

The association between arterial stiffness, initial stroke severity, and 3 week outcomes in ischaemic stroke patients

Emma ORMEROD^{a,b}, Khalid ALI^b, James CAMERON^{b,c}, Muzaffar Malik^f, Richard LEE^{b,d}, Spas GETOV^{b,e}, Chakravarthi RAJKUMAR^b.

^a Bristol University Hospitals NHS Trust, Bristol, U.K

^b Academic Department of Geriatrics, Brighton & Sussex Medical School, Brighton, U.K.

^c Monash Cardiovascular Research Centre, Department of Medicine (Southern Clinical School), Monash University and Monash Heart, Clayton, Australia

^d NIHR Biomedical Research Centre, Guy's and St Thomas' NHS Foundation Trust, U.K

^e Wellcome Trust Centre for Neuroimaging, Centre of Neurology, University College London, U.K

^f Division of Medical Education, Postgraduate, Brighton and Sussex Medical School, University of Brighton, U.K

Correspondence to: Dr Khalid Ali, Audrey Emerton Building, Royal Sussex County Hospital, Eastern Road, Brighton, BN2 5BE

Telephone: 01273 523368 Fax: 01273 523366 Email: khalid.ali@bsuh.nhs.uk

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Abstract

Objectives: Vascular compliance is emerging as a useful cardiovascular risk factor.

The aim of this study was to investigate the association between arterial stiffness and stroke severity at presentation and at three weeks.

Methods: From an initial sample of 73 patients, 42 were included (55% male, mean age 71 years) with acute ischaemic stroke, over a 15 month period. Stroke subtypes were classified into LACI, PACI and POCI. Arterial stiffness was measured by QKD using 24-hour ambulatory blood pressure and ECG monitoring. The measured QKD values were then corrected for a heart rate of 60bpm and a systolic blood pressure (SBP) of 100 mmHg (QKD₁₀₀₋₆₀). Stroke severity was assessed on admission and after 3 weeks, using the National Institute of Health Stroke Scale (NIHSS).

Results: There was a non-significant weak correlation between initial stroke severity and QKD₁₀₀₋₆₀ ($r = -0.3$, $p = 0.08$). This correlation was weaker at 3 weeks ($r = 0.125$, $p = 0.47$). There was no difference in NIHSS at week 0 and 3, or QKD₁₀₀₋₆₀, between the different stroke types (LACI, PACI and POCI) or dipper versus non-dippers and reverse dippers.

Conclusions: This study highlights the need for further research into the association between QKD and initial stroke severity.

Keywords: stroke outcome, arterial stiffness, QKD, QKD₁₀₀₋₆₀, NIHSS

Introduction

The concept of arterial compliance as a risk factor in incident ischaemic stroke has been discussed in several studies¹⁻⁵. Most of the studies exploring the association of arterial compliance with stroke have measured arterial stiffness using pulse wave velocity (PWV)^{5,6}. However PWV measurements might be difficult to perform in the context of an acute stroke. Indirect assessment of arterial compliance based on QKD measurements can offer a less invasive alternative in providing a validated method for assessing arterial stiffness⁷. The use of the QKD interval (which is the time interval between the appearance of the Q wave on the ECG and the disappearance of the Kortokoff sound during diastole on blood pressure measurements) in acute stroke is appealing as it is relatively easy to measure and does not require observer input, and can be corrected for variation in BP and heart rate⁷.

The Oxfordshire Community Stroke Project Classification (OCSP), which provides prognostic information about stroke outcomes in the short and long term periods⁸⁻¹⁰, is based on epidemiological observational studies and no pathophysiological measurements were undertaken in its development. Saji et al report that arterial stiffness measured by PWV is independently associated with progressive neurological deficit after acute stroke¹¹. However, there are no studies assessing the prognostic value of arterial stiffness measured by QKD and its relation to presenting stroke symptoms and short term functional outcomes.

The aim of this study was therefore to explore the association between arterial stiffness (measured by QKD) and the initial and 3-week stroke severity measured by

the National Institute of Health Stroke Scale (NIHSS) in a cohort of acute ischaemic stroke patients. We hypothesised that increased arterial stiffness (shorter QKD intervals) at baseline is associated with more severe strokes at baseline as well as worse outcomes at 3 weeks.

