*Original Article*

# Migraine Is Associated with Enhanced Arterial Stiffness

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**Migraine is a common subtype of headache. Epidemiological studies have revealed that migraine could be an independent risk factor for ischemic stroke even in elderly subjects. Arterial stiffness is one of the major pathophysiological bases of stroke. In the present study, we cross-sectionally investigated the possible relationship between migraine and arterial stiffness in community-dwelling subjects. The study subjects were independently recruited from two sources (Group A, $n$=134, 68±5 years; Group B, $n$=138, 68±7 years). Augmentation index (AI), the ratio of augmented pressure by the reflection pressure wave to the pulse pressure, was obtained from the radial arterial waveform as an index of arterial stiffness. Brachial blood pressure was also measured simultaneously. Migraine was diagnosed using a previously validated questionnaire. The prevalence of migraine was 5.2% (Group A) and 16.7% (Group B). Subjects with migraine had higher radial AI in both Group A (migraine, 101±15%; other headache, 88±12%; no headache, 86±12%, $p$=0.003) and Group B (95±11%, 90±11%, 91±14%, $p$=0.058). Multiple linear regression analysis revealed that migraine was an independent determinant of AI ($\beta$=0.154, $p$=0.002) after adjustment for other confounding factors: age ($\beta$=–0.024, $p$=0.654); sex ($\beta$=0.141, $p$=0.069); body height ($\beta$=–0.215, $p$=0.005); systolic blood pressure ($\beta$=0.174, $p$=0.001); medication for hypertension, hyperlipidemia, and diabetes mellitus ($\beta$=–0.014, $p$=0.787); and heart rate ($\beta$=–0.539, $p$<0.001). In a separate analysis by sex, migraine was also a significant determinant for AI (male, $\beta$=0.246, $p$=0.019; female, $\beta$=0.159, $p$=0.008). Migraine in the elderly could be a clinical manifestation of enhanced arterial stiffness. (*Hypertens Res* 2007; 30: 577–583)**

***Key Words*: migraine, arterial stiffness, elderly, augmentation index**

## Introduction

Migraine is a common subtype of headache with specific characteristics including unilaterality, throbbing pain, photophobia or phonophobia, and nausea or vomiting (*1*). Several large-scale epidemiological studies have revealed that the prevalence of migraine ranges from 6 to 13% in the general population (*2–6*). The prevalence is approximately three to four times higher in females, and is highest among women aged in their thirties and forties (*7*, *8*). Migraine is also commonly observed in the elderly (*8*, *9*).

Headaches, in particular migraine, are known to be an independent risk factor for ischemic stroke (*4–6*, *10–16*). The association between migraine and stroke is more prominent in young women, particularly in those taking oral contraceptives (*11–14*). However, in the middle-aged to elderly of either sex, the association is controversial. Several epidemiological studies have indicated that severe headache and migraine should be considered risk factors for future stroke prior to the age of

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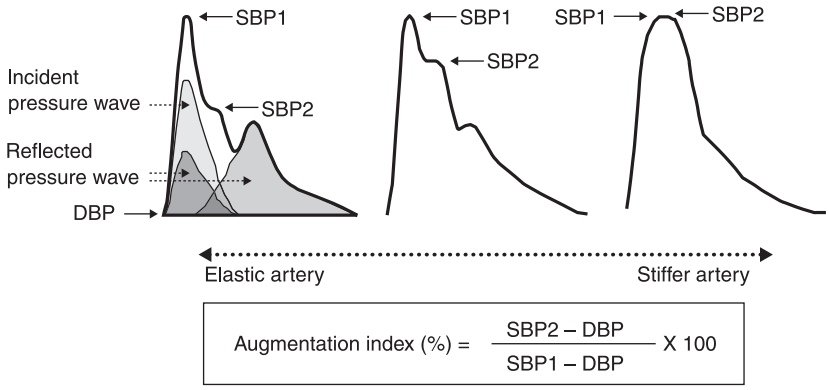


**Fig. 1.** *Tracing of radial arterial waveform. The radial augmentation index was calculated as follows: (second peak of SBP [SBP2] − DBP)/(first peak of SBP [SBP1] − DBP) × 100 (%). SBP, systolic blood pressure; DBP, diastolic blood pressure.*

70 (*5*, *15*). In contrast, no significant association was found in a case-control study with elderly subjects aged 60 or older (*17*).

