Vascular retinal, neuroimaging and ultrasonographic markers of lacunar infarcts

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Background **Lacunar infarcts may be caused by macro- or microvascular disease due to several mechanisms.**

Aim **This study aims to demonstrate that retinal vascular disturbances in patients with lacunar infarcts associated with neuroimaging and ultrasound markers can help to identify small-vessel disease.**

Methods **Prospective ambulatory study of patients with ischaemic stroke and a control group. A retinographic study was performed by 20° bilateral optic disc stereophotography and 50° bilateral optic fundus retinography. Microangiopathy was evaluated as the presence of nonparenchymal vascular affectation and retinopathy as at least one retinal disturbance. Ultrasonographic study evaluated carotid disorder parameters and the mean pulsatility index. The MRI protocol included T1-weighted, T2-weighted, DP-weighted and FLAIR.**

Results **We included 156 nonlacunar infarcts, 39 lacunar infarcts and 50 controls. Microangiopathy was more frequent in hypertensive (62·6% vs. 35·7%, $P<0·0001$) and vascular retinopathy in diabetic patients (11·7% vs. 3·8%, $P=0·039$). Microangiopathy (97·4% vs. 41·1%, $P<0·0001$) and leukoaraiosis (94·4% vs. 50·3%, $P<0·0001$) were more frequent and the mean pulsatility index was higher ($1·9\pm0·2$ vs. $1·4\pm0·5$, $P<0·0001$) in patients with lacunar infarcts. Lacunar infarcts were independently associated with microangiopathy (odds ratio 12·81, 95% CI 1·52–107·86), the mean pulsatility index (odds ratio 8·13, 95% CI 1·17–56·20) and leukoaraiosis (odds ratio 3·45, 95% CI 1·09–10·93). The presence of leukoaraiosis plus microangiopathy was associated with lacunar infarcts with odds ratio 21·31 (95% CI 8·74–51·93).**

Conclusions **The association of retinal microangiopathy (but not vascular retinopathy) and leukoaraiosis is linked to small-vessel disease and may be a useful marker of lacunar infarcts not secondary to a macrovascular lesion.**

Key words: lacunar infarct, leukoaraiosis, pulsatility index, retinal microangiopathy

Lacunar infarcts represent a quarter of all ischaemic strokes (1), and although they are generally considered as a good outcome, in one-third of the cases, they cause neurological disability (2). Despite advances in the understanding of cerebrovascular disease, the aetiology of small-vessel disease is, in many cases, unknown (3).

Embryological, anatomical and physiological similarities between brain and retinal circulation (4, 5) offer an excellent opportunity to study the contribution of the microcirculation in cerebrovascular disease. Studies in the last two decades demonstrated a major relationship between vascular retinopathy and cardiovascular mortality (6), coronary heart disease in women (7), elderly and high blood pressure (8) and cognitive impairment (9); however, this relationship was not demonstrated with retinal vascular microangiopathy without retinopathy. Population studies have found that both vascular microangiopathy and retinopathy are predictors of ischaemic stroke (10–13). One population-based study (13) and a recent prospective study in cortical and lacunar infarcts showed no association with the presence of retinopathy (14).

The relationship between vascular retinal disturbances and the presence of leukoaraiosis and silent lacunar infarcts in magnetic resonance, with or without clinical manifestations, has been demonstrated, although with no consistent results (11, 13, 15). Furthermore, ultrasonographic disturbances are markers of small-vessel disease (16), but their relationship with retinal microangiopathy has not been demonstrated.

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The objective of this study is to demonstrate that the retinal vascular disturbances in patients with lacunar infarcts in association with neuroimaging and ultrasound markers can help to identify patients with small-vessel disease.

Patients and methods

Study population and patient characteristics

We included all patients who attended the first outpatient consultation post the first hospitalisation for ischaemic stroke from February to September 2007 (96 ± 47 days after discharge); 50 control subjects were randomly selected from patients who had no known cardiovascular disease or stroke. All patients had been admitted to the stroke unit and treated by trained neurologists.

