study was approved by King's College Hospital Ethics Committee and all patients provided informed consent.

Assessment of 24-hour ambulatory BP and cerebral small vessel disease lesion load

Non-invasive 24-hour ambulatory BP measurements (Tracker NIBP2, Reynolds Medical Limited, UK) were obtained on weekdays, with measurements being taken every 30 minutes during the day and every 60 minutes at night. Ambulatory BP monitor recordings were deemed to be insufficient if less than 70% of readings were successful.¹⁶ Day-time episodes were defined from 08:00 – 22:59 and night-time episodes from 23:00 – 07:59. CardioNavigator software (Reynolds Medical Limited, UK) was used to evaluate 24-hour, daytime and night-time systolic, diastolic and mean BP levels and pulse pressures. Nocturnal dipping of BP was calculated as described previously, where nocturnal dip rate = ((mean day BP - mean night BP)/mean day BP).¹⁷

Using a 1.0 T Siemens Magnetom Expert MR Scanner, whole brain axial fluid attenuated inversion recovery (FLAIR) and turbo spin-echo axial T2-weighted images were acquired to allow detailed visualisation of white matter disease. Images were transferred to a Centricity PACS workstation and WML volumes were calculated using a manual tracing technique as described previously.¹⁸ Intra-rater variability of WML volume measurements was assessed on 2 separate occasions in 10 subjects and the intra-class correlation coefficient was 0.99 (95% CI: 0.95-1.0).

TCD assessments

Instrumentation

Subjects were in a supine position with their heads slightly elevated. TCD was used to measure the changes in middle cerebral artery velocity (MCAV) in response to changes in BP and inspired CO₂. MCAV was recorded bilaterally simultaneously via the transtemporal window using 2 MHz transducers (DWL, Langerach). Continuous BP recording was made via a servo-controlled finger plethysmograph (Finapres 2300, Ohmeda), with the subject's hand maintained at the same level as the head. Finapres measurements were initially corroborated by standard measurements of BP with an automated arm cuff (Omega 1400 series, In Vivo Laboratories Inc). End-tidal CO₂ was measured with an automated capnograph (Normacap 200, Datex Instrumentation).

Assessment of dynamic cerebral autoregulation

In order to assess dynamic cerebral autoregulation, a sudden stepwise drop in BP was induced by rapid deflation of bilateral thigh cuffs that had been inflated suprasystolically for 3 minutes. Autoregulatory responses were analysed off-line using the time-averaged mean velocities of the maximum velocity outlines of the Doppler spectrum and mean BP. Dynamic autoregulation was assessed as previously described using the software program supplied by the TCD manufacturers which compares the rate of return of BP and MCAV to baseline following the drop in BP.^{15, 19} Starting at the moment of cuff release and based on the actual BP curve of the 30 seconds that followed, a series of 10 hypothetical MCAV autoregulatory curves were calculated that model between a passive MCAV and BP relationship (an autoregulatory index (ARI) of 0) and rapid rates of rise in MCAV with increased ARI (maximum ARI: 9; normal range: 5-9) (Figure 1). Full details of the equations used have been published previously.¹⁵ Five cycles of inflation/deflation were performed per subject with a 3-minute rest interval between cycles. A mean ARI was calculated for each subject only from runs in which a sufficient magnitude of BP fall (>10 mm Hg) was attained. End-tidal CO₂ was recorded during and between repeated assessments of ARI. .

Assessment of CO₂ reactivity

CO₂ was administered as 8% CO₂ in air from a Douglas bag reservoir through a mask with inspiratory and expiratory limbs protected by one-way valves. End-tidal CO₂ was monitored by continuous sampling from the expiratory limb using the automated capnograph. CO₂ was administered until MCAV recordings had plateaued. CO₂ reactivity was calculated off-line as the percentage increase in MCAV during 8% CO₂ inspiration, compared with baseline MCAV while breathing room air.^{5,7} Assessments

of CO₂ reactivity and autoregulation were performed on the same day but autoregulation was always evaluated first to avoid lasting effects of CO₂ on the cerebral circulation. All reactivity and autoregulation traces were analysed by an experienced researcher blinded to patient identity and traces of poor quality were excluded prior to data analysis.