Methods

Seventy three patients with an initial diagnosis of acute ischaemic stroke who were admitted to the Royal Sussex County Hospital, Brighton, UK between 1st December 2006 and 31st March 2008 were included. Inclusion criteria were a confirmed World Health Organisation (WHO) diagnosis of acute ischaemic stroke¹². Exclusion criteria were intracerebral haemorrhage, inability to consent, terminal illness, a previous stroke, previous direct current cardioversion, myocardial infarction or cardiac arrest within the preceding 6 months, antiarrhythmic medications or symptom duration of greater than 48 hours. All patients or their legal representative provided informed written consent. Ethical approval for the study was obtained from East Sussex Local Research and Ethics Committee (number 06/Q1905/70).

A thorough history and examination, in combination with a CT or MRI head scan, was used to confirm the diagnosis of stroke. We used the Oxford Community Stroke Project Classification (OCSP, Bamford Classification) to classify stroke subtypes into four categories: total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), posterior circulation infarct (POCI), and lacunar circulation infarct (LACI)^{9,13}.

Using ambulatory blood pressure measurements, patients were divided into dippers and non-dippers (dippers are individuals whose blood pressure drops by 10-20% at night time compared to daytime, non-dippers are those whose blood pressure drops by less than 10% at night time compared to daytime readings and reverse dippers are those whose blood pressure rises at night time compared to daytime).¹⁴

Additional cardiovascular risk factors, including smoking and alcohol consumption, were recorded. Twenty-four-hour ambulatory monitoring (Novocor, France) was used to measure heart rate (HR), blood pressure (BP) and QKD interval. QKD interval is an indirect measure of arterial stiffness based on the time interval between the onset of the QRS complex on the ECG and detection of the last Korotkoff sound from the blood pressure cuff. A longer QKD interval indicates more compliant arteries, as harder (stiffer) arteries propagate the blood flow quicker in a shorter QKD interval.

BP, HR and QKD interval readings were taken every 30 minutes between 07:00 and 22:00 and every 60 minutes between 22:01 and 06:59 providing a total of 39 measurements. These measurements were used to derive mean QKD values, as well as mean values for 24-hour Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), and Pulse Pressure (PP). Mean patient QKD was further corrected for a heart rate of 60bpm and a SBP of 100mmHg to obtain a value of QKD₁₀₀₋₆₀. These measurements were done at baseline only.

We measured stroke severity at baseline (on admission, day 0) and at week three using the NIHSS scoring system.¹⁵ LACI (group 1) was compared with PACI and POCI

stroke subtypes (group 2). PACI and POCI (group 2) were grouped together because they are larger strokes affecting more brain tissue. Patients with a TACI were excluded as they either had low GCS, speech impairments, or were too unwell to provide informed consent.

The stroke scale variables are described using medians and interquartile range (IQR). Counts and proportions are given for categorical or ordinal variables. Baseline characteristics (NIHSS, QKD₁₀₀₋₆₀, SBP, DBP, pulse pressure, and MAP) measured in all patients is presented in Table 1.

Pearson's correlation coefficient was used to analyse the relationship between NIHSS (at 0 and 3 weeks) and QKD₁₀₀₋₆₀, SBP, DPP, PP, and MAP, and the dipping profile was analysed too. T-Test was used to compare differences of NIHSS and QKD₁₀₀₋₆₀ between Group 1 (LACI) and Group 2 (PACI+POCI) stroke subtypes.

Results

From the initial sample of 73 patients, 42 patients were included in the final analysis (2 withdrew, 3 had a subsequent haemorrhagic transformation, 9 had a diagnosis of TIA, 2 were unable to complete formal assessment, and the remaining 15 did not have full data available for QKD, BP and NIHSS measurements). The mean age for the study sample was 71 (28-90) years of which 23 (55%) were male. Twenty-three patients (55%) had a diagnosis of PACI, 17 (41%) had a diagnosis of LACI, and 2 (5%) had a diagnosis of POCI. Table 1 shows the baseline characteristics of the study population according to stroke group.