A total of 215 patients with ischaemic stroke were included. Six patients were excluded due to stroke severity, eight patients refused to participate in the study and six patients did not complete the study.

Clinical variables

Previous history of vascular risk factors and functional status determined by modified Rankin scales were recorded. Previous history of hypertension (defined as evidence of at least two blood pressure measurements $>140/90$ mmHg recorded on different days, a physician's diagnosis or use of antihypertensive treatment), diabetes (fasting serum glucose level >120 mg/dl, a physician's diagnosis or use of diabetic medication), hyperlipidaemia (serum cholesterol concentration >200 mg/dl or serum triglyceride concentration >200 mg/dl, a physician's diagnosis or use of medication), heart disease (a physician's diagnosis or use of medication), alcohol consumption (>60 g/day) and smoking habit before stroke or diagnosed during hospitalisation were recorded. At the time of inclusion in the study, retinographic, ultrasonographic and magnetic resonance studies were performed. According to the TOAST criteria (17), stroke subtype was classified as follows:

large-artery atherosclerosis
cardioembolic stroke
small-vessel disease
cryptogenic stroke, and
stroke of other determined cause.

The presence of hypertension or diabetes was not considered for the diagnosis of small- vessel disease subtype (18). A local Ethical Committee approved the protocol and signed, informed consent was given by the patients or relatives and controls.

Retinographic study

The same explorer (I. L.), blinded to clinical data, performed the retinographic study using frequency duplication perimetry, 20° optic disc stereophotography and 50° fundus retinography, on both eyes of each subject, using IMAGENET 2000, a software that stores 32-bit images under WINDOWS 95 and WINDOWS NT. A dynamic link library module controls the capture selection of IMAGENET 2000. The additional support for TWAIN devices can capture and store images from a film scanner and digital camera interface. In two controls and five patients, the retinographic study could not be performed.

The diagnosis of retinal microangiopathy was made according to the presence of changes in arteriovenous nicking, generalised arterial narrowing, focal arterial narrowing, arteriovenous narrowing or vascular tortuosity. We defined AV nicking as a reduced width of a venule on either side of an arteriole where the arteriole crossed the venule. Generalised arteriolar narrowing was defined as generalised arteriolar attenuation with decreased arteriolar diameter. Focal arteriolar narrowing was defined as focal length of narrowing to at least two-thirds of the width of the proximal and distal arteriole. Vascular tortuousness is defined as the loss of the slight winding of arterioles and venules, assuming the appearance of a corkscrew. Changes in arteriovenous nickings were classified as Grade I (arteriolar attenuation), Grade II (deflection vein at the nicking) and Grade III (vein interruption on both sides of the nicking), according to the Hayreh classification (19).

Microangiopathy was diagnosed as the presence of one arteriovenous nicking type III, one arteriovenous nicking and other signs of vascular disturbance, or two signs of vascular disturbance. We defined retinopathy as the presence of at least one alteration of the parenchyma: intraretinal haemorrhage, microaneurisms, hard exudates, soft exudates, neovascularisation or retinal oedema (20).

Ultrasonographic study

The same explorer (M. B.), blinded to clinical data, performed the ultrasonographic study using high-resolution B-mode ultrasound [Aplio 50 (Toshiba aplio 50, MCM1754TSA, Rome, Italy) Toshiba SSA-700 (Toshiba Medical Systems Corporation, Otawara-SHI, Japan)] with a 7·5 MHz, linear-array transducer (Linear array transducer PLT-704AT, Toshiba, Tochigi, Japan; Phased array transducer PST-20CT, Toshiba, Tochigi, Japan). Briefly, the image was focused on the posterior (far) wall of the left carotid artery. A minimum of four measurements of the common carotid far wall was taken 10 mm proximal to the bifurcation, to derive the mean carotid intima–media thickness (IMT) (21). Carotid artery plaque was assessed according to standardised scanning and reading protocols (22). The internal carotid and common carotid arteries, as well as their bifurcations, were examined for the presence of atherosclerotic plaques, defined as focal structure encroaching into the arterial lumen of al least 0·5 mm or 50% of the surrounding IMT value, or when a thickness $>1·5$ mm was demonstrated as measured from the media–adventitia interface to the intima–lumen interface. A 2 MHz sectoral

sound was used for a transcranial study through a trans temporal window. Velocity waves of both middle cerebral arteries in the middle third (M1) were measured using a Doppler-colour window in a midbrain section. The mean pulsatility index was automatically measured by ultrasound software using the Gosling method (23), choosing the highest value. Transcranial ultrasound examination was performed in 47 controls and 186 patients.