The pathophysiological mechanism by which migraine may lead to ischemic stroke is unclear. Kruit *et al*. (*18*) showed that a combination of migraine attack–related hypoperfusion and embolism could be an underlying mechanism of infarction frequently observed in the posterior circulation territory in migraine patients. However, during a migraine attack, vascular changes are not limited to the cranial circulation. Iversen *et al*. (*19*) reported that migraine attacks are accompanied by generalized peripheral vasoconstriction. Furthermore, migraine patients have displayed increased diameter and/or decreased distensibility of cranial and peripheral blood vessels even in the interictal period (*20*). These observations indicate the importance of vascular properties in the link between migraine and ischemic stroke.

Recently, several parameters have been introduced to assess vascular stiffness (*21*). Augmentation index (AI) is a parameter of arterial stiffness that can be obtained from the central arterial waveform as the ratio of augmentation pressure by the reflection pressure wave to the pulse pressure. It has been reported that central AI is closely related to several risk factors for atherosclerosis (*22*) and future cardiovascular events (*23*, *24*). AI can also be obtained from the radial arterial waveform (*25*). Since radial AI is closely associated with aortic AI (*25*), radial AI itself could provide information on vascular properties.

In the present study, we measured radial AI as an index of arterial stiffness to investigate the possible association between migraine and enhanced arterial stiffness in community-dwelling elderly subjects.

## Methods

### Study Subjects

The study subjects were independently recruited from two sources: attendees of a public exercise seminar held by the city of Matsuyama ($n$=134, Group A), the largest city in Japan's Ehime Prefecture; and participants of a medical check-up program at Ehime University Hospital ($n$=138, Group B). These cross-sectional investigations were carried out as parts of the Shimanami Health Promoting Program (J-SHIPP study), a longitudinal study evaluating factors related to cardiovascular disease, dementia, and death (*26–29*). The exercise seminar was held twice a week for a 9-month period (from July 2002 to March 2003). Participants in the seminar ($n$=208) were recruited from among the general residents of Matsuyama City. Measurement of blood pressure (BP) and AI was carried out before exercise training during July 2002 to January 2003. The number of participants who gave written informed consent and completed all measurements was 134 (67.0%). None of these subjects had a known history or symptoms of cerebrovascular diseases. The medical check-up, called the "anti-aging dock," which is designed specifically for evaluating aging-related disorders, was also carried out among general residents of Ehime Prefecture. Among the participants from March to August 2006 ($n$=185), those who provided informed consent ($n$=161, 87.0%) and were free from any history or symptoms of cerebrovascular disease ($n$=138, 74.6%) were enrolled in this analysis. The series of studies was approved by the ethics committee of Ehime University School of Medicine, and all participants gave written informed consent to participate in the procedure.

### Measurement of BP and AI

Brachial BP and radial arterial waveform were measured simultaneously, and radial AI was calculated from the waveform using a semi-automatic waveform analyzer (HEM-9000AI, OMRON HEALTHCARE Co., Ltd., Kyoto, Japan). In brief, the arterial waveform was non-invasively obtained from the left radial artery by tonometric tracing. The tonometric sensor consisted of 40 arrayed microtransducers within 8 mm, and the most appropriate one was automatically selected

