Atherosclerosis 213 (2010) 311–318

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Immune-inflammatory markers and arterial stiffness indexes in subjects with acute ischemic stroke

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ARTICLE INFO

Article history:
Received 16 February 2010
Received in revised form 10 July 2010
Accepted 16 August 2010
Available online 26 August 2010

Keywords:
Stroke
Cytokines
PWV
Aix

ABSTRACT

No study has yet evaluated the relationship between arterial stiffness indexes and immuno-inflammatory pathway in patients with an acute cardiovascular or cerebrovascular event. The aim of our study was to evaluate in patients with acute ischemic stroke the relationship between immune-inflammatory markers and arterial stiffness indexes.

Methods: 107 subjects with acute ischemic stroke and 107 controls without stroke. We evaluated plasma levels of C-reactive protein (CRP), interleukin-1beta (IL-1β), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-10 (IL-10), E-selectin, P-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), von Willebrand Factor (vWF), tissue plasminogen activator (TPA), plasminogen activator inhibitor-1 (PAI-1). Carotid-femoral pulse wave velocity (PWV) and augmentation index (Aix) were evaluated.

Results: There was a significant positive relationship, corrected for age, and gender, between PWV and CRP, TNF-α, IL1β, VWF and IL-6. Aix was significantly related to VWF, IL-6 and TNF-α levels. Among Lacunar subtype PWV was significantly related to CRP, IL-1β, IL-6, TNF-α and vWF. In LAAS subjects PWV was significantly related to CRP, IL-1β, IL-6, TNF-α but not with vWF. Among CEI subtype, PWV was significantly and positively related to CRP, IL-1β, TNF-α and vWF.

Discussion: Our findings show that both aortic stiffness and wave reflection are related to the degree of systemic inflammation in stroke subjects, suggesting that circulating inflammation mediators can influence the stiffness of vessels distant to those involved in the disease process itself.

1. Introduction

Inflammation markers such as C-reactive protein (CRP) are predictive of stroke occurrence [1] and CRP has been reported elevated in stroke patients [2], whereas our group [3,4] and other authors [5,6] reported that some pro-inflammatory cytokines are systematically increased after ischemic stroke.

Although there are some inconsistencies, a number of recent studies have suggested that in a healthy population, there may be a significant relationship between CRP and measures of arterial stiffness. Yasmin et al. found CRP to be related to pulse wave velocity (PWV) but not to augmentation index (Aix) [9]. In contrast, Kampus et al. found CRP to be independently and significantly associated with Aix. Moreover in patients with systemic vasculitis, in which CRP levels are markedly elevated, they were positively correlated with PWV and Aix [11].

Arterial stiffness is increasingly recognized as an important determinant of cardiovascular risk [13–16] and may be directly involved in the process of atherosclerosis [17]. The factors underlying increased arterial stiffness are incompletely understood, but both functional and structural alterations in the vessel wall are thought to be important. Indeed, some investigators have shown that endothelial-derived nitric oxide (NO) regulates large artery stiffness in vivo [12,18–21]. This may explain why other cardiovascular risk factors such as diabetes mellitus and hypercholesterolemia, which are associated with endothelial dysfunction, are linked to premature arterial stiffening.

Few studies examined the relationship between arterial stiffness indexes and systemic inflammation markers such as pro-inflammatory cytokines [22], whereas no study has evaluated the relationship between these indexes and immune-inflammatory markers in patients with an acute cardiovascular or cerebrovascular event. Only one study [23] indirectly evaluated this relationship and only with regard to erythrocyte sedimentation rate (ESR).

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doi:10.1016/j.atherosclerosis.2010.08.065

On this basis the aim of our study was to evaluate the relationship between arterial stiffness and cytokine, selectin, adhesion molecule and von Willebrand Factor plasma levels in subjects with acute ischemic stroke.

2. Methods

2.1. Patient selection

We enrolled all consecutive patients with a diagnosis of acute ischemic stroke admitted to the Internal Medicine Department at the University of Palermo between November 2006 and January 2008, and hospitalized control patients without a diagnosis of acute ischemic stroke. Control subjects were patients admitted, in the same period, to our Internal Medicine Department, for any cause other than acute cardiovascular and cerebrovascular events.

