Blood pressure variability and leukoaraiosis in acute ischaemic stroke

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David Alexander Dickie, PhD[a,b,c] and Benjamin Aribisala, PhD[a,b,c] performed the analysis and wrote the manuscript. Grant Mair, MB ChB[a,b,c] supported the analysis and edited the manuscript.

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Abstract

Higher blood pressure (BP), BP variability and leukoaraiosis are risk factors for early adverse events and poor functional outcome after ischaemic stroke, but prior studies differed on whether leukoaraiosis was associated with BP variability, including in ischaemic stroke.

In the Third International Stroke Trial, BP was measured in the acute phase of ischaemic stroke immediately prior to randomization, and at 0.5, 1 hour and 24 hours after randomization. Masked neuroradiologists rated index infarct, leukoaraiosis and atrophy on CT using validated methods. We characterised BP variation by coefficient of variance (CV) and three other standard methods. We measured associations between BP, BP variability and leukoaraiosis using generalized estimating equations, adjusting for age, and a number of covariates related to treatment and stroke type/severity.

Amongst 3017 patients, mean (±SD) systolic and diastolic BP decreased from 155(±24)/82(±15)mmHg pre-randomization to 146(±23)/78(±14)mmHg 24 hours later (P<0.005). Mean within-subject CV was 0.09±0.05 for systolic and 0.11±0.06 for diastolic BP. Patients with most leukoaraiosis were older and had higher BP than those with least (P<0.0001). Although statistically significant in simple pairwise comparisons, no measures of BP variability were associated with leukoaraiosis when adjusting for confounding variables (P>0.05), e.g., age.

Our results suggest that BP variability is not a potential mechanism to explain the association between leukoaraiosis and poor outcome after acute stroke.

Introduction

Higher blood pressure (BP) level and BP variability are risk factors for early adverse events and later poor functional outcome after stroke(1, 2). Higher long-term BP has consistently been associated cross-sectionally with a higher burden of leukoaraiosis, which is itself a major risk factor for stroke, dementia, and death(3-8); and independently predicts poor outcome after stroke(9). However, there are conflicting reports on the association between higher long-term BP variability and the burden of leukoaraiosis(6, 7, 10, 11) and short-term BP variability and leukoaraiosis(10, 12, 13). This discord among a relatively small number of studies, mostly with N<250 and only one with greater than 500 participants, is in contrast to the often studied and well characterized associations between higher absolute BP and more leukoaraiosis(14).

The sample sizes in these studies were often relatively small (N<500)(10, 12, 13) and/or were in community-dwelling participants(6, 11), or during long-term follow-up after stroke(7), which might contribute to differing results. We found no previous investigations of the associations between pre-existing leukoaraiosis and variability in BP during the acute phase of stroke. Yet the acute phase of stroke is a time when BP is likely to be highly variable(15, 16).

We previously studied the effect of BP variability(1) and of leukoaraiosis(9) on outcome after ischaemic stroke. Given the independent negative prognostic impacts that we found in these previous studies, we aimed to clarify the relationship between BP variability and leukoaraiosis in the acute phase of ischaemic stroke using data from a large randomized trial, the Third International Stroke Trial (IST-3)(9, 17-19).

Methods

Participants

IST-3 was conducted with 3035 participants recruited from 156 centres in 12 countries(19). All participating centres had a national co-ordinator and local ethics approval. The trial, registered at ISRCTN.com, number ISRCTN25765518, was run according to the local procedures and law of each centre(18). All patients or an assigned patient relative/representative (where patients did not have capacity) gave informed consent. Full details of trial procedures, including imaging assessments, patient characteristics and the main trial results, have been published(9, 17-19).

BP measurement

BP was recorded by trained personnel for trial purposes at five time points: pre-randomization, start of treatment (or immediately after randomization for control patients), and at 30 minutes, 60 minutes, and 24 hours after treatment. We recorded whether BP was treated prior to admission in the trial, within the first 24 hours, and/or between 24 hours and seven days after randomization.

