Age and Ageing 2015; **44:** 655–661
doi: 10.1093/ageing/afv011
Published electronically 25 February 2015

Ischaemic stroke or TIA in older subjects associated with impaired dynamic blood pressure control in the absence of severe large artery stenosis

D. J. Ryan[1], R. A. Kenny[1], S. Christensen[2], J. F. M. Meaney[3], A. J. Fagan[3], J. Harbison[1]

[1]Department of Medical Gerontology, Trinity College, Dublin 2, Ireland
[2]Department of Neurology, Stanford University, Stanford, CA, USA
[3]Centre for Advanced Medical Imaging, St. James's Hospital/School of Medicine, Trinity College, Dublin 2, Ireland

Address correspondence to: J. A. Harbison. Tel: (+353) 142 841 08; Fax: (+353) 141 034 54; Email: jharbiso@tcd.ie

Abstract

Background: older subjects may require higher baseline blood pressures to maintain cerebral perfusion. We investigated whether episodic hypotension is associated with tissue infarction in subjects with syncopal symptoms at stroke onset.
Methods: over 30 months, all acute strokes/TIAs were prospectively screened for symptoms of syncope or presyncope at stroke onset. Subjects with severe large vessel stenosis were excluded, while cases were referred for syncope unit investigation. All underwent 1.5 T MRI acutely, and suspected borderzone infarctions (BZI) were confirmed through Matlab-derived perfusion software. Case–control comparison was derived from stroke controls with no prior syncope history.
Results: thirty-eight of 772 stroke patients described presyncope or syncope at stroke onset and had patent large vessels (4.9% of all strokes). Median age was 72 years (IQR 21.4). Twenty-two patients (58%) were prescribed antihypertensive agents at symptom onset. Twenty-six (68.4%) reported focal neurology <24 h in duration. 63.2% ($n = 24$) of cases reported prior syncope history, compared with 33% ($N = 103$) of controls, $P < 0.001$. Cases exhibited greater orthostatic BP drop than controls, $P < 0.05$ Twenty-four patients were diagnosed with vasovagal syncope through head-up tilt symptom reproduction, 9 with orthostatic hypotension, 4 with cardiac syncope and 1 with carotid sinus syndrome. Nineteen (50%) patients had an acute infarct on MRI, 14 of these were in the arterial borderzone (73.6%). The BZI group were significantly older than the non-BZI group, 79.2yrs versus 63.3 yrs, $P = 0.002$.
Conclusion: subjects reporting hypotensive symptoms at stroke onset have a higher prevalence of borderzone infarction, despite being normotensive or hypertensive at baseline.

Keywords: *neuroimaging, older people, syncope, stroke*

Introduction

Whilst most published guidelines make a clear distinction between stroke [1], TIA and syncope, clinicians occasionally encounter patients who have suffered syncopal symptoms at stroke onset. Syncope is caused by drops in blood pressure and loss of consciousness due to transient global cerebral hypoperfusion. Up to 45% of people will experience a syncope event in their lifetime and the cumulative incidence of syncope rises with age, from 6.2/1,000 person-years in the general population, to 19.5/1,000 person-years in those over 80 years of age [2, 3]. It is recognised that syncope or presyncope may rarely potentiate stroke as global hypoperfusion can induce tissue infarction but such events are generally reported to occur in the presence of severe large artery stenosis or during cardiac arrest [4, 5]. Thus, hypotensive stroke is relatively rare as only 0.2–4.1% of the population exhibit severe carotid stenosis and <1% (Caucasian) exhibit severe middle cerebral artery stenosis [6, 7]. Moreover, incidence of stroke in those with severe large artery disease is only 2–3% per year [8].

Hypotension-induced infarction preferentially occurs in flow-vulnerable, borderzone regions of the brain. Laminar flow through a vessel is proportional to the fourth power of the radius and is inversely proportional to eight times its length, so hypotension preferentially affects longer, distant, narrow vessels that supply the borderzone region. The reported prevalence of borderzone infarction is 9.6–12.5%, which is significantly higher than its attributed causes [4, 9, 10]. This may be due to misclassification of infarcts [11], but may be due to a heretofore unidentified cause. The most likely at-risk population are older, frail patients.

Evidence suggests older patients possibly exhibit rightward shift in their cerebral autoregulatory curve and consequently need higher baseline blood pressures, and in this population the J-shaped correlation between BP and cardiovascular outcomes is well recognised [12–14]. Excluding those with severe large artery disease, we performed this study to determine the prevalence, characteristics and associations of borderzone infarction occurring in subjects with presyncopal or syncopal symptoms at onset.