**Table 1. Baseline Characteristics of Study Subjects**

| | Study group | | |
|---|---|---|---|
| | A (134) | B (138) | *p* |
| Age (years) | 68±5 | 68±7 | 0.901 |
| Sex (male/female) | 16/118 | 56/82 | <0.001 |
| Body height (cm) | 154±7 | 158±9 | <0.001 |
| Body weight (kg) | 54±9 | 58±12 | 0.001 |
| Systolic blood pressure (mmHg) | 139±20 | 144±19 | 0.038 |
| Diastolic blood pressure (mmHg) | 78±11 | 81±12 | 0.031 |
| Medication (%) | | | |
| Hypertension | 22.4 | 31.2 | 0.132 |
| Hyperlipidemia | 9.7 | 20.3 | 0.017 |
| Diabetes mellitus | 2.2 | 0.0 | 0.118 |
| Heart rate (beats/min) | 73±10 | 68±12 | <0.001 |
| Radial augmentation index (%) | 88±13 | 91±12 | 0.021 |
| History of cardiovascular disease (*n*) | 2 | 9 | 0.060 |

Cardiovascular disease consisted of 1 case of myocardial infarction, 8 cases of angina pectoris and 2 cases of atrial fibrillation.

**Table 2. Prevalence and Frequency of Headache**

| | Study group | |
|---|---|---|
| | A (134) | B (138) |
| Subjects with headache (*n*) | | |
| Migraine | 7 | 23 |
| Other headache | 40 | 62 |
| Response to ID Migraine questionnaire items (*n*) | | |
| Nausea or vomiting | 7 | 18 |
| Disability of working, study or other activity | 0 | 3 |
| Photophobia | 1 | 5 |
| Frequency of headache (*n*) | | |
| Several time a year | 29 | 26 |
| 1 or 2 times a month | 14 | 36 |
| 1 or 2 times a week | 2 | 14 |
| 3 or 4 times a week | 2 | 4 |
| Daily or nearly daily | 0 | 5 |

for the optimal observation. The sensor head's hold-down pressure was also automatically adjusted for each subject. Waveforms were measured for 30 s and digitized at 500 Hz. Brachial BP was simultaneously measured in the right upper arm by the cuff-oscillometric method. All measurements were carried out with subjects in the sitting position after at least 5 min of rest. The exercise seminar employed a prototype analyzer that is identical to HEM-9000AI except that it uses a laptop computer for the acquisition and analysis of waveforms. Brachial BP was measured using another cuff-oscillometric device (HEM-907, OMRON HEALTHCARE Co., Ltd.).

Radial AI was calculated as the ratio of late systolic pressure to pulse pressure: (late systolic BP [SBP2] – diastolic BP [DBP])/(systolic BP [SBP1] – DBP) ×100 (%) (Fig. 1), which was automatically calculated using a fourth-order differential equation for radial arterial waveform (HEM-9000AI) (*30*). The intra- and inter-measurement variability of radial AI was 4.6% and 3.4%, respectively. A nomogram of radial AI and its correlation with aortic AI has been described elsewhere (*25*).

## Evaluation of Migraine

Episodes of migraine were evaluated using ID Migraine, a self-administered questionnaire (*31*). This questionnaire consists of three questions on disability (How many days did your headache limit your ability to work, study, or do what you needed to do?), nausea (You felt nauseated or vomiting during migraine attack), and photophobia (Light bothered you during migraine attack [a lot more than when you don't have headaches]). The validity and reproducibility of ID Migraine has been confirmed previously using the International Headache Society–based migraine diagnosis as a reference (*31*). Cross-validation over sex, age, presence of other comorbid types of headache, or previous diagnosis of migraine has also been performed (*31*). Subjects with any of these three complaints were considered to have migraine.