BP variability

We assessed variability in BP via measures of systolic, diastolic, pulse, and mean arterial pressure taken pre-randomization, at the start of treatment, and 30 minutes, 60 minutes, and 24 hours after treatment.

We calculated mean arterial pressure (MAP) via equation 1:

$$\mathrm{MAP}=\mathrm{DBP}+\frac{\mathrm{SBP}-\mathrm{DBP}}{3} \quad (1)$$

According to previous studies(6, 7, 13), we used standard deviation, coefficient of variance (CV), average real variability, and successive variation to quantify variance in each measure of BP.

Average real variability (ARV) was computed for all four measures of BP via equation 2:

$$ARV=\frac{|BP_{start}-BP_{rand}|+|BP_{30m}-BP_{start}|+|BP_{60m}-BP_{30m}|+|BP_{24h}-BP_{60m}|}{4} \quad (2)$$

Successive variability (SV) was computed for all four measures of BP via equation 3:

$$SV=\frac{(BP_{start}-BP_{rand})^2+(BP_{30m}-BP_{start})^2+(BP_{60m}-BP_{30m})^2+(BP_{24h}-BP_{60m})^2}{4} \quad (3)$$

Pre-existing brain damage

Leukoaraiosis, including anterior and posterior (each scored 0-2), burden and whole brain atrophy, were rated by trained neuroradiologists on computed tomography (CT) masked to all clinical details using previously validated procedures(9, 20, 21). Anterior and posterior leukoaraiosis scores were summed to compute a total leukoaraiosis score (on a continuum of 0 to 4; with 4 being the greatest leukoaraiosis burden). Whole brain atrophy was scored for central and cortical structures as none, moderate, or severe, then dichotomised into a single variable as either absent (0) or present in one or both regions (1).

Statistical analyses

All statistical analyses were performed in the Statistical Analysis System (SAS) version 9.4 (© 2002-2012 SAS Institute Inc.). We used longitudinal multiple regression (generalized estimating equations) to model absolute BP (separate models for systolic, diastolic, pulse, and mean arterial pressure) over time according to leukoaraiosis burden and adjusted for age, atrophy, NIHSS, stroke subtype, time to randomization, treatment allocation, and BP lowering treatment before the trial, during the first 24 hours, and between 24 hours and seven days. This analysis is summarised in equation 4:

$$BP=\beta\_Time+\beta\_Age+\beta\_Leukoaraiosis+\beta\_Atrophy+\beta\_NIHSS+\beta\_StrokeSubtype+\beta\_TimeRand+\beta\_TreatmeentAlloc+\beta\_BPlowPrior+\beta\_BPlowDay1+\beta\_BPlowDay2\text{-}7+error \quad (4)$$

We also used generalized estimating equations to measure associations between leukoaraiosis and BP variability with the same adjustment variables. This analysis is summarised in equation 5:

$$Leukoaraiosis=\beta\_DBPV+\beta\_SBPV+\beta\_PPV+\beta\_MAPV+\beta\_Age+\beta\_NIHSS+\beta\_Atrophy+\beta\_StrokeSubtype+\beta\_TimeRand+\beta\_TreatmeentAlloc+\beta\_BPlowPrior+\beta\_BPlowDay1+\beta\_BPlowDay2\text{-}7+error \quad (5)$$

We defined leukoaraiosis as the dependent variable in equation 5 as this allowed all measures of BP (systolic, diastolic, pulse, and mean) to be assessed in one model (rather than four separate models where each measure of variability was the dependent variable). We assessed collinearity using variance inflation factor and stepwise removal of potentially volatile variables. The generalized estimating equations used here are parametric (mean-based) and although leukoaraiosis often has highly skewed distributions, we found this to have a nominal effect on mean-based regression results(14). We used an exchangeable correlation matrix in our generalized estimating equations because repeated BP measures were correlated but not autoregressive. We assessed overfitting by comparing raw and adjusted R-squared. These models were designed to assess the influence of several variables known to have adverse prognostic effects in acute stroke (e.g., atrophy and stroke severity)(9) and whether their effects were attenuated/mediated in fully adjusted models. We determined the influence of adjustment variables by firstly modelling pairwise associations (unadjusted models) between BP variability and leukoaraiosis.