Methods

Screening

Ethical approval was obtained in advance from the local Research Ethics Committee. All patients that presented with an acute stroke to St James's Hospital between 1 July 2010 and 10 January 2013 were screened by the stroke team for the reported presence of presyncopal or syncopal symptoms at the onset of their stroke (Figure 1). Suspected cases were referred to a syncope-trained stroke fellow and, if confirmed after comprehensive evaluation, were referred to an on-site syncope unit. Patients were excluded from the study if they exhibited severe carotid stenosis (>70%), severe middle cerebral artery stenosis (>50%) or significant cognitive impairment (a mini-mental state exam score <23/30). All subjects participating in the study gave informed consent prior to inclusion.

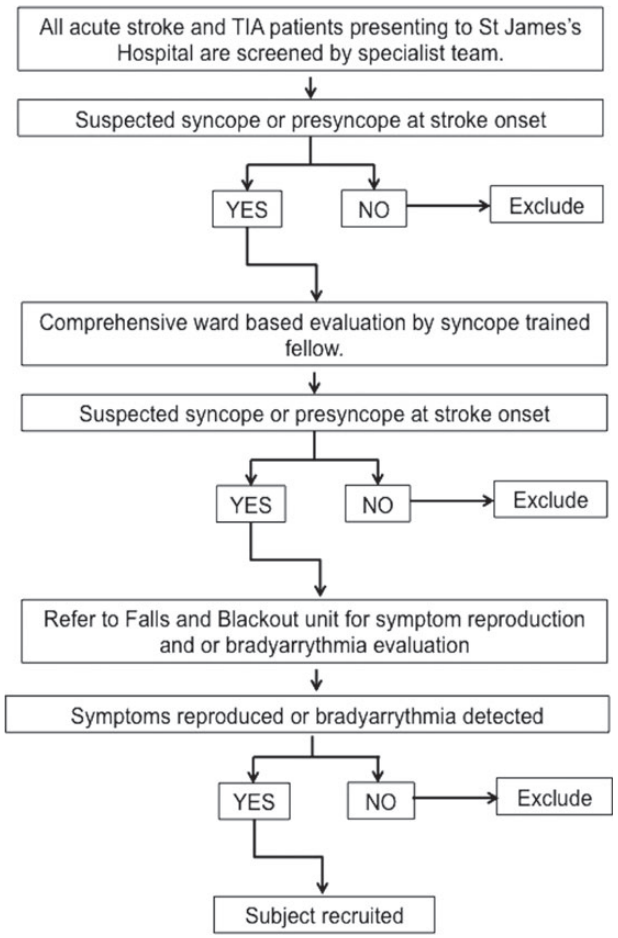

Figure 1. Screening pathway for subjects.

Syncope evaluation

Syncope evaluation took place at least 6 weeks after the stroke event to minimise bias from impaired post-stroke autoregulation [15, 16]. Antihypertensive medications were not altered in the intervening time. All patients underwent a detailed history, examination and electrocardiogram and were consequently divided into suspected cardiac syncope or reflex syncope and investigated in accordance with the European Syncope Guidelines [1, 17].

All subjects underwent an active stand assessment using phasic blood pressure assessment equipment recording beat-to-beat blood pressure values. Symptom reproduction from the stroke event was deemed to have occurred if the patient experienced similar presyncope/syncope sensations while simultaneous systolic BP of <90 mmHg was recorded.

Patients suspected as having reflex syncope underwent head-up tilt assessment using a front loaded head-up tilt protocol, using standard protocols and beat-to-beat BP was recorded during the procedure [18]. A tilt-positive response was defined as symptom reproduction with a systolic BP <90 mmHg [19]. If carotid sinus syndrome was suspected, patients underwent carotid sinus massage.

Of note, head-up tilt is a provocation test and as such may induce a haemodynamic response in normal controls (~6–27%) [18, 20]. However, this study utilized head-up tilt to elicit symptom reproduction (syncope/presyncope similar to the stroke event) rather than just a haemodynamic response. If induced presyncope/syncope sensation differed from that of the stroke event, the patient was excluded.

Data were collected regarding the patients' prior hypotensive symptoms. Syncope prevalence and frequency were determined using validated syncope questions [21]. Presyncope severity was determined using the Sheldon Presyncope scale, which grades symptom severity from 0 (no symptoms) to 10 (complete loss of consciousness) [22].

Stroke diagnosis

A clear report of focal neurology, defined as unilateral weakness or numbness, aphasia or monocular visual loss, and consensus agreement between stroke physicians, was required to establish

a diagnosis of stroke or TIA. Subjects with non-focal symptoms such as dysarthria or vertigo, in isolation, were excluded.