## Statistical Analysis

Values are expressed as means±SD unless otherwise specified. All statistical analyses were performed using the SPSS software package (SPSS Inc., Chicago, USA). The differences among categories were analyzed using one-way analysis of variance (ANOVA). Differences in prevalence or frequency were analyzed by $\chi^2$ test. Factors independently associated with AI were assessed using multiple linear regres-

**Table 3. Clinical Characteristics of Subjects with Migraine**

| | Migraine | Other headache | No headache | *p* |
|---|---|---|---|---|
| Study group A | | | | |
| *n* | 7 | 40 | 87 | |
| Age (years) | 67±3 | 68±5 | 68±6 | 0.559 |
| Sex (female %) | 100.0 | 87.5 | 87.4 | 0.402 |
| Body height (cm) | 151±4 | 154±7 | 154±7 | 0.239 |
| Body weight (kg) | 51±7 | 54±7 | 55±9 | 0.372 |
| Systolic blood pressure (mmHg) | 129±10 | 140±20 | 139±21 | 0.171 |
| Medication (%) | 14.3 | 40.0 | 26.4 | 0.674 |
| Heart rate (beats/min) | 72±10 | 73±11 | 74±10 | 0.637 |
| Augmentation index (%) | 101±15 | 88±12 | 86±12 | 0.003 |
| Study group B | | | | |
| *n* | 23 | 62 | 53 | |
| Age (years) | 66±10 | 68±7 | 69±6 | 0.180 |
| Sex (female %) | 91.3 | 56.5 | 49.1 | <0.001 |
| Body height (cm) | 157±6 | 157±8 | 159±9 | 0.414 |
| Body weight (kg) | 55±7 | 57±12 | 61±12 | 0.157 |
| Systolic blood pressure (mmHg) | 144±23 | 143±19 | 145±19 | 0.916 |
| Medication (%) | 26.1 | 41.9 | 47.2 | 0.163 |
| Heart rate (beats/min) | 68±12 | 70±11 | 66±12 | 0.980 |
| Augmentation index (%) | 95±11 | 90±11 | 91±14 | 0.058 |
| Combined | | | | |
| *n* | 30 | 102 | 140 | |
| Age (years) | 66±9 | 68±6 | 68±6 | 0.130 |
| Sex (female %) | 93.3 | 68.6 | 72.9 | 0.005 |
| Body height (cm) | 155±6 | 156±8 | 156±8 | 0.661 |
| Body weight (kg) | 54±8 | 56±11 | 57±11 | 0.268 |
| Systolic blood pressure (mmHg) | 141±21 | 142±19 | 141±20 | 0.823 |
| Medication (%) | 23.3 | 41.2 | 34.3 | 0.160 |
| Heart rate (beats/min) | 69±12 | 72±11 | 71±11 | 0.390 |
| Augmentation index (%) | 97±12 | 89±11 | 88±13 | <0.001 |

Values are mean±SD. Statistical significance was assessed between subjects with and without migraine. Total number of subjects under treatment of hypertension, hyperlipidemia, and diabetes mellitus is described as frequency.

sion analysis. Analysis of covariance was used to obtain adjusted AI and its group differences. A $p$ value of less than 0.05 was considered statistically significant.

## Results

Baseline anthropometric and clinical characteristics of the two study groups are shown in Table 1. Two subjects in Group A had a history of myocardial infarction and angina pectoris. Nine subjects in Group B had a history of several cardiovascular diseases; 7 with angina pectoris and 2 with atrial fibrillation. There were no significant differences in age or use of antihypertensive medication. The proportion of male subjects was higher in Group B. Radial AI was significantly higher in Group B.

The prevalence of migraine is summarized in Table 2. In Group A, 47 subjects (35.1%) had headaches, and 7 (5.2%) were diagnosed as having migraine by the ID Migraine questionnaire. The prevalence of headaches (61.6%, $p<0.001$) and the proportion of migraine subjects (16.7%, $p=0.003$) were significantly higher in Group B. Among the three items of the ID Migraine questionnaire, nausea was the most frequently observed complaint. The number of subjects reporting disability in daily work was quite small, which may reflect Japanese cultural traits. The majority of migraine subjects (79.5%) had headache attacks less than once or twice a month. This frequency was not different between the subtypes of headache (83.4% for migraine, 78.4% for other).