Results

Patient characteristics

Full characteristics of the N=3035 patients, including treatment for hypertension prior to trial admission, stroke subtypes, atrophy and leukoaraiosis CT findings, are provided in supplement; 18 patients did not have CT scans so did not contribute leukoaraiosis or atrophy scores in this analysis. Mean age was 77.3±12.2 years with median NIHSS 11 (IQR=11), and TACI (N=1306, 43%) was the most frequent stroke subtype. BP values by leukoaraiosis group, unadjusted for covariates, are provided in supplement.

Association between leukoaraiosis and acute absolute BP

The following are all adjusted analyses; beta coefficients and *P*-values are in Table 1.

Systolic (155±24 mmHg to 146±23 mmHg) and diastolic (82±15 mmHg to 78±14 mmHg) BP generally fell with time from pre-randomization to 24 hours after start of treatment ($P<0.005$). Systolic BP was 3.58 (95% confidence interval, CI, ±2.5) mmHg lower and diastolic BP was 3.80 (95% CI ±1.5) mmHg lower throughout the measurement period in patients with leukoaraiosis grade zero versus grade four. Systolic BP was higher ($\beta=0.23$, $P<0.0001$) and diastolic BP was lower ($\beta=-0.14$, $P<0.0001$) in older patients.

Mean arterial pressure was lower in those with leukoaraiosis grade zero versus grade four, but not associated with age, while pulse pressure was higher in older people but not associated with leukoaraiosis (Table 1).

Unadjusted associations between leukoaraiosis and acute BP variability

Unadjusted pairwise associations between leukoaraiosis and BP variability (systolic, diastolic, pulse, mean) characterized by CV were not statistically significant ($P>0.05$). All other measures of BP variability (except successive variability in pulse pressure, $P>0.05$) were significantly associated with leukoaraiosis, where greater variability was associated with increased burden of leukoaraiosis, when not adjusting for covariates ($P<0.05$; see supplement).

Adjusted associations between leukoaraiosis and acute BP variability

The following are all adjusted analyses; beta coefficients and *P*-values are in Table 2.

In contrast to the unadjusted pairwise associations, leukoaraiosis was not associated with BP variability in the acute phase of ischaemic stroke, whether measured by CV (column 1 Table 2), standard deviation (column 2 Table 2), average real variability (column 3 Table 2), or successive variability (column 4 Table 2) when adjusting for age, atrophy, stroke severity, subtype, and treatment groups.

Discussion

In this large study including 3017 patients, we found that leukoaraiosis was associated with high absolute BP, but not with BP variability, over the first 24 hours after ischaemic stroke when adjusting for relevant covariates. At first there did appear to be a positive association between leukoaraiosis and acute BP variability measured by standard deviation, average real variability, and successive variability, however these associations disappeared when adjusting for age and other relevant covariates. Therefore, while BP variability is associated with poor outcome in IST-3(1), it is not likely to explain the association between leukoaraiosis and poor outcome after acute stroke, that we also found in IST-3(9). Higher absolute BPs were associated with the presence of grade four leukoaraiosis versus grade zero; but patients with grade four leukoaraiosis did not have higher absolute BP compared to patients with leukoaraiosis grades one to three, after adjusting for age.

Our finding that short-term BP variability in acute ischaemic stroke is not independently associated with leukoaraiosis is consistent with two previous studies (N total=68), including one of non-acute lacunar stroke patients (N=43)(10, 12). Additionally, the lack of association between leukoaraiosis and BP variability is consistent with the largest previous study we found (N=694), that was conducted in community-dwelling subjects(6). However, our finding contrasts with previous smaller studies (N=66; N=210; N=155) of community-dwelling older subjects that found an association between increased variability in short-term BP and leukoaraiosis(13, 22). Additionally, positive associations between leukoaraiosis and BP variability have been found in primary hypertensive (N=487)(23) and cardiovascular disease (N=39)(24) patients. This discord may be due to acute ischaemia masking associations between BP variability and leukoaraiosis, the physiology of patient groups versus community dwelling participants, continual monitoring versus intermittent BP measures, or that previous sample sizes were much smaller (generally N<250) than here. Independent studies of absolute BP and leukoaraiosis may have similar differences in their study design, however, these have still produced generally consistent associations between higher absolute BP and more leukoaraiosis; and the number of these studies far outweighs the number of studies into BP variability and leukoaraiosis(14).