Imaging

All subjects underwent a CT and 1.5 T MRI, where possible, of the brain during the acute period (<2 weeks after focal neurology). The MRI sequence consisted of an axial T_2-weighted Turbo spin-echo, an axial FLAIR sequence and an axial DWI sequence with ADC maps. All underwent carotid duplex ultrasound imaging categorised according to Strandness criteria [23]. An acute infarct was defined as a lesion that exhibited restricted diffusion (high-signal intensity) on DWI.

All subjects were offered repeat neuroimaging using 3 T MR, which consisted of standard stroke sequences and included intracranial MR angiography (MRA). A very high spatial resolution ($0.25 \times 0.49 \times 0.5$ mm^3) time-of-flight angiography was performed to detect intracranial large artery stenosis of the posterior or anterior circulation. In addition to standard sequences, subjects exhibiting acute infarcts on 1.5 T MR were offered 3 T MR perfusion to characterise their infarct.

MR perfusion sequence consisted of a high-resolution gradient echo–echo planar imaging sequence, achieving voxel sizes of $2.5 \times 2.5 \times 5$ mm^3 and field of view 85 mm. Because of the known variability in location of cortical borderzone regions, MRI processing methods were employed [11, 24]. A Matlab-derived iteration process was used, which utilised first-moment properties of perfusion bolus arrival to identify the main vascular perfusion territories for each patient (MCA, ACA and PCA) and consequently locate the borderzone regions (Figure 2, Supplementary data Appendix 1 available in *Age and Ageing* online). Post-processing analysis was carried out on MRA images using *ITK-Snap* software. Seeds were placed at proximal arteries and an iteration process generated images of arterial distributions (Figure 2) [25]. Where internal borderzone infarction (BZI) was suspected, classification was conducted using vascular supply maps by Damasio and Van der Zwan as the aforementioned processing methods cannot