Reproducibility study

Ten subjects consented to assessment of ARI and eight subjects consented to assessment of CO₂ reactivity at the same time and in the same environment on two consecutive days in order to assess reproducibility. The subjects were representative of the patients studied. The repeatability coefficient, which is equal to twice the SD of the differences between the pairs of measurements,²⁰ was 2.4 for ARI assessment and 35.4% for CO₂ reactivity assessment.

Statistical analysis

Data were tested for normality using the Kolmogorov-Smirnov test. Categorical data were compared using Chi-squared tests. Pearson's correlation coefficient (r) was used to examine correlations between normally distributed variables and logarithmic transformation of non-parametric data. Linear regression models with stepwise deletion were undertaken to examine the independent predictors of ARI and CO₂ reactivity after adjusting for covariation in baseline characteristics of age, gender, vascular risk factor profile including BP level and duration of hypertension, and

WML load and for variables significant at $p < 0.1$ on univariate analyses. All evaluations used SPSS statistical analysis software (version 13).

Results

Patient characteristics including 24-hour BP and WML volume measurements are shown in Table 1. Of the 64 patients, 45 were on diuretics, 25 were on calcium channel antagonists, 33 were on ACE-inhibitors, 15 were on angiotensin II receptor antagonists and 20 were on alpha-adrenoceptor antagonists. 8 individuals (13%) had a history of diabetes mellitus (mean (SD) duration: 7.5 (7.8) years), of whom 3 were insulin-dependent and 5 were taking oral hypoglycaemic therapy. 25 patients had evidence of nocturnal BP dipping (nocturnal reduction of BP by $>10\%$ of daytime BP),¹⁹ with a mean (SD) BP dip of 15.7 (5.4) mm Hg.

The MCAV was insonated at a mean (SD) depth of 51.6 (5.4) mm. Mean (SD) MCAV was 56.8 (16.5) cm/s. Measurement of ARI was possible in 45 of the 64 patients. 10 individuals were unable to tolerate thigh cuff inflation/deflation, a stepped BP reduction >10 mm Hg with thigh cuff deflation could not be induced in 1 individual and in another 8 individuals, undulations in the continuous BP and/or MCAV recording traces precluded evaluation of ARI. There was no significant change in resting CO_2 during or between repeated assessments of dynamic cerebral autoregulation. Mean (SD) ARI was 5.6 (1.4). In univariate analyses, ARI correlated significantly with 24-hour systolic BP ($r=0.327$, $p=0.030$) and 24-hour mean BP ($r=0.350$, $p=0.020$) (Figure 2) but not with diastolic BP or WML volume. In those individuals with a history of hypertension for more than 10 years, ARI also correlated

significantly with nocturnal BP dipping ($r=0.806$, $p=0.002$) (Figure 3). Regression analyses showed 24-hour mean BP to be an independent determinant of ARI (R^2 : 0.127, coefficient 0.060 (95% CI: 0.010 to 0.109), t : 2.440, $p=0.019$).

CO₂ reactivity was assessed in 57 patients. 3 individuals were unable to tolerate CO₂ inhalation and in another 4 individuals, undulations in the continuous BP and/or MCAV recording traces precluded assessment of CO₂ reactivity. CO₂ reactivity was not affected by patients' BP levels or WML volume but correlated negatively with duration of hypertension ($r=-0.292$, $p=0.027$) (Figure 4). Duration of hypertension remained an independent predictor of CO₂ reactivity in regression analyses (R^2 : 0.085, coefficient -0.974 (95% CI: -1.845 to -0.104), t : -2.244 , $p=0.029$). No significant relationships existed between ARI and CO₂ reactivity and results were not affected by the class of antihypertensive treatment.

Discussion

This study in hypertensive patients with WML on MRI as a manifestation of cerebral small vessel disease showed that autoregulatory capacity was determined by BP levels and correlated with nocturnal BP dipping in individuals with longstanding hypertension. CO₂ reactivity was not affected by patients' BP levels but was dependent on duration of hypertension. Neither ARI nor CO₂ reactivity were significant determinants of WML volume.