Neuroimaging study

An MRI study was conducted in all controls and 183 patients. In 104 patients with ischaemic stroke, MRI was performed within the first 24 h from stroke onset (24 patients had a lacunar infarct and 21 had a positive image in DWI). In the remaining patients (18 with lacunar infarcts), MRI was performed at inclusion in the study. In the remaining 12 patients, the diagnosis was confirmed by CT. Magnetic resonance images were obtained on a 1·5 T system (1·5 Magneton Symphony, Siemens, Erlangen, Germany), with echo planar capabilities of 25 mT/m gradients and 300–350 μs rise times. The MRI protocol included T1-weighted (TR/TE: 370/7.7 ms), T2-weighted (TR/TE: 6020/113 ms), DP-weighted (TR/TE 6020/113 ms) and FLAIR (TR/TE: 9000/114 ms). One neurologist (R. L.) who was blinded to the clinical data carried out the evaluation of the MRI. The presence of territorial and lacunar infarcts was evaluated. The diagnosis of a lacunar infarct was considered as the presence of a lesion suggestive of infarction lower than 1·5 cm in diameter in the territory of deep perforating arteries (basal ganglia, internal capsule, corona radiata) and the brainstem. Leukoaraiosis was classified according to the modified Fazekas scale (24): grade I, lesion limited to frontal and/or occipital ventricle horn; grade II, lateral ventricle bands; grade IIIa, disperse periventricular and/or subcortical white matter lesions; grade IIIb, confluent white matter and/or subcortical lesions; and grade IIIc, homogeneous white matter and/or subcortical lesions.

Statistical analysis

The sample size calculation was performed using the program EPIDAT 3·1 (http://dxsp.sergas.es/apliedatos/epidat/cas/), based on the prevalence data of retinal microangiopathy in a population study (10, 25). To detect a difference in the prevalence of retinal microangiopathy between 10% and 15%, assuming α-risk = 0·05 and β-risk = 0·20, between 120 and 160 nonlacunar infarcts and 32–39 lacunar infarcts are needed.

The statistical analysis was performed using SPSS 16 for Mac. Qualitative variables were expressed as number and percentage. Quantitative variables with a normal distribution were expressed as average $\pm$ standard deviation and those with a nonnormal distribution were expressed as average (p25, p75). The Kolmogorov–Smirnov test was used to determine which variables had a normal distribution. Pearson's χ^2-test was used to compare dichotomous variables, both for a normal as well as a nonnormal distribution. To compare two continuous variables, the Student *t*-test was used for normal distributions and the Mann–Whitney test for nonnormal distributions. To compare multiple variables, the ANOVA test was used. Correlations between two variables were performed using Spearman's or Pearson's coefficient.

To identify the best discriminant cut-off point of the mean pulsatility index to identify lacunar infarcts, a ROC analysis was performed.

The influence of different variables on the presence of lacunar infarcts was determined using logistic regression models, which included variables that achieved statistical significance in univariate analysis. We consider, in all the statistical analyses, a significance level for probabilities $<0·05$.

Results

Twenty per cent of the strokes included in this study were lacunar infarcts ($n = 39$). The basal characteristics of the patients and controls are shown in Table 1. The mean pulsatility index and the frequency and intensity of leukoaraiosis were significantly higher in patients with lacunar infarcts in relation to nonlacunar infarcts. Retinal microangiopathy was present in 50% of atherothrombotic, 41·9% of cardioembolic, 97·4% of lacunar and 34·7% of undetermined infarcts. The results of the different signs in patients with lacunar and nonlacunar infarcts are shown in Table 2. The presence of retinopathy was found in 9·1% of atherothrombotic, 1·6% of cardioembolic, 10·3% of lacunar and 6·9% of undetermined infarcts.