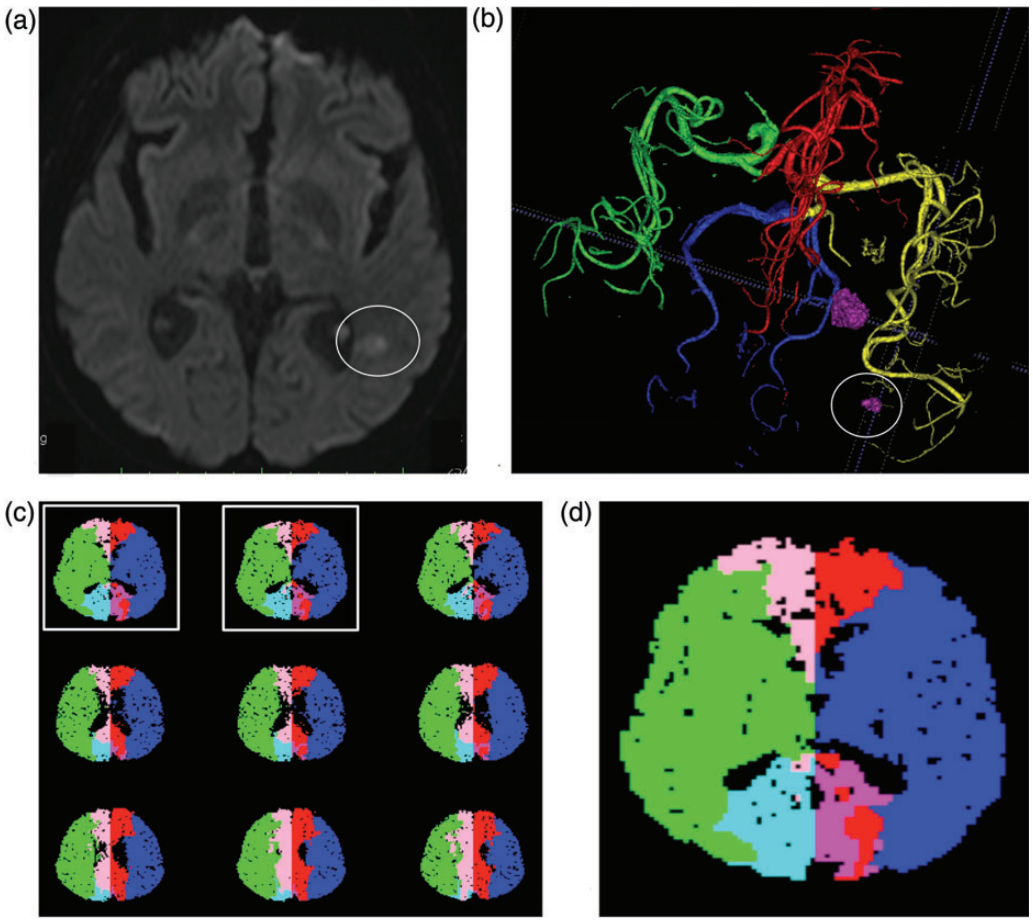

Figure 2. (a) Axial DWI image from a 74-year-old man that presented with right hemiparesis and an associated presyncope event secondary to dehydration. (b) Processed MRA using ITK-snap software. The acute cortical borderzone infarct is represented by the purple lesion surrounded by the white circle. (c) Processed axial MR perfusion images. The vascular supply regions of the MCA are highlighted in blue and green, the ACA in pink and red and PCA by purple and cyan. The slices with the acute infarct are highlighted with white squares. (d) The selected axial MR perfusion slice relating to the infarct, which demonstrates its proximity to the PCA (purple) and also the ACA (red) territories.

separate the deep and superficial perfusion territories for the MCA [24, 26]. Where patients declined repeat MR perfusion, imaging textbook maps were applied instead [27, 28].

Infarcts were reviewed by two independent assessors, a senior radiologist and a senior stroke physician, both blind to each other and to the patient's hypotensive disorder but informed of the nature of the stroke presentation.

Case–control comparison

Cases were compared with controls from The Irish LongituDinal study of Ageing (TILDA). In TILDA, a history of prior syncope is elicited. Selected controls described (a) prior stroke or TIA and (b) denied prior syncope. Cases were compared with controls for baseline demographics, co-morbid disease and blood pressure response to active stand.

Cases were also compared with stroke controls from the North Dublin Population Stroke study according to baseline demographics and the prevalence of co-morbid conditions.

Statistical analysis for both comparisons was conducted in Stata 12 using the chi-squared test, Student's *t*-test and Wilcoxon rank-sum test where non-parametric continuous data were concerned.

Lastly, a case–case comparison was conducted between cases that experienced acute borderzone infarction and cases that did not experience acute borderzone infarction. Here, multivariate regression analysis was conducted, controlling for the effects of age. When age was the dependant variable in the model, then multivariate analysis was carried out controlling for the effects of antihypertensive medication and co-morbid disease. Age was dichotomised as old (>65 years) and young (≤65 years).

Results

Screening

Over 30 months, 772 acute stroke/TIA patients were questioned for the presence of syncopal or presyncopal symptoms at stroke onset. In all, 46 patients without severe large artery disease described probable presyncope/syncope at stroke onset and were referred for syncope unit evaluation. Of these 8 were excluded: 3 because a diagnosis of syncope/presyncope was felt less likely on closer evaluation and 5 because no symptom reproduction or bradyarrythmia was detected on investigation (Figure 1).

Prevalence

Table 1 shows the baseline demographics for the remaining 38 (4.9%) patients. Median age was 72 years (IQR 21.4), 21 were female (55%). Median carotid stenosis on the side ipsilateral to the stroke was 20–50% while the median carotid stenosis on the contralateral side was 0–20%, $P = 0.36$. Twenty-four patients had a history of hypertension (63%), 26 (68%) had a focal neurological deficit of <24 h duration. Median NIHSS score was 2 (IQR 7.6). Twenty-two (57.9%) described presyncopal symptoms at stroke onset and 16 (42.1%) described syncope. At onset, most patients were engaged in activities known to induce hypotension; 12 had just stood up from a supine or seated position, 15 were standing or walking and 2 had passed urine.

Table 1. Baseline characteristics of the patients diagnosed with an ischaemic stroke or TIA with hypotensive symptoms at onset