Whilst cerebral autoregulation has previously been suggested to be impaired in patients with small vessel disease,¹⁰⁻¹² the mean \pm SD ARI in this study population

was 5.6 ± 1.4 (normal range: 5-9)¹⁵ suggesting that ARI is preserved in patients with early cerebral small vessel disease. This study differed from previous investigations in terms of excluding patients with large-vessel cerebrovascular disease and/or recent stroke that may have acted as confounding variables.^{6, 21} Whilst ARI was unrelated to small vessel disease lesion load, ARI was associated with BP levels consistent with studies in normal volunteers.²²⁻²³ ARI increased with elevated 24-hour mean BP levels and also with nocturnal BP dipping in individuals with longstanding hypertension. The former relationship may be explained by ARI improving by increased vascular tone; acute elevation of BP with agents such as noradrenaline is associated with increased ARI.²³ The latter relationship suggests that ARI is preserved even in longstanding hypertensives with cerebral small vessel disease. Recent studies have suggested that the threshold of BP needed to maintain CBF may shift to a higher level in elderly hypertensive individuals with small vessel disease and that physiological episodes of low BP may provoke ischaemic injury.²⁴ Preservation of autoregulatory function in small vessel disease patients at greatest risk of reduced CBF may be a protective response analogous to the increase in oxygen extraction fraction seen in such patients.²⁵

The linear relationship demonstrated between impaired CO₂ reactivity and duration of hypertension has been suggested previously in animal studies.²⁶ It has been proposed that an increased duration of exposure to systemic hypertension accelerates arteriosclerotic changes in the cerebral vasculature predisposing to increasing vessel wall rigidity and impaired cerebrovascular vasodilatory capacity. CO₂ reactivity was unrelated to WML volume and this is consistent with previous studies that similarly excluded patients with concomitant large vessel disease or recent stroke.⁸⁻⁹

The findings of this study support the view that impaired cerebral autoregulation and limited vasodilatory capacity are not pathogenetic hallmarks of leukoaraiosis.²⁷ In addition, they support the concept that the cerebrovascular responsiveness to CO₂ operates independently from cerebral autoregulation. In hypertensive subjects, cerebral autoregulation appears to be determined by the level of BP and is preserved in long-standing hypertensives, whereas responsiveness to CO₂ is influenced by the duration of hypertension. Literature supports the concept of the two processes being distinct, having separate effector mechanisms, and interacting in a complex way.^{21,28,29} Although the physiology responsible for controlling CBF autoregulation and vasoreactivity is not fully understood,²⁷ dynamic cerebral autoregulation has been suggested to be a more sensitive measure of haemodynamic impairment than CO₂ reactivity.²¹

In contrast to studies undertaken in untreated hypertensives or in patients whose antihypertensive treatment was discontinued, this study allowed patients to remain on pre-existing antihypertensive medications. This ensured the study population to be representative of the “norm”, facilitating generalisability to the general population and it prevented participants having poorly controlled hypertension (clinic BP>160/100 mmHg) that could act as a confounding influence. However, antihypertensive medications taken by patients may have exerted effects on the cerebral vasculature³⁰ and the duration of undetected hypertension and effectiveness of previous BP control remain unquantifiable variables.

The findings of this study are limited by the relatively small sample size, its cross-sectional nature and the lack of a control group for comparison. This makes it possible that more subtle disturbances in haemodynamics or non-linear relations with small effect size in subjects with WML may have been missed. In addition, causal inferences should be made with caution, particularly with reference to the relationships between nocturnal BP falls and autoregulation, where both may be interlinked via other factors. Indeed, controversy exists in the literature with regard to prolonged and/or marked nocturnal dipping being physiological or abnormal, beneficial or harmful, and representing the cause or effect of end-organ damage.^{14,17,31}

The high temporal resolution of TCD has made it the recognised method for estimating changes in CBF velocity in studies of cerebral autoregulation and vasoreactivity.^{4,32,33} Middle cerebral artery (MCA) blood flow velocity rather than blood flow has been used to determine cerebral haemodynamics. This is based on observations that changes in MCAV induced by BP drops during surgery correlate very closely with changes in internal carotid artery flow¹⁹ and that there is little change in MCA diameter during CO₂ inhalation,³⁴ suggesting that any change in MCAV measured by TCD is directly proportional to the change in flow. As TCD assessments measure the entire MCA territory and more blood flow goes to the grey matter than to the white matter, it is likely that TCD assessments reflect cortical more than the subcortical blood flow change.³⁵ Although this is a potential limitation, it is likely that the pathology of small vessel disease is diffuse and TCD measurements provide a simple, non-invasive method for assessing cerebral autoregulation and vasoreactivity in these patients.