Table 3 shows the anthropometric and clinical characteristics of the subjects with migraine. In both study groups, migraine subjects had higher AI, while other major confounding factors including age, body height, BP, and heart rate (HR) were not different. Combined analysis further revealed a higher AI in subjects with migraine. To further clarify the

**Table 4. Multiple Liner Regression Analysis for Augmentation Index**

| | Unstandardized coefficient (95% CI) | Standardized coefficient | *p* |
|---|---|---|---|
| Age (years) | −0.046 (−0.245 to 0.154) | −0.024 | 0.654 |
| Sex (female) | 3.977 (−0.319 to 8.272) | 0.141 | 0.069 |
| Body height (cm) | −0.334 (−0.566 to −0.102) | −0.215 | 0.005 |
| Systolic blood pressure (mmHg) | 0.1109 (0.046 to 0.173) | 0.174 | 0.001 |
| Medications | −0.352 (−2.923 to 2.218) | −0.014 | 0.787 |
| Heart rate (beats/min) | −0.597 (−0.704 to −0.490) | −0.539 | <0.001 |
| Migraine (yes) | 6.095 (2.239 to 9951) | 0.154 | 0.002 |

CI, confidence interval.

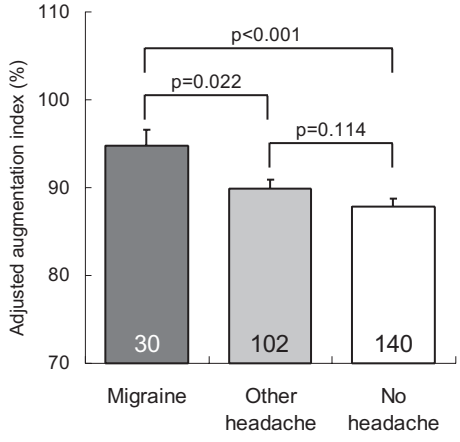


**Fig. 2.** *Migraine and adjusted augmentation index. Adjusted augmentation indices are represented as means±SEM. Adjusted confounding factors are age, sex, body height, systolic blood pressure, heart rate, and medications. The differences among groups were assessed by analysis of covariance (ANCOVA). The number of subjects in each group is shown in the column.*

relationship between migraine and AI, multiple linear regression analysis was carried out (Table 4). Short stature could be an independent determinant for AI by affecting the arrival time of wave reflection. It is also known that higher HR reduces AI by shortening the cardiac ejection time. However, migraine was an independent determinant of AI after adjustment for these confounding factors. Adjusted AI and its group differences are illustrated in Fig. 2.

To eliminate the effect of medications, multiple linear regression analysis was carried out again in the subjects not taking any medications ($n$=175). The relationship between AI and migraine remained statistically significant ($\beta$=0.204, $p$=0.002) along with body height ($\beta$=−0.263, $p$=0.011) and HR ($\beta$=−0.44, $p$<0.001). After further exclusion of 3 subjects with a history of cardiac disease ($n$=172), migraine was still a significant determinant for AI ($\beta$=0.202, $p$=0.002). Furthermore, regression analysis was separately performed in each sex because of the higher prevalence of migraine in female subjects (Table 3). The presence of migraine was an independent determinant of AI in both male ($\beta$=0.246, $p$=0.009) and female ($\beta$=0.159, $p$=0.008) subjects.

## Discussion

The present study revealed that subjects with migraine had greater arterial stiffness than migraine-free subjects in the two study groups independently recruited from community residents. This association was independent of other confounding factors including age, sex, body height, BP, and HR. These observations suggest the possibility that migraine could be a manifestation of arterial stiffness in the elderly.