Description	*N* = 38
Baseline characteristics	
Age, median (IQR)	72.8 (21.4)
Female gender, *n* (%)	21 (55.3)
Comorbid conditions, *n* (%)	
Hypertension	24 (63.2)
Ischaemic heart disease/myocardial infarction	16 (42.1)
Diabetes	4 (13.8)
Atrial fibrillation	8 (21)
Anti-hypertensive medication	22 (57.9)
Beta-blocker, *n* (%)	12 (31.6)
Diuretic, *n* (%)	8 (21)
BP medication number, median (IQR)	1 (2)
Mean 24-h BP	
Time to 24-h BP monitor, median days (IQR)	69 (60)
Systolic BP, mean (SD) mmHg	137 (19)
Diastolic BP, mean (SD) mmHg	77 (11)
Stroke category	
Stroke, *n* (%)	12 (31.6)
TIA, *n* (%)	26 (68.4)
NIHSS, median (IQR)	2 (7.6)
Stroke cause (TOAST classification)[a], *n* %	
Large artery atherosclerosis	5 (13.2)
Cardioembolism	12 (31.6)
Small vessel	9 (23.6)
Undetermined	12 (31.6)
Reported symptoms: orthostatic intolerance or presyncope	
Hx. of orthostatic intol./presyncope symptoms, *n* (%)	35 (92.1)
Sheldon presyncope scale, median severity (0–10)[a], (IQR)	5.5 (3)
Duration since first event, median years (IQR)	5.5 (13.5)
Monthly frequency of symptoms, median (IQR)	2 (7.6)
Reported symptoms: syncope	
History of syncope, *n* (%)	24 (63.2)
Lifetime quantity of syncope events, median (IQR)	2.5 (8)
Infarct type and location (19 exhibited acute infarction)	
Borderzone infarct, *n* (%)	14 (73.7)
Deep borderzone infarct (lacunar)	8
Cortical borderzone infarct	5
Cerebellar borderzone infarct	1
Non-borderzone infarct, *n* (%)	5 (13.2)
Lacunar infarct	3
Cerebral cortical infarct	1
Cerebellar infarct	1

[a]Sheldon presyncope scale; 0 = no symptoms, 10 = syncope.
[b]Defined as a drop of >40 mmHg systolic on standing with associated symptoms of presyncope.

Prior hypotensive symptoms and attributed hypotensive disorder (Table 1)

Thirty-five (92%) patients described a history of either previous orthostatic intolerance or presyncopal symptoms but not loss of consciousness. Twenty-four patients described a history of syncope (63.2%). Median lifetime frequency of syncope was 2.5 events.

Table 2. Infarct type and location among the 19 patients that exhibited infarction

Description		$N = 19$
Infarct type and location, *n* (%)		
Borderzone infarct		14 (73.7)
Deep borderzone infarct (lacunar)	8	
Cortical borderzone infarct	5	
Cerebellar borderzone infarct	1	
Non-borderzone infarct		5 (13.2)
Lacunar infarct	3	
Cerebral Cortical infarct	1	
Cerebellar infarct	1	

On comprehensive evaluation, in 24 cases (Table 2), symptoms were reproduced on head-up tilt in conjunction with a systolic BP < 90 mmHg, and in a further 5 cases symptoms occurred during active stand, again with a systolic BP < 90 mmHg. Four patients were too frail to undergo head-up tilt but on active stand exhibited symptom reproduction and a systolic BP drop of >40 mmHg, sufficient to diagnose OH. Four exhibited a cardiac conduction deficit on 7-day ECG recording and 1 exhibited a 5-s pause on carotid sinus massage. Although it was not our intention to induce hypotension to the point of reproducing focal neurology it occurred in 2 of the 38 patients. In all, 24 patients received a diagnosis of vasovagal syncope, 9 of orthostatic hypotension, 4 of arrythmogenic cardiac syncope and 1 of carotid sinus syndrome.

Neuroimaging

All patients underwent 1.5 T neuroimaging in the acute phase (<2 weeks). An acute infarct was detected in 19 of 38 patients (50%), 18 on MRI and 1 on CT scan in whom MRI was contraindicated. Fifteen patients (83%) agreed to repeat neuroimaging in the 3 T scanner and 3 patients declined repeat MR scanning. Using high-resolution MR angiography, none of the 15 patients exhibited any large artery intracranial stenosis of the anterior or the posterior circulation (Figure 2b). One of the three had a cerebellar infarct, one had a centrum semiovale infarct and one had a cortical infarct. Of the 19 acute infarcts detected, 14 (73.6%) were identified as borderzone infarcts (Table 3).

A univariate analysis was carried out to determine the baseline demographic characteristics that predicted which patients experienced a borderzone region infarct. Patients with BZI were older 79.2 years (SD 9.3) versus 63.3 years (SD 15.8), $P = 0.002$ and were also more likely to have hypertension ($P = 0.03$), atrial fibrillation ($P = 0.01$) and a higher 24-h mean systolic blood pressure (147.8 mmHg (SD 20.5) compared with 131.8 mmHg (SD 16.6), $P = 0.02$).

Using multivariate logistic regression, controlling for the effects of age, the between-group difference in the prevalence of hypertension and atrial fibrillation became non-significant, as did the difference in mean systolic blood pressure.

Using multivariate logistic regression with age as the dependent variable, controlling for the effects of mean systolic BP, atrial fibrillation, category of ipsilateral carotid stenosis and the use of antihypertensive medication, age (over 65 years) remained a consistent predictor of borderzone infarction, $P = 0.04$, R^2 model 0.31, *f*-ratio 13.35. The odds ratio for those with a BZI being over 65 years was 17.15 (95% CI 1.1, 273), $P = 0.04$.