The Finapres continuous BP recording used provided a reliable assessment of rapid changes in BP, but its accuracy for absolute measurement is affected by baseline shifts and unpredictable offsets.²¹ For the purposes of the autoregulation model, absolute measures of BP were not required but a lack of such values during assessment of CO₂ reactivity did not demonstrate if CO₂ inhalation produced a significant increase in BP that may have affected cerebrovascular reactivity.³⁶ CO₂ inhalation was not tolerated by all patients and the thigh cuff technique was associated with pain on cuff inflation/deflation and difficulties in inducing significant BP drops with cuff deflation. The thigh cuff technique also could not be undertaken in subjects with peripheral vascular disease and it has been suggested that the technique may produce sympathetic activation.³⁷ Although the thigh cuff method has been the most common approach for assessment of dynamic cerebral autoregulation, a number of other dynamic pressor or depressor stimuli exist but all have methodological limitations.³³ Computerised coherent averaging of the CBF velocity response to spontaneous BP transients has also been developed, allowing calculation of ARI from spontaneous BP oscillations, but this was not available.³⁸

In conclusion, this study demonstrated that cerebral autoregulation and CO₂ reactivity appear to be two distinct processes that are not related to WML volume but are related to BP levels and duration of hypertension respectively. Greater nocturnal dipping was associated with higher ARI values in long-standing hypertensives with cerebral small vessel disease, suggesting preservation of autoregulation in patients with increased vulnerability to reduced cerebral perfusion. These findings suggest a complex interaction between BP, cerebral haemodynamics and chronic ischaemic injury to the

brain that merits further investigation in the context of the increasing importance of cerebral small vessel disease and dementia in recent years.³⁹

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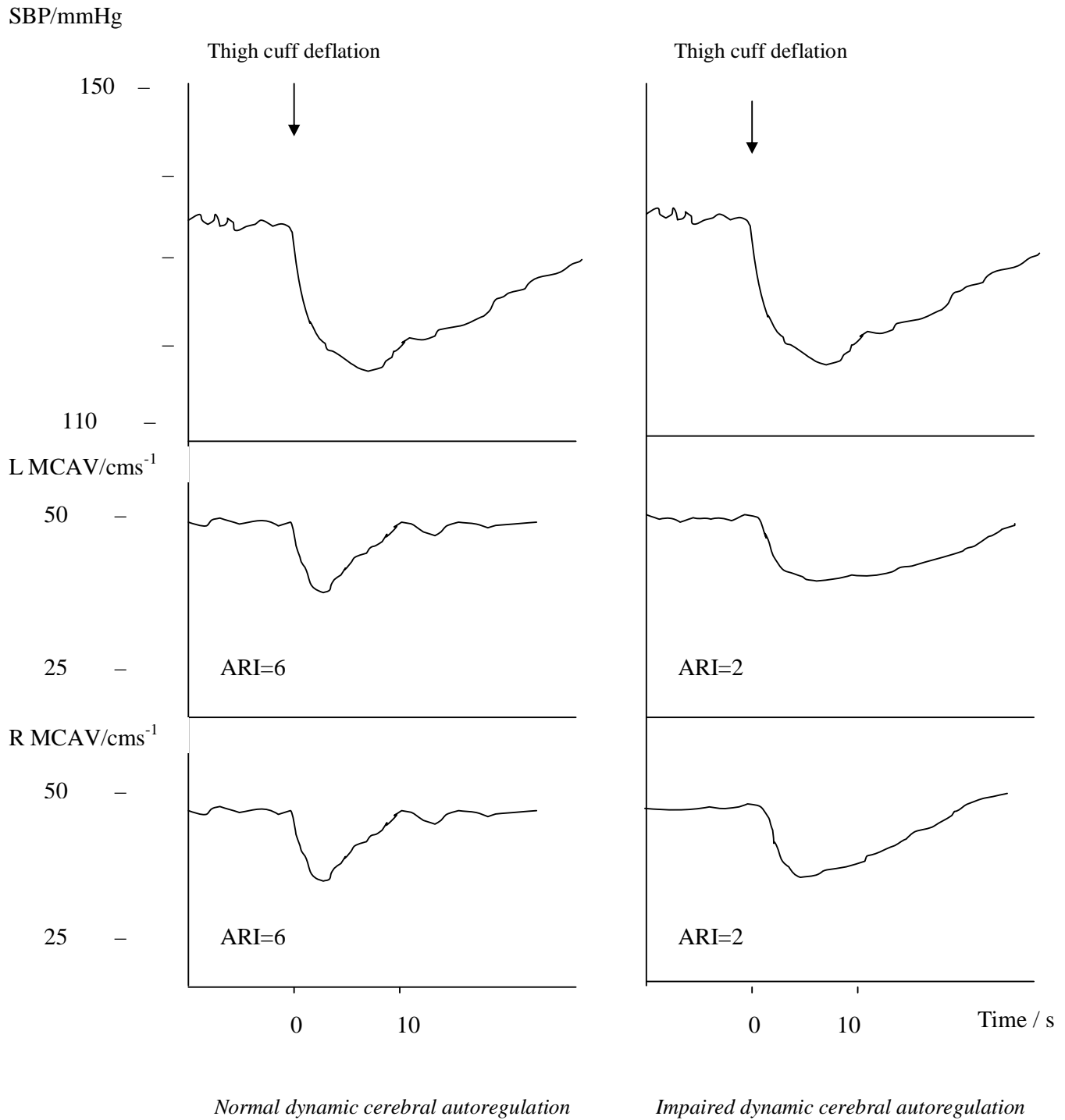
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Table 1: Patient characteristics including 24-hour BP and WML volume measurements