The strengths of our study include the large number of acute ischaemic stroke patients with BP

monitoring within the first 24 hours of stroke at fixed intervals according to standardised protocols; and recording of BP lowering treatment before, during the first 24 hours, and between two and seven days after trial enrolment. IST-3 settings and patients reflect a broad range of hospital environments charged with the care of ischaemic stroke. The number of participants studied here is over four times greater than the largest study of BP variability and leukoaraiosis that we found(6). Finally, we assessed a range of BP variability measures compared with previous studies that used only one measure(11, 12).

Despite these strengths, our study has some limitations. As we used data from a randomized-controlled trial, there is always a risk of confounding. For example, we were not able to control for some vascular risk factors such as cholesterol, which may have an influence on associations between BP and leukoaraiosis(14). MRI has greater sensitivity than CT for detecting leukoaraiosis but CT is much more widely used in acute stroke and detects established leukoaraiosis. We had limited information on BP prior to enrolment in the trial, beyond reported use of antihypertensive treatment, therefore do not know the duration of elevated BP prior to the trial. This means that we cannot ascertain whether those with higher BP and more leukoaraiosis had chronically high BP or only acutely high BP. Continuous monitoring of BP may identify subtle associations between BP variability and leukoaraiosis that we were not able to detect here. Other limitations related to BP measurements and the lack of random allocation to BP lowering treatment in IST-3 have previously been discussed at length(1). Our results may not apply to patients with haemorrhagic stroke as IST-3 only included ischaemic stroke. However, several completed or ongoing trials of BP lowering in haemorrhagic stroke also use similar scan assessments and therefore could assess leukoaraiosis and BP variability.

Notwithstanding, we have shown that patients with leukoaraiosis have high BP but do not have increased BP variability immediately after ischaemic stroke. While additional work is required in this area, our results suggest that BP variability is not a potential mechanism to explain the association between leukoaraiosis and poor outcome after acute ischaemic stroke.

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Conflict of interest

E. Berge is a member of the Second RIGHT-2 advisory committee. R.I. Lindley received support from Boehringer Ingelheim and Covidien. P. Sandercock and J.M. Wardlaw received support from the Medical Research Council, the Stroke Association, the Health Foundation, and Boehringer Ingelheim, and J.M. Wardlaw also received support from Chest Heart Stroke Scotland. All other authors report no conflicts.

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Table 1. Regression-based associations between absolute BP (dependent variable) and leukoaraiosis (independent variable) with relevant covariates

		Diastolic BP		Systolic BP		Pulse Pressure		Mean arterial pressure	
Parameter	Level	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value
Time (from pre-rand to 24 hours)		**-1.28**	**<0.0001***	**-2.32**	**<0.0001***	**-1.05**	**<0.0001***	**-1.63**	**<0.0001***
Age		**-0.14**	**<0.0001***	**0.23**	**<0.0001***	**0.38**	**<0.0001***	-0.02	0.52
Leukoaraiosis versus grade 4	0	**-3.80**	**<0.0001***	**-3.58**	**0.0042***	0.21	0.85	**-3.73**	**<0.0001***
	1	-1.73	0.06	0.37	0.81	2.09	0.10	-1.03	0.29
	2	-0.44	0.57	0.37	0.78	0.80	0.47	-0.18	0.83
	3	-0.40	0.74	-0.07	0.97	0.31	0.86	-0.30	0.82
No atrophy		0.09	0.89	0.41	0.69	0.33	0.69	0.20	0.77
NIHSS		-0.06	0.13	-0.05	0.46	0.01	0.82	-0.06	0.19
Stroke subtype versus LACI	PACI	-0.54	0.45	-0.55	0.68	0.04	0.97	-0.53	0.52
	POCI	-0.55	0.55	-0.05	0.98	0.53	0.69	-0.39	0.70
	TACI	-0.04	0.96	1.47	0.33	1.56	0.21	0.47	0.62
Time to randomization (hours)		0.21	0.19	0.50	0.08	0.29	0.23	0.31	0.09
Control versus rt-PA		0.62	0.14	0.63	0.37	0.01	0.99	0.63	0.17
BP lowering prior to study		**-1.35**	**0.0092***	-0.92	0.29	0.39	0.57	**-1.21**	**0.0339***
BP lowering in 1st 24 hours		**2.57**	**<0.0001***	**3.83**	**<0.0001***	1.27	0.09	**3.00**	**<0.0001***
BP lowering 24hr-7days		1.04	0.07	**5.24**	**<0.0001***	**4.22**	**<0.0001***	**2.44**	**<0.0001***