Serotonin (5-HT) is a key mediator of migraine (*32*). It is known that stimulation of the 5-HT1 receptor leads to cranial vasoconstriction, peripheral neuronal inhibition, and inhibition of transmission through second-order neurons of the trigeminocervical complex, and thus alleviates migraine and associated symptoms (*33*). Most studies have shown that the systemic 5-HT content of platelets in migraine patients is lower than that in healthy controls (*34*). It has also been reported that plasma norepinephrine levels are significantly lower in migraine subjects (*35*). Since sympathetic nervous activity regulates AI by changing arterial tone, the observations in this study may conflict with the autonomic and humoral properties underlying migraine. However, arterial stiffness is also determined by vessel wall structure. de Hoon *et al*. (*20*) have shown higher intima-media thickness in the brachial artery in middle-aged migraine patients. Elevated serum elastase activity has also been reported in migraine subjects (*36*). Abnormalities in the extracellular matrix are a possible explanation for the relationship between migraine and enhanced AI. Measurement of AI during migraine attacks may lead to a better understanding of the observed relationship.

Even in elderly subjects, migraine could be an independent risk factor for ischemic stroke. However, the relationship was weaker in the elderly than in young subjects despite the higher incidence of stroke in the former (*5*). Enhanced arterial stiffness is known to be a potent risk factor for stroke in the

elderly, after adjustment for other conventional risk factors (*37*, *38*). A significant relationship between AI and cardiovascular events including stroke has also been reported (*39*). In younger subjects, decreased regional cerebral blood flow, neurogenic inflammation, and platelet activation have been proposed as pathophysiological mechanisms of migraine-related stroke (*40–42*). Different mechanisms, such as enhanced arterial stiffness, may be involved in the link between migraine and late-onset stroke in the elderly.

Medications from a broad range of classes have been demonstrated to be effective in preventing migraine attack (*33*, *43*). Several antihypertensive drugs, such as β-blockers, calcium-channel antagonists, and angiotensin-converting enzyme inhibitors, also have preventive effects. In this study, approximately 30% of subjects were receiving antihypertensive treatment. Accordingly, the possibility could not be excluded that the medication might affect the assessment of vascular properties, as well as the diagnosis of migraine. Additionally, β-blockade increases AI mainly by reducing HR. Ergotamine, a vasoconstrictor for migraine treatment, also reduces arterial distensibility (*44*) and increases AI (*45*). However, the observed association between migraine and enhanced AI was still significant after adjustment for HR. The association was also significant in subjects without medication.

We used ID Migraine as a questionnaire to diagnose migraine. Although the questionnaire's validity and reproducibility were verified previously, it cannot differentiate migraine with aura from that without aura. Migraine can be divided into two major subtypes according to the existence or absence of aura (*1*). Aura is a combination of various reversible visual symptoms (flickering lights, spots or lines, loss of vision), sensory symptoms (pins and needles, numbness), and dysphasic speech disturbance that usually occur just before or at the onset of migraine headache. Several reports have shown that migraine with aura carries a higher risk for ischemic stroke than simple migraine (*13*). Further study is required to determine whether or not there is a subtype-specific association between migraine and enhanced arterial stiffness.

We observed consistent findings between subjects recruited from two distinct populations. Replication of the findings could strengthen our hypothesis that migraine is associated with enhanced arterial stiffness in elderly subjects. However, the prevalence of migraine was significantly different between the two populations, which could be due to several undefined biases in the study subjects. Accordingly, before it is appropriate to generalize about the observation in this study further confirmation would be necessary in a larger population adjusted for other potential confounding factors.

In summary, the present study showed that migraine is independently associated with enhanced arterial stiffness in community-dwelling elderly subjects, indicating the pathophysiological importance of the vasculature in linking migraine and stroke in the elderly. Migraine in the elderly requires careful attention as a clinical risk factor for future cardiovascular events.