Retinal microangiopathy was more frequent in hypertensive (62·6% vs. 35·7%, $P<0·0001$) and diabetic (55·0% vs. 41·6%, $P = 0·049$) patients. Retinopathy was more frequent in diabetic (11·7% vs. 3·8%, $P = 0·039$) but not in hypertensive (4·5% vs. 7·1%, $P = 0·271$) patients.

Retinal microangiopathy was more frequent in patients with leukoaraiosis (89·5% vs. 10·5%, $P = 0·008$). In patients with lacunar infarcts, the frequency of retinal microangiopathy was higher in those with leukoaraiosis grade IIIb and IIIc ($P<0·0001$) (Fig. 1). In patients with leukoaraiosis, microangiopathy was more prevalent in the subgroup of patients with lacunar infarcts (100% vs. 62·2%, $P<0·0001$). The mean pulsatility index was higher in patients with retinal microangiopathy ($1·83 \pm 0·31$ vs. $1·05 \pm 0·47$, $P<0·0001$) and was related to the intensity of arteriovenous nicking (Fig. 2). The mean pulsatility index was also higher in patients with a higher grade of leukoaraiosis, especially in lacunar infarcts (Fig. 3).

In a logistic regression model, lacunar infarcts were independently associated with a previous modified Rankin scale, the mean pulsatility index (evaluated as a continuous variable, because in the ROC analysis the area under curve was 0·346), the presence of leukoaraiosis and retinal microangiopathy (Table 3). On including only patients with hypertension (71·8% of lacunar infarcts) in the logistic regression model, the adjusted odds ratio (OR) for retinal microangiopathy was

Table 1 Basal characteristics of patients and controls

Variable	Controls ($n = 50$)	Ischaemic stroke: Nonlacunar ($n = 156$)	Ischaemic stroke: Lacunar ($n = 39$)	P
Age, years	68·3 ± 8.2	71·6 ± 8·1	69·7 ± 10·8	0·486
Male, *n* (%)	30 (60·0)	76 (48·7)	23 (59·0)	0·167
History of hypertension, *n* (%)	9 (18·0)	96 (61·5)	28 (71·8)	0·158
History of diabetes, *n* (%)	7 (14·0)	40 (25·6)	13 (33·3)	0·220
History of hypercholesterolaemia, *n* (%)	7 (14·0)	48 (30·8)	13 (33·3)	0·448
History of heart disease, *n* (%)	5 (10·0)	62 (39·7)	11 (28·2)	0·125
History of alcohol consumption, *n* (%)	3 (6·0)	13 (8·3)	3 (7·7)	0·598
History of smoke habit, *n* (%)	5 (10·0)	23 (14·7)	9 (23·1)	0·155
Previous modified Rankin scale	0 [0, 0]	0 [0, 1]	0 [0, 0]	0·008
Intima–media thickness (mm)	0·8 ± 0·1	0·8 ± 0·2	0·8 ± 0·2	0·152
Carotid atheromatosis, *n* (%)	1 (2·0)	24 (15·4)	3 (7·7)	0·162
Mean pulsatility index*	0·9 ± 0·3	1·4 ± 0·5	1·9 ± 0·2	< 0·0001
Grade of leukoaraiosis, *n* (%)†				< 0·0001
Grade I	0	13 (8·8)	0	
Grado II	1 (2·0)	24 (16·3)	3 (8·3)	
Grade IIIa	3 (6·0)	27 (18·4)	10 (27·8)	
Grade IIIb	1 (2·0)	9 (6·1)	17 (47·2)	
Grade IIIc	0	1 (0·7)	4 (11·1)	
Categorised leukoaraiosis, *n* (%)	5 (10·0)	74 (50·3)	34 (94·4)	< 0·0001
Stroke subtype, *n* (%)				
Atherothrombotic		22 (14·1)		
Cardioembolic		62 (39·7)		
Lacunar			39 (100)	
Undetermined		72 (46·2)		
Retinal microangiopathy, *n* (%)‡	10 (20·8)	62 (41·1)	38 (97·4)	< 0·0001
Retinopathy, *n* (%)‡	2 (4·2)	8 (5·3)	4 (10·3)	0·263