Mean (SD) age (years)	63.7 (9.0)
% Male	64
Mean (SD) duration of known hypertension (years)	8.5 (10.8)
Mean (SD) HbA1c (%)	6.0 (1.2)
Mean (SD) serum cholesterol (mmol/l)	4.9 (0.9)
% Current cigarette smokers	16
% Ex-cigarette smokers	47
Mean (SD) alcohol use (units/week)	8.6 (16.3)
Mean (SD) 24-hour SBP (mmHg)	133.0 (12.9)
Mean (SD) 24-hour DBP (mm Hg)	76.1(9.0)
Mean (SD) 24-hour mean BP (mm Hg)	93.6 (8.9)
Mean (SD) 24-hour pulse pressure (mm Hg)	56.9 (9.6)
Mean (SD) day SBP (mmHg)	135.8 (13.0)
Mean (SD) day DBP (mm Hg)	78.4 (9.4)
Mean (SD) day mean BP (mm Hg)	96.0 (9.4)
Mean (SD) day pulse pressure (mm Hg)	57.4 (10.0)
Mean (SD) night SBP (mmHg)	127.4 (15.5)
Mean (SD) night DBP (mm Hg)	71.4 (10.4)
Mean (SD) night mean BP (mm Hg)	88.2 (10.5)
Mean (SD) night pulse pressure (mm Hg)	56.0 (10.0)
Median (IQR) Total WML volume (mm ³)	7169.4 (20497.0)

SBP = systolic BP; DBP = diastolic BP

Figure 1: Assessment of dynamic cerebral autoregulation



SBP = systolic blood pressure/mmHg; ARI = index of dynamic cerebral autoregulation; L MCAV and R MCAV = left and right middle cerebral artery velocities respectively/cms⁻¹
Adapted from Tiecks FP, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. Stroke. 1995; 26: 1014-9