Table 3. Univariate analysis of the baseline demographics, anti-hypertensive medication, co-morbid conditions and hypotensive behaviour in both groups

Characteristics $N = 38$	Non-BZI ($n = 24$)	BZI ($n = 14$)	*P*-value
Baseline demographics			
Age, years, mean (SD)	63.3 (15.8)	79.2 (9.3)	0.002
Female gender, *n* (%)	14 (58.3)	7 (50)	0.62
Blood pressure (BP) characteristics			
24-h systolic BP, mean (SD)	132 (17)	148 (20)	0.02
24-h diastolic BP, mean (SD)	74 (9)	81 (12)	0.07
BP medication, yes, *n* (%)	12 (50)	10 (71.4)	0.2
BP medication number, mean (SD)	2 (2)	2 (2)	0.78
Beta blocker, *n* (%)	8 (33.3)	4 (28.6)	0.76
Diuretics, *n* (%)	4 (16.7)	4 (28.6)	0.39
Carotid stenosis			
Ipsilateral carotid stenosis <50%, *n* (%)	18 (75.0)	12 (85.7)	0.68
Ipsilateral carotid stenosis 50–70%, *n* (%)	6 (25.0)	2 (14.3)	0.65
Contralateral carotid stenosis <50%, *n* (%)	22 (91.7)	12 (85.7)	0.61
Contralateral carotid stenosis 50–70%, *n* (%)	2 (8.3)	2 (14.3)	0.37
Co-morbid conditions, *n* (%)			
Hypertension	12 (50)	12 (85.7)	0.03
Previous stroke	5 (20.8)	5 (35.7)	0.32
MI/IHD	11 (45.8)	5 (35.7)	0.54
Atrial fibrillation	2 (8.3)	4 (42.9)	0.01
Hypotensive symptoms			
Orthostatic intolerance/presyncope, *n* (%)	21 (87.5)	14 (100)	0.17
Frequency/month, median (IQR)	1.4 (5.8)	2 (9)	0.41
Syncope, *n* (%)	16 (66.7)	8 (57.1)	0.56
Quantity of events, median (IQR)	2 (9)	3 (4)	0.41
Hypotensive disorder, *n* (%)			
Reflex syncope	19 (79.1)	6 (42.9)	0.02
Orthostatic hypotension	2 (8.3)	7 (50.0)	0.004
Arrythmia-related cardiac syncope	3 (12.5)	1 (7.1)	0.6
Life style			
Smoker, *n* (%)	11 (45.8)	4 (28.6)	0.29
Alcohol excess, *n* (%)	5 (20.8)	4 (28.6)	0.59
years >30 units/week, mean (SD)	15 (14)	20 (8.5)	0.54
Brain Imaging			
Time to acute imaging, days median (IQR)	3 (4)	4.5 (7)	0.16

Case–control comparison

Cases were compared with population-derived controls from The Irish LongituDinal Study of Ageing. The prevalence of syncope was 33% ($n = 103$) among stroke controls ($n = 312$), which was significantly lower than the prevalence of syncope among cases (66%, $n = 24$), $P = 0.0003$.

Controls for comparison were then selected based on the presence of prior stroke or TIA and the *absence* of prior syncope (Supplementary data Appendix 3 available in *Age and Ageing* online). Age and gender were similar for both groups; however, cases exhibited significantly greater drop in BP ($P = 0.01$) on standing and a greater rate of drop in BP as they achieved a nadir BP more quickly ($P < 0.005$).

Cases were also compared with the North Dublin Population Stroke Study, a cross-sectional study, and the findings are outlined in Supplementary data Appendix 3 available in *Age and Ageing* online.

Discussion

Apart from in the presence of severe large artery stenosis, it is a widely held that syncope and stroke do not overlap [5, 27]. Our findings confirm the clinical impression that syncopal symptoms occur at the onset of stroke or TIA in a small proportion of patients with no significant stenosis.

There were some limitations to our methodology. The head-up tilt assessment may induce hypotension in normal controls, which may confound our diagnosis. However, symptom reproduction was sought, not just a haemodynamic response [18]. A time-delay existed between stroke onset and dynamic blood pressure investigation to allow recovery of post-stroke autoregulation [16]. This delay may have introduced a recall bias regarding symptoms. Symptom reproduction on head-up tilt is somewhat flawed as it is based on subjective reporting; however, all subjects previously experienced hypotensive symptoms and thus were very familiar with them.