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## References

1. Headache Classification Committee of the International Headache Society: The International Classification of Headache Disorders. *Cephalalgia* 2004; **24**: 1–160.
2. Scher AI, Terwindt GM, Picavet HS, Verschuren WM, Ferrari MD, Launer LJ: Cardiovascular risk factors and migraine: the GEM population-based study. *Neurology* 2005; **64**: 614–620.
3. Takeshima T, Ishizaki K, Fukuhara Y, *et al*: Population-based door-to-door survey of migraine in Japan: the Daisen study. *Headache* 2004; **44**: 8–19.
4. Kurth T, Slomke MA, Kase CS, *et al*: Migraine, headache, and the risk of stroke in women: a prospective study. *Neurology* 2005; **64**: 1020–1026.
5. Merikangas KR, Fenton BT, Cheng SH, Stolar MJ, Risch N: Association between migraine and stroke in a large-scale epidemiological study of the United States. *Arch Neurol* 1997; **54**: 362–368.
6. Stang PE, Carson AP, Rose KM, *et al*: Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study. *Neurology* 2005; **64**: 1573–1577.
7. Sakai F, Igarashi H: Prevalence of migraine in Japan: a nationwide survey. *Cephalalgia* 1997; **17**: 15–22.
8. Rasmussen BK, Jensen R, Schroll M, Olesen J: Epidemiology of headache in a general population—a prevalence study. *J Clin Epidemiol* 1991; **44**: 1147–1157.
9. Camarda R, Monastero R: Prevalence of primary headaches in Italian elderly: preliminary data from the Zabut Aging Project. *Neurol Sci* 2003; **24**: S122–S124.
10. Tzourio C, Iglesias S, Hubert JB, *et al*: Migraine and risk of ischaemic stroke: a case-control study. *BMJ* 1993; **307**: 289–292.
11. Etminan M, Takkouche B, Isorna FC, Samii A: Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *BMJ* 2005; **330**: 63–65.
12. Carolei A, Marini C, De Matteis G, The Italian National Research Council Study Group on Stroke in the Young: History of migraine and risk of cerebral ischaemia in young adults. *Lancet* 1996; **347**: 1503–1506.
13. Tzourio C, Tehindrazanarivelo A, Iglesias S, *et al*: Case-control study of migraine and risk of ischaemic stroke in young women. *BMJ* 1995; **310**: 830–833.
14. Chang CL, Donaghy M, Poulter N: Migraine and stroke in young women: case-control study. The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *BMJ* 1999; **318**: 13–18.
15. Jousilahti P, Tuomilehto J, Rastenyte D, Vartiainen E: Headache and the risk of stroke: a prospective observational cohort study among 35,056 Finnish men and women. *Arch*