Figure 2: Relationship between 24-hour mean BP and ARI

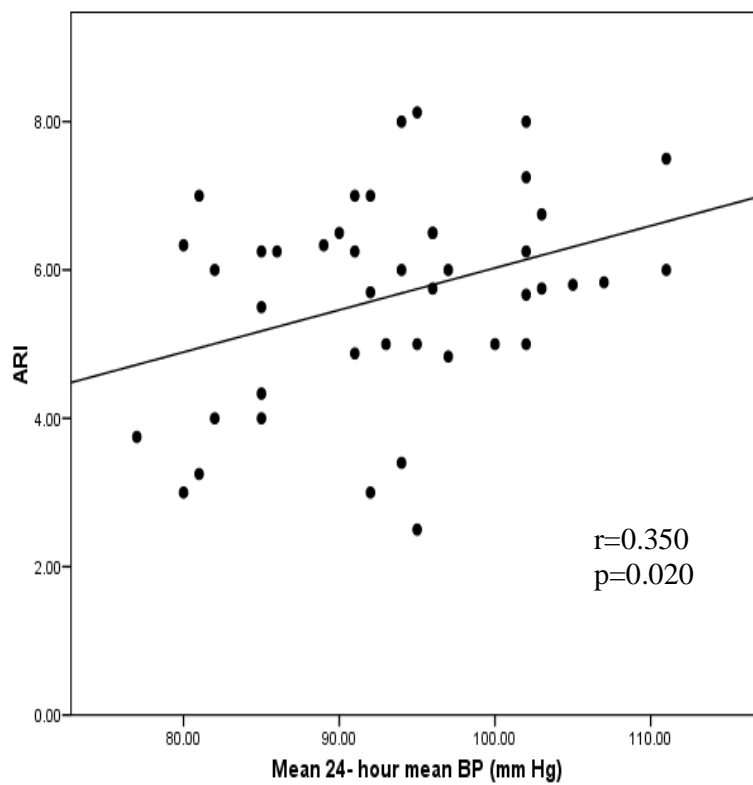


Figure 3: Relationship between nocturnal BP dipping and ARI
in individuals with a history of hypertension for more than 10 years

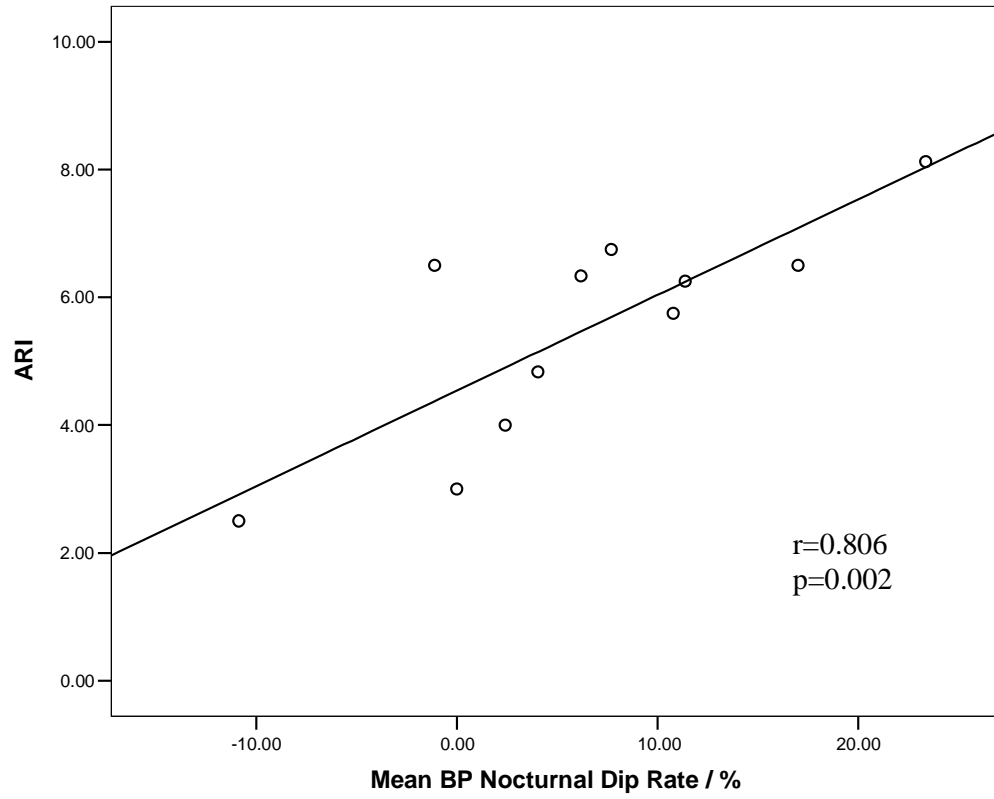


Figure 4: Relationship between duration of hypertension and CO₂ reactivity