*47 controls, 151 nonlacunar infarcts and 35 lacunar infarcts. †50 controls, 147 nonlacunar infarcts and 36 lacunar infarcts. ‡48 controls, 151 nonlacunar infarcts and 39 lacunar infarcts.

24·33 (95% CI 5·14–481·52), $P < 0·0001$. Assessed together, the presence of retinal microangiopathy and leukoaraiosis are associated with lacunar infarcts with an OR of 16·26 (95% CI 5·98–44·19), $P < 0·0001$; on including only patients with leukoaraiosis grade III, the association between retinal microangiopathy and lacunar infarcts increases to an OR of 21·31 (95% CI 8·74–51·93), $P < 0·0001$.

Discussion

In our study, we found a clear and strong relationship between retinal microangiopathic disturbances and neuroimaging and ultrasonographic markers of brain small-vessel disease. In our series of lacunar infarcts, only two patients showed no leukoaraiosis, one patient had a normal fundus oculi and no patients had a pulsatility index below the average ± 2 SD, of the patients with nonlacunar infarcts. The existence of retinal microangiopathy and leukoaraiosis grade III together was associated with the presence of lacunar infarcts with an OR of 21·31 (95% CI 8·74–51·93).

In the literature, we found no studies that have investigated the association of vascular retinal, ultrasound and neuroimaging markers in different subtypes of ischaemic stroke. The population study ARIC (10) and the Blue Mountains Eye Study (12) showed that the presence of retinopathy is associated with an increased risk of developing stroke, and the Cardiovascular Heart Study (26) demonstrated their association with a history of stroke. More recently, a prospective study of 105 lacunar infarcts showed no association with the presence of retinopathy (14). Some of these discrepancies may be due to methodological problems. Only the study of Doubal *et al.* (14) specifically examines the strokes associated with small-vessel disease, as well as the relationship between retinopathy and neuroimaging disturbances; also, the relationship between retinopathy and abnormalities in neuroimaging has only been determined in two studies (14, 26), but only in one in the different stroke subtypes. Other differences emerge from the ophthalmological study, which analyses retinal microangiopathic changes (arteriovenous nicking, focal or generalised arterial narrowing, arteriovenous narrowing or vascular tortuosity) or the presence of retinopathy (intra retinal haemorrhages, microaneurysms, soft or hard exudates, neovascularisation or retinal oedema).

The prevalence of retinal microangiopathy in our controls was 20·8%, higher than that found in the cohort of 10 358 subjects in the ARIC study (10) (14·9%); however, the average

Table 2 Different signs of retinal microangiopathy in patients with lacunar and nonlacunar infarcts

	Nonlacunar ($n = 156$)	Lacunar ($n = 39$)	P
Retinal micropangiopathy, n (%)	62 (41·1)	38 (97·4)	<0·0001
Arteriovenous nicking:			<0·0001
Grade I, *n* (%)	1 (0·6)	2 (5·1)	
Grade II, *n* (%)	24 (15·4)	11 (28·2)	
Grade III, *n* (%)	37 (23·7)	25 (64·1)	
Generalized arteriolar narrowing, *n* (%)	23 (14·7)	15 (38·5)	0·002
Focal arteriolar narrowing, *n* (%)	23 (14·7)	6 (15·4)	0·546
Arteriovenous narrowing, *n* (%)	16 (10·3)	19 (48·7)	<0·0001
Vascular tortuosity, *n* (%)	23 (14·7)	13 (33·3)	0·010