*Intern Med* 2003; **163**: 1058–1062.
16. Buring JE, Hebert P, Romero J, *et al*: Migraine and subsequent risk of stroke in the Physicians' Health Study. *Arch Neurol* 1995; **52**: 129–134.
17. Mosek A, Marom R, Korczyn AD, Bornstein N: A history of migraine is not a risk factor to develop an ischemic stroke in the elderly. *Headache* 2001; **41**: 399–401.
18. Kruit MC, Launer LJ, Ferrari MD, van Buchem MA: Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study. *Brain* 2005; **128**: 2068–2077.
19. Iversen HK, Nielsen TH, Olesen J, Tfelt-Hansen P: Arterial responses during migraine headache. *Lancet* 1990; **336**: 837–839.
20. de Hoon JN, Willigers JM, Troost J, Struijker-Boudier HA, van Bortel LM: Cranial and peripheral interictal vascular changes in migraine patients. *Cephalalgia* 2003; **23**: 96–104.
21. Nichols WW: Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. *Am J Hypertens* 2005; **18**: 3S–10S.
22. Izzo JL Jr: Arterial stiffness and the systolic hypertension syndrome. *Curr Opin Cardiol* 2004; **19**: 341–352.
23. London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME: Arterial wave reflections and survival in end-stage renal failure. *Hypertension* 2001; **38**: 434–438.
24. Weber T, Auer J, O'Rourke MF, *et al*: Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation* 2004; **109**: 184–189.
25. Kohara K, Tabara Y, Oshiumi A, Miyawaki Y, Kobayashi T, Miki T: Radial augmentation index: a useful and easily obtainable parameter for vascular aging. *Am J Hypertens* 2005; **18**: 11S–14S.
26. Tachibana R, Tabara Y, Kondo I, Miki T, Kohara K: Home blood pressure is a better predictor of carotid atherosclerosis than office blood pressure in community-dwelling subjects. *Hypertens Res* 2004; **27**: 633–639.
27. Tabara Y, Tachibana-Iimori R, Yamamoto M, *et al*: Hypotension associated with prone body position: a possible overlooked postural hypotension. *Hypertens Res* 2005; **28**: 741–746.
28. Tabara Y, Nakura J, Kondo I, Miki T, Kohara K: Orthostatic systolic hypotension and the reflection pressure wave. *Hypertens Res* 2005; **28**: 537–543.
29. Yamamoto M, Jin JJ, Wu Z, *et al*: Interaction between serotonin 2A receptor and endothelin-1 variants in association with hypertension in Japanese. *Hypertens Res* 2006; **29**: 227–232.
30. Takazawa K, Tanaka N, Takeda K, Kurosu F, Ibukiyama C: Underestimation of vasodilator effects of nitroglycerin by upper limb blood pressure. *Hypertension* 1995; **26**: 520–523.
31. Lipton RB, Dodick D, Sadovsky R, *et al*: A self-administered screener for migraine in primary care: the ID Migraine validation study. *Neurology* 2003; **61**: 375–382.
32. Ferrari MD, Saxena PR: On serotonin and migraine: a clinical and pharmacological review. *Cephalalgia* 1993; **13**: 151–165.
33. Goadsby PJ, Lipton RB, Ferrari MD: Migraine—current understanding and treatment. *N Engl J Med* 2002; **346**: 257–270.
34. Evers S, Quibeldey F, Grotemeyer KH, Suhr B, Husstedt IW: Dynamic changes of cognitive habituation and serotonin metabolism during the migraine interval. *Cephalalgia* 1999; **19**: 485–491.
35. Peroutka SJ: Migraine: a chronic sympathetic nervous system disorder. *Headache* 2004; **44**: 53–64.
36. Tzourio C, El Amrani M, Robert L, Alperovitch A: Serum elastase activity is elevated in migraine. *Ann Neurol* 2000; **47**: 648–651.
37. Mattace-Raso FU, van der Cammen TJ, Hofman A, *et al*: Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation* 2006; **113**: 657–663.
38. Tsivgoulis G, Vemmos K, Papamichael C, *et al*: Common carotid arterial stiffness and the risk of ischaemic stroke. *Eur J Neurol* 2006; **13**: 475–481.
39. Chirinos JA, Zambrano JP, Chakko S, *et al*: Aortic pressure augmentation predicts adverse cardiovascular events in patients with established coronary artery disease. *Hypertension* 2005; **45**: 980–985.
40. Friberg L, Olesen J, Lassen NA, Olsen TS, Karle A: Cerebral oxygen extraction, oxygen consumption, and regional cerebral blood flow during the aura phase of migraine. *Stroke* 1994; **25**: 974–979.
41. Crassard I, Conard J, Bousser MG: Migraine and haemostasis. *Cephalalgia* 2001; **21**: 630–636.
42. Waeber C, Moskowitz MA: Migraine as an inflammatory disorder. *Neurology* 2005; **64**: S9–S15.
43. Rapoport AM, Bigal ME: Migraine preventive therapy: current and emerging treatment options. *Neurol Sci* 2005; **26**: s111–s120.
44. Barenbrock M, Spieker C, Witta J, *et al*: Reduced distensibility of the common carotid artery in patients treated with ergotamine. *Hypertension* 1996; **28**: 115–119.
45. Vanmolkot FH, de Hoon JN: Acute effects of sumatriptan on aortic blood pressure, stiffness, and pressure waveform. *Clin Pharmacol Ther* 2006; **80**: 85–94.