For all stroke patients recruited to the study, there was a statistically non-significant correlation between stroke severity on admission (NIHSS 0) and arterial stiffness indicator (QKD₁₀₀₋₆₀) ($r = -0.3$, $p = 0.08$). This correlation was even weaker at week 3 bearing in mind that the comparison was made with arterial stiffness measured at baseline only ($r = 0.125$, $p = 0.47$). No statistically significant correlations were observed between NIHSS and mean MAP or mean PP (Table 2).

There was no statistically significant difference of NIHSS score observed at baseline (week 0) or at 3 weeks between either LACI vs. PACI+POCI groups or between dippers versus the non-dippers + reverse dippers groups (Table 3). In addition there was no statistically significant difference of QKD₁₀₀₋₆₀ between LACI vs. PACI+POCI groups ($p = 0.69$) or between dippers versus non-dippers + reverse dippers ($p = 0.56$).

A correlation test was carried out to explore the relationship between MAP and NIHSS score at baseline. That too did not reveal any correlation between these two variables ($r = 0.07$, $p = 0.68$).

Discussion

Prognostic information relating to important cardiovascular parameters such as arterial stiffness at stroke presentation is relevant to individual patient outcomes and epidemiological population studies. In our study population, we found a correlation between arterial stiffness and initial stroke severity, but it did not reach statistical significance. This finding would be in keeping with our knowledge of the pathophysiology of stroke; atherosclerosis is a chronic process which occurs over

several years, causing thickening of the arteries with plaques which will then result in stiffer and less compliant arteries over time, leading to a quicker propagation time of the pulse wave velocity and shorter QKD. This process is likely to be more associated with larger stroke subtypes (e.g. TACI, PACI, POCI), whereas the impact of atherosclerosis is less significant in smaller strokes such as LACI. The trend we have shown between QKD and initial NIHSS therefore highlights an important area of that should be explored in more detail in future studies.

We would expect that patients with larger strokes would have a worse long-term outcome compared to those patients with less severe strokes. Indeed, Osmani et al¹⁶ showed that TACIs were associated with poor outcome and the highest mortality rates of stroke subtypes, whereas LACIs had the best outcome with the most patients functionally independent at six months. However, in contrast to previous studies exploring the predictive value of arterial stiffness using PWV with outcomes from stroke^{17,18}, we found that there was no relationship between stroke outcome at 3 weeks with either stroke subtype or QKD₁₀₀₋₆₀. This is most likely due to the small sample size of the patient numbers in each group. It is also interesting to note that there was no statistically significant difference in QKD properties or the BP-dipping status between group 1 and group 2 in our patient population. There are prognostic factors other than BP and QKD which will affect outcomes at 3 weeks which we did not look at, such as maintenance of physiological parameters, atrial fibrillation, and whether or not the patient was thrombolysed.

There was no correlation between a variety of ambulatory blood pressure measurements (SBP, DPP, PP, and MAP, and dipping profile) and stroke severity at baseline and at 3 weeks in our study. Whether or not high BP is associated with poor outcome after acute ischaemic stroke has been extensively debated with conflicting results. Recently, three meta-analyses have neither supported nor opposed early BP lowering in acute ischaemic stroke with respect to the effect on short or long term morbidity and mortality^{19,20,21}. It may instead be BP variability^{22,23} and extremes of BP^{24,25} that have an influence on poorer outcomes in the acute post-stroke phase. Furthermore, a reverse-dipping profile in diastolic BP has previously been shown to be associated with increased arterial stiffness in post-stroke patients²⁶, as well as with poorer neurological outcomes at baseline and at weeks 1 and 3 compared to dippers and nondippers²⁷. Lack of nocturnal decline in BP is postulated to occur as a result of autonomic centre damage, but it is still uncertain whether changes to night-time dipping in BP occur prior to or as a result of stroke. Overall, BP is a highly variable physiological parameter, and our results would suggest that BP alone may not be a robust marker of initial stroke severity.