Borderzone regions vary in their location so BZI classification is challenging [24]. Previous studies have relied on standardised vascular perfusion maps [9, 26]. Because of the variability of borderzones between subjects we primarily used MR perfusion and MR angiography images to accurately identify cortical BZI. We feel our methods are reliable, individualised MR-perfusion-derived vascular territory maps were used to classify all but one of the cortical borderzone infarcts and accepted reference material was used to classify internal borderzone infarcts, we must concede that it is currently impossible to define borderzones with absolute certainty in living subjects.

To date established causes for BZI are cardiac asystole and severe carotid or MCA stenosis [28, 29]. However, pathological and radiological case series suggest that BZI accounts for 9.6–12.5% of all cerebral infarction [4, 9, 10]. Prevalence estimates of this magnitude suggest that an undetected cause may exist for BZI as the prevalence of severe carotid stenosis (>80%) is 0.2–4.1%, and that of severe MCA stenosis approximates to 1% (in Caucasians) [4]. In subjects with severe large artery disease, the yearly incidence of infarction is only 2–3% [8] thus another cause, such as hypotension, is likely to exist.

When cases were compared with controls, they exhibited a greater tendency for prior syncope ($P < 0.0003$) and greater magnitude of orthostatic hypotension ($P = 0.01$). Both suggest greater hypotensive tendencies and indeed acute borderzone infarction occurred in cases was 74% ($N = 14$ or 19). Unfortunately, infarct topography was unavailable in controls; however, several studies to date have estimated borderzone infarction at 9.6–12.5% in the general stroke population [4, 9, 10]).

When cases that exhibited borderzone infarction were compared with cases that did not, the former were significantly older. This finding persisted after controlling for potential confounders. The latter group in this comparison consisted of cases that exhibited either non-borderzone infarction or exhibited no acute infarction. Collapsing data in this way may be considered inappropriate; however, our aim was to define those with acute, hypotension-induced, borderzone infarction and distinguish them from those that did not experience such an infarction.

Evidence to date suggests that older patients exhibit a J-shaped relationship between their blood pressure and their risk of stroke [29]. Ovbiagele observed that hypotensive (<120 mmHg) post-stroke patients over 75 years have a relative risk for recurrent stroke of 1.29 (1.07–1.56) when compared with normotensive (130–140 mmHg) post-stroke patients over 75 years; a trend that was not observed in patients under 65 years [14]. Odden *et al.* studied a population of 2,300 older people (>65 years) and demonstrated that frail older hypertensive patients had lower mortality than frail older hypotensive patients, $P = 0.01$ [30]. These findings may be explained by hypotension induced-cardiovascular/stroke disease or may be merely associations, as hypotension may associate with frailty, which in turn leads to increased cardiovascular/stroke disease. This is the first study that demonstrates a link between older people, episodic hypotension and low-flow-vulnerable infarction in the absence of severe large artery disease. Possibly, individualised anti-hypertensive management may be appropriate in this group; however, future work is required to validate such a statement.

Key points

- 4.9% of patients suffered syncopal symptoms at onset of stroke or TIA.
- All had histories of orthostatic symptoms.
- 74% of those with MR confirmed stroke had infarcts in their borderzone.

Conflicts of interest

No author has a relevant conflict of interest.

Funding

The Study was supported through The Health Research Board Ireland (HRA/2009/208) and through the Lundbeck Neuroscience Bursary 2010.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