Note: BP=blood pressure; SE=standard error; **P*<0.05; NIHSS=National Institutes of Health Stroke Scale; LACI=lacunar infarcts; PACI=partial anterior circulation infarcts; POCI=posterior circulation infarcts, TACI=total anterior circulation infarcts; rt-PA=recombinant tissue-type plasminogen activator.

Beta are not standardised.

Table 2. Regression-based associations between leukoaraiosis (dependent variable) and BP variability (independent variables) with relevant covariates

		Coefficient of variance		Standard deviation		Average real variability		Successive variability	
Parameter	Level	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value	Beta	*P*-value
Diastolic BP		-1.71	0.09	0.02	0.38	0.01	0.55	0.00	0.94
Systolic BP		-1.89	0.16	0.01	0.37	0.01	0.31	0.00	0.12
Pulse pressure		0.41	0.30	-0.01	0.23	-0.01	0.20	0.00	0.14
Mean arterial pressure		2.36	0.21	-0.02	0.38	-0.01	0.58	null	.
Age		**0.02**	**<0.0001***	**0.02**	**<0.0001***	**0.03**	**<0.0001***	**0.03**	**<0.0001***
NIHSS		0.00	0.63	0.00	0.70	0.00	0.38	0.00	0.40
No atrophy		**-0.79**	**<0.0001***	**-0.78**	**<0.0001***	**-0.76**	**<0.0001***	**-0.76**	**<0.0001***
Stroke subtype versus LACI	PACI	-0.13	0.09	-0.14	0.09	**-0.18**	**0.0303***	**-0.18**	**0.0339***
	POCI	-0.02	0.82	-0.03	0.79	-0.08	0.48	-0.08	0.50
	TACI	-0.13	0.14	-0.14	0.13	**-0.20**	**0.0347***	**-0.20**	**0.0398***
Time to randomization (hours)		-0.02	0.21	-0.02	0.24	-0.01	0.75	-0.01	0.75
Control versus rt-PA		0.03	0.56	0.03	0.54	0.05	0.29	0.05	0.27
BP lowering prior to study		0.06	0.26	0.06	0.28	0.03	0.58	0.03	0.59
BP lowering in 1st 24 hours		0.10	0.07	0.10	0.06	0.09	0.15	0.08	0.16
BP lowering on days 2-7		-0.04	0.54	-0.04	0.52	0.00	0.96	0.00	0.97

Note: Leukoaraiosis is the dependent variable in this table, all associations shown are with Leukoaraiosis. BP=blood pressure; SE=standard error; *P<0.05; NIHSS=National Institutes of Health Stroke Scale; LACI=lacunar infarcts; PACI=partial anterior circulation infarcts; POCI=posterior circulation infarcts, TACI=total anterior circulation infarcts; rt-PA=recombinant tissue-type plasminogen activator.

Mean arterial pressure parameter Beta for successive variation was set to null because it is a linear combination of successive variation in diastolic (SV_DBP), systolic BP (SV_SBP), and pulse pressure (SV_PP), i.e., 0.66667 * SV_DBP + 0.33333 * SV_SBP - 0.22222 * SV_PP (see equations 1 and 3).

Beta are not standardised.