Conclusion

Low QKD representing worse arterial stiffness is a non-invasive indication of poor arterial health and may be a useful tool for predicting initial stroke severity. This study highlights an important area for further research. It remains to be seen whether modifying pathological arterial stiffness parameters in the acute stroke phase has benefits on short term outcomes, such as functional recovery and mortality.

Study limitations

This study was limited by the limited sample size. In addition, no TACI stroke patients were able to be recruited to this study because of the difficulty in providing informed consent. We were only able to include patients with good cognitive function at the time of presentation to hospital, thus the results may not be generalisable to patients with more severe strokes who lack capacity.

References

1. Mattace-Raso FUS, van der Cammen TJM, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation*. 2006;113:657–63.
2. Yang EY, Chambless L, Sharrett AR, et al. Carotid arterial wall characteristics are associated with incident ischemic stroke but not coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) study. *Stroke J Cereb Circ*. 2012;43:103–8.
3. Sutton-Tyrrell K, Najjar SS, Boudreau RM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation*. 2005;111:3384–90.
4. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*. 2001;37:1236–41.
5. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588–605.
6. Pannier BM, Avolio AP, Hoeks A, et al. Methods and devices for measuring arterial compliance in humans. *Am J Hypertens*. 2002;15:743–53.
7. Gosse P, Lasserre R, Minifié C, et al. Arterial stiffness evaluated by measurement of the QKD interval is an independent predictor of cardiovascular events. *Am J Hypertens*. 2005;18:470–6.
8. Wardlaw JM, Dennis MS, Lindley RI, et al. The validity of a simple clinical classification of acute ischaemic stroke. *J Neurol*. 1996;243:274–9.
9. Bamford J, Sandercock P, Dennis M, et al. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet*. 1991;337:1521–6.
10. Sprigg N, Gray LJ, Bath PMW, et al. Stroke severity, early recovery and outcome are each related with clinical classification of stroke: data from the “Tinzaparin in Acute Ischaemic Stroke Trial” (TAIST). *J Neurol Sci*. 2007;254:54–9.
11. Saji N, Kimura K, Kawarai T, et al. Arterial stiffness and progressive neurological deficit in patients with acute deep subcortical infarction. *Stroke J Cereb Circ*. 2012;43:3088–90.

12. Thorvaldsen P, Asplund K, Kuulasmaa K, et al. Stroke incidence, case fatality, and mortality in the WHO MONICA project. World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease. *Stroke J Cereb Circ.* 1995;26:361–7.
13. Bamford JM. The role of the clinical examination in the subclassification of stroke. *Cerebrovasc Dis Basel Switz.* 2000;10:2–4.
14. Holt-Lunstad J, Jones BQ, Birmingham W. The influence of close relationships on nocturnal blood pressure dipping. *Int J Psychophysiol.* 2009; 71:211-7.
15. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke J Cereb Circ.* 1989;20:864–70.
16. Osmani AH, Durrani RK, Ara J. Comparison of outcome in different types of stroke due to cerebral ischemia. *J Coll Physicians Surg--Pak JCPSP.* 2010;20:42–6.
17. Gasecki D, Rojek A, Kwarciany M, et al. Aortic stiffness predicts functional outcome in patients after ischemic stroke. *Stroke J Cereb Circ.* 2012;43:543–4.
18. Gąsecki D, Rojek A, Kwarciany M, et al. Pulse wave velocity is associated with early clinical outcome after ischemic stroke. *Atherosclerosis.* 2012;225:348–52.
19. Liu S, Li C, Li T, et al. Effects of Early Hypertension Control after Ischaemic Stroke on the Outcome: A Meta-Analysis. *Cerebrovasc Dis Basel Switz.* 2015;40:270–8.
20. Zhao R, Liu F-D, Wang S, et al. Blood Pressure Reduction in the Acute Phase of an Ischemic Stroke Does Not Improve Short- or Long-Term Dependency or Mortality: A Meta-Analysis of Current Literature. *Medicine (Baltimore).* 2015;94:896.
21. Lee M, Ovbiagele B, Hong K-S, et al. Effect of Blood Pressure Lowering in Early Ischemic Stroke: Meta-Analysis. *Stroke J Cereb Circ.* 2015;46:1883–9.
22. Kang J, Ko Y, Park JH, et al. Effect of blood pressure on 3-month functional outcome in the subacute stage of ischemic stroke. *Neurology.* 2012;79:2018–24.
23. Yong M, Kaste M. Association of characteristics of blood pressure profiles and stroke outcomes in the ECASS-II trial. *Stroke J Cereb Circ.* 2008;39:366–72.
24. Geeganage CM, Bath PMW. Relationship between therapeutic changes in blood pressure and outcomes in acute stroke: a metaregression. *Hypertension.* 2009;54:775–81.