References

1. Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB *et al*. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 2009; 30: 2631–71.
2. Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ *et al*. Incidence and prognosis of syncope. N Engl J Med 2002; 347: 878–85.
3. Ganzeboom KS, Mairuhu G, Reitsma JB, Linzer M, Wieling Wvan Dijk N. Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35–60 years. J Cardiovasc Electrophysiol 2006; 17: 1172–6.
4. Bladin CF, Chambers BR. Frequency and pathogenesis of hemodynamic stroke. Stroke 1994; 25: 2179–82.
5. Dobkin BH. Orthostatic hypotension as a risk factor for symptomatic occlusive cerebrovascular disease. Neurology 1989; 39: 30–4.
6. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. Stroke 1995; 26: 14–20.
7. Rockman CB, Hoang H, Guo Y, Maldonado TS, Jacobowitz GRTalishinskiy T *et al*. The prevalence of carotid artery stenosis varies significantly by race. J Vasc Surg 2013; 57: 327–37.
8. Hennerici M, Hulsbomer HB, Hefter H, Lammerts D, Rautenberg W. Natural history of asymptomatic extracranial arterial disease. Results of a long-term prospective study. Brain 1987; 110(Pt 3): 777–91.
9. Yong SW, Bang OY, Lee PH, Li WY. Internal and cortical border-zone infarction: clinical and diffusion-weighted imaging features. Stroke 2006; 37: 841–6.
10. Jorgensen L, Torvik A. Ischaemic cerebrovascular diseases in an autopsy series. 2. Prevalence, location, pathogenesis, and clinical course of cerebral infarcts. J Neurol Sci 1969; 9: 285–320.
11. Lang EW, Daffertshofer M, Daffertshofer A, Wirth SB, Chesnut RM, Hennerici M. Variability of vascular territory in stroke. Pitfalls and failure of stroke pattern interpretation. Stroke 1995; 26: 942–5.
12. Ruland S, Aiyagari V. Cerebral autoregulation and blood pressure lowering. Hypertension 2007; 49: 977–8.
13. Verwoert GC, Mattace-Raso FU, Hofman A, Heeringa J, Stricker BH, Breteler MM *et al*. Orthostatic hypotension and risk of cardiovascular disease in elderly people: the Rotterdam study. J Am Geriatr Soc 2008; 56: 1816–20.
14. Ovbiagele B. Low-normal systolic blood pressure and secondary stroke risk. J Stroke Cerebrovasc Dis 2013; 22: 633–8.
15. Eames PJ, Blake MJ, Dawson SL, Panerai RB, Potter JF. Dynamic cerebral autoregulation and beat to beat blood pressure control are impaired in acute ischaemic stroke. J Neurol Neurosurg Psychiatry 2002; 72: 467–72.
16. Brodie FG, Panerai RB, Robinson TG. Dynamic cerebral autoregulation is impaired acutely following inschaemic stroke but demonstrates early recovery. Cerebrovasc Dis 2009; 27(Suppl 6): 1–241.
17. Mitro P, Kirsch P, Valocik G, Murin P. A prospective study of the standardized diagnostic evaluation of syncope. Europace 2011; 13: 566–71.
18. Parry SW, Gray JC, Newton JL, Reeve P, O'Shea D, Kenny RA. 'Front-loaded' head-up tilt table testing: validation of a rapid first line nitrate-provoked tilt protocol for the diagnosis of vasovagal syncope. Age Ageing 2008; 37: 411–5.
19. Parry SW, Reeve P, Lawson J, Shaw FE, Davison J, Norton M *et al*. The Newcastle protocols 2008: an update on head-up tilt table testing and the management of vasovagal syncope and related disorders. Heart 2009; 95: 416–20.
20. Raviele A, Menozzi C, Brignole M, Gasparini G, Alboni P, Musso G *et al*. Value of head-up tilt testing potentiated with sublingual nitroglycerin to assess the origin of unexplained syncope. Am J Cardiol 1995; 76: 267–72.
21. Kearney PM, Cronin H, O'Regan C, Kamiya Y, Savva GM, Whelan B *et al*. Cohort profile: the Irish Longitudinal Study on Ageing. Int J Epidemiol 2011; 40: 877–84.
22. Sheldon RS, Amuah JE, Connolly SJ, Rose S, Morillo CA, Talajic M *et al*. Design and use of a quantitative scale for measuring presyncope. J Cardiovasc Electrophysiol 2009; 20: 888–93.
23. Strandness DE. Duplex Scanning in Vascular Disorders. Extracranial Arterial Disease. New York: Raven Press, 1992.
24. van der Zwan A, Hillen B, Tulleken CA, Dujovny M, Dragovic L. Variability of the territories of the major cerebral arteries. J Neurosurg 1992; 77: 927–40.
25. Christensen S, Calamante F, Hjort N, Wu O, Blankholm AD, Desmond P *et al*. Inferring origin of vascular supply from tracer arrival timing patterns using bolus tracking MRI. J Magn Reson Imaging 2008; 27: 1371–81.
26. Damasio H. A computed tomographic guide to the identification of cerebral vascular territories. Arch Neurol 1983; 40: 138–42.
27. Ferro JM, Falcao I, Rodrigues G, Canhao P, Melo TP, Oliveira V *et al*. Diagnosis of transient ischemic attack by the nonneurologist. A validation study. Stroke 1996; 27: 2225–9.
28. Bladin CF, Chambers BR. Clinical features, pathogenesis, and computed tomographic characteristics of internal watershed infarction. Stroke. 1993; 24: 1925–32.
29. Belden JR, Caplan LR, Pessin MS, Kwan E. Mechanisms and clinical features of posterior border-zone infarcts. Neurology 1999; 53: 1312–8.
30. Odden Mc PC. Rethinking the association of high blood pressure with mortality in elderly adults: The impact of frailty. Arch Intern Med 2012; 172: 1162–8.

Received 13 August 2014; accepted in revised form 28 November 2014