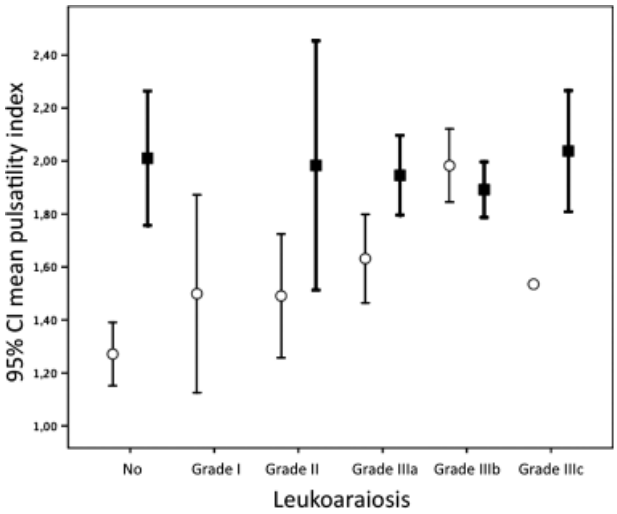


Fig. 1 Mean pulsatility index in relation to leukoaraiosis grade in lacunar (■) and nonlacunar (○) infarcts.

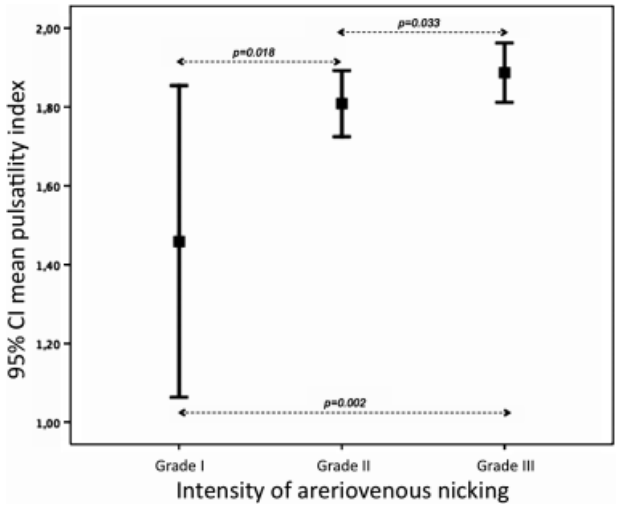
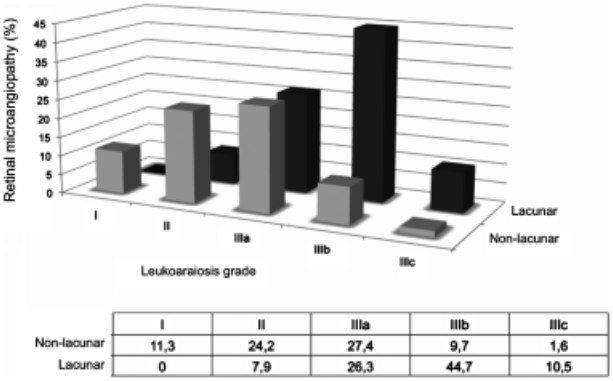


Fig. 2 Mean pulsatility index in relation to the intensity of arteriovenous nicking in patients with stroke.



	I	II	IIIa	IIIb	IIIc
Non-lacunar	11,3	24,2	27,4	9,7	1,6
Lacunar	0	7,9	26,3	44,7	10,5

Fig. 3 Percentage of retinal microangiopathy according to the grade of leukoaraiosis in patients with lacunar and nonlacunar infarcts. Below, percentages of microangiopathy.

age was 53·6 years in the ARIC and 68·3 years in our controls. We believe that the age difference justifies the variation in prevalence and supports our findings.

We have found no association between vascular retinopathy and the presence of lacunar infarcts, and this lack of relationship was also found in diabetic patients, although it may be due to an insufficient number of patients. The prevalence of vascular retinopathy in our series of lacunar infarcts was 10·3%, lower than that found by Doubal *et al.* (14) (19%) but higher than that of the ARIC study (10) (7%) and the Cardiovascular Health Study (26) (8%).