25. Keezer MR, Yu AXY, Zhu B, et al. Blood pressure and antihypertensive therapy as predictors of early outcome in acute ischemic stroke. *Cerebrovasc Dis Basel Switz.* 2008;25:202–8.
26. Saeed S, Waje-Andreassen U, Tone Lønnebakken M, et al. Covariates of non-dipping and elevated night-time blood pressure in ischemic stroke patients: the Norwegian Stroke in the Young Study. *Blood Press.* 2015;1–7.
27. Ali K, Leong KMW, Houlder S, et al. The relationship between dipping profile in blood pressure and neurologic deficit in early acute ischemic stroke. *J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc.* 2011;20:10–5.

Table and figure legends

Table 1: Patient baseline characteristics

Table 2: Correlation of NIHSS with variables given below

Table 3: Difference of NIHSS between LACI vs. PACI+POCI and between dippers versus Non + reverse dippers at baseline and 3 weeks

Table 1: Patient baseline characteristics

Mean (SD) or count (%)

Variable	Total (n=42)	Group 1 (LACI) (n=17)	Group 2 (PACI or POCI) (n=25)
Mean age	71 (15)	65 (15)	74 (14)
Male	23 (55)	13 (77)	10 (40)
Mean 24-hour SBP (mmHg)	131 (20)	137 (27)	129 (14)
Mean 24-hour DBP (mmHg)	82 (15)	85 (20)	79 (11)
Mean 24-hour PP	51 (13)	53 (15)	49 (12)
Mean 24-hour MAP (mmHg)	98 (15)	101 (20)	96 (10)
QKD ₁₀₀₋₆₀	198 (30)	200 (34)	196 (28)
NIHSS 0 week	7 (5)	6 (4)	8 (6)
NIHSS 3 week	4 (5)	2 (2)	5 (6)

Key: LACI = lacunar circulation infarct, PACI = partial anterior circulation infarct, POCI = posterior circulation infarct, SBP = systolic blood pressure, DBP = diastolic blood pressure, PP = pulse pressure, MAP = mean arterial pressure, NIHSS = National Institute of Stroke Scale

Table 2: Correlation of NIHSS with QKD 100-60, mean MAP, mean PP

NIHSS score time	Variable	Overall correlation (<i>r</i>)	<i>p</i> value
Week 0	QKD100-60	-0.3	0.08
	mean MAP	0.07	0.68
	mean PP	-0.02	0.88
Week 3	QKD100-60	-0.1	0.47
	mean MAP	-0.1	0.47
	mean PP	-0.1	0.46

Key: NIHSS = National Institute of Health Stroke Scale, MAP = Mean arterial pressure, PP = Pulse pressure
Please note that QKD 100-60, mean MAP and mean PP were measured at baseline only.

Table 3: Difference of NIHSS between LACI vs PACI+POCI and between Dippers vs Non + reverse dippers at baseline and 3 weeks

NIHSS score time	Grouping	<i>p value</i>
Week 0	LACI vs PACI+POCI	0.1
	Dippers (n=14) vs Non + reverse dippers n=26)	0.08
Week 3	LACI vs PACI+POCI	0.05
	Dippers (n=14) vs Non + reverse dippers n=26)	0.29

Key: NIHSS = National Institute of Health Stroke Scale, LACI = Lacunar circulation infarct, PACI = Partial anterior circulation infarct, POCI = Posterior circulation infarct