In our opinion, the presence of retinal microangiopathy, rather than retinopathy, is a sensitive marker associated with the development of brain small-vessel disease, both clinical (lacunar infarcts) and subclinical (identified by the presence or the leukoaraiosis and alterations in the pulsatility index). This increased sensitivity of the microangiopathy of retinopathy has been confirmed in other studies (5, 26).

Seventy-two per cent of our patients with lacunar infarcts had hypertension and elevated blood pressure, and even a moderate increase in retinal arterial narrowing (27). The retinal microangiopathic findings are particularly evident in hypertensive patients, but lose their statistical significance in diabetic patients (data not shown). The lack of a relationship of diabetes with lacunar infarcts has been postulated in other studies (28, 29).

Leukoaraiosis is a marker associated with age and the existence of several stroke risk factors, although the mechanism of their production is not well known. Chronic ischaemia, alterations of the blood–brain barrier, inadequate venous return in the white matter, vasogenic oedema or alterations in the circulation of cerebrospinal fluid are the different mechanisms involved in the development of leukoaraiosis (30).

In our study, we have observed that leukoaraiosis is more prevalent (87·2% vs. 47·4%, $P < 0·0001$) and more intense in patients with lacunar than with nonlacunar infarcts. One interesting finding is the higher association of leukoaraiosis and retinal microangiopathy in lacunar infarcts (Fig. 1), supporting the hypothesis of different mechanisms in its

Table 3 Multivariate analysis of association with lacunar infarcts

Variable	Nonadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Previous Rankin scale	0·25 (0·08–0·74)	0·012	0·22 (0·06–0·71)	0·012
Mean pulsatility index	19·61 (5·21–73·82)	<0·0001	8·13 (1·17–56·27)	0·034
Leukoaraiosis	7·53 (2·80–20·27)	<0·0001	3·45 (1·09–10·93)	0·035
Microangiopathy	57·61 (7·70–430·54)	<0·0001	12·81 (1·52–107·86)	0·019

production, as secondary to large- (31) or small-(32) vessel disease. This hypothesis is also supported by the increasing power of the association of retinal microangiopathy plus leukoaraiosis as a marker of lacunar infarcts demonstrated in our study.

The pulsatility index reflects the distal vascular resistance to the middle cerebral artery, and this is in relation to small-vessel disease (16) and has been associated with the development of leukoaraiosis (33). Previous studies have linked the elevation in the pulsatility index to the presence of small-vessel disease determined in MRI as peri ventricular and deep white matter hyperintensities and lacunar infarcts, with 89% sensitivity and 86% specificity (34), especially in diabetic patients (35). In our series, the pulsatility index was higher in patients with lacunar infarcts and was related to the intensity of the microangiopathy (Fig. 2) and the leukoaraiosis (Fig. 3). However, the association of retinal microangiopathy plus pulsatility index did not increase the OR for association with lacunar infarctions (data not shown). This finding, and the powerful association of a higher pulsatility index and diabetes (16, 35), raises the hypothesis that this haemodynamic measurement could express more the affectation of large brain vessel. The three patients with carotid atheromatosis and lacunar infarcts were diabetic.

Our study has some limitations: although the ophthalmological and ultra sonographic study was performed by the same experienced experimenter, the intra-observer variability has not been determined. The number of diabetic patients ($n = 14$) in the subgroup of lacunar infarcts is too small to conclude on its relationship with the development of microangiopathy, a higher pulsatility index and leukoaraiosis. Also, in the subgroup of patients with nonlacunar infarcts, the proportion of atherothrombotic compared with cardioembolic/undetermined infarcts is low, and may increase the difference between the markers studied between stroke subtypes.

Our results support the hypothesis that lacunar infarcts with retinal microangiopathy are probably due to small-vessel disease. Recently, this hypothesis has also been strongly supported by studies of Doubal *et al.* (36) and Lindley *et al.* (37). If this hypothesis is confirmed, the use of thrombolytic therapy and/or antiplatelet drugs in these patients could be questioned.

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