Stroke was defined by focal neurological signs or symptoms thought to be of vascular origin that persisted for >24 h confirmed by brain CT and/or MRI in baseline conditions and brain CT with contrast medium after 48–72 h [9].

In order to match patients with acute ischemic stroke and controls for cardiovascular risk and previous cardiovascular morbidity, controls were included if they had vascular risk factors or a history of myocardial infarction or cerebrovascular disease or peripheral vascular disease, but they were excluded if they had either current or recent (within 6 months) cerebrovascular disease or one of the exclusion criteria (see above).

Cardiovascular risk factors were evaluated for both cases and controls on the basis of the criteria shown below. Hypercholesterolemia was defined as the presence of total cholesterol blood levels $\geq$200 mg/dl. Hypertension was defined as present if subjects had been previously diagnosed according to the World Health Organization/International Society of Hypertension guidelines and were routinely receiving antihypertensive therapy. Patients were defined as type 2 diabetics if they had known diabetes treated by diet, oral hypoglycaemic drugs or insulin before stroke.

Previous coronary artery disease was determined on the basis of a history of physician-diagnosed angina, myocardial infarction, or any previous revascularization procedure assessed by a questionnaire.

Previous cerebrovascular disease (TIA/ischemic stroke) was assessed by history, specific neurologic examination performed by specialists, and hospital or radiological (brain computer tomography or brain magnetic resonance) records of definite previous stroke.

Subjects were classified as having previous peripheral artery disease (PAD) when they had an history of ABI <0.9 and/or of intermittent claudication or of critical limb ischemia or when they had undergone a peripheral arterial bypass or amputation.

The study protocol was approved by the local ethics committee, and all participants gave written informed consent Every subject with ischemic stroke was matched for age ($\pm$3 years), sex, and cardiovascular risk factor prevalence with one control subject.

The type of acute ischemic stroke was classified according to the TOAST classification [24]: (1) Large Artery AtheroSclerosis (LAAS); (2) CardioEmbolic Infarct (CEI); (3) LACunar infarct (LAC); (4) stroke of Other Determined Etiology (ODE); (5) stroke of UnDetermined Etiology (UDE).

2.1.1. Large Artery AtheroSclerosis (LAAS)

These patients have clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis. Clinical findings include those of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.) or brain stem or cerebellar dysfunction. Cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter on CT or MRI are considered to be of potential large-artery atherosclerotic origin. Supportive evidence by duplex imaging or arteriography of a stenosis of greater than 50% of an appropriate intracranial or extracranial artery is needed. Diagnostic studies should exclude potential sources of cardiogenic embolism.

2.1.2. CardioEmbolic Infarcts (CEI)

This category includes patients with arterial occlusions presumably due to an embolus arising in the heart. Cardiac sources are divided into high-risk and medium-risk groups based on the evidence of their relative propensities for embolism. At least one cardiac source for an embolus must be identified for a possible or probable diagnosis of cardioembolic stroke. Clinical and brain imaging findings are similar to those described for large-artery atherosclerosis. Evidence of a previous TIA or stroke in more than one vascular territory or systemic embolism supports a clinical diagnosis of cardiogenic stroke. Potential large-artery atherosclerotic sources of thrombosis or embolism should be eliminated. Stroke in a patient with a medium-risk cardiac source of embolism and no other cause of stroke is classified as a possible cardioembolic stroke.

2.1.3. LACunar infarct (LAC)

The patient should have one of the traditional clinical lacunar syndromes and should not have evidence of cerebral cortical dysfunction. A history of diabetes mellitus or hypertension supports the clinical diagnosis. The patient should also have a normal CT/MRI examination or a relevant brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm demonstrated.

2.1.4. Stroke of Other Determined Etiology (ODE)

This category includes patients with rare causes of stroke, such as non-atherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders. Patients in this group should have clinical and CT or MRI findings of an acute ischemic stroke, regardless of the size or location. Diagnostic studies such as blood tests or arteriography should reveal one of these unusual causes of stroke. Cardiac sources of embolism and large-artery atherosclerosis should be excluded by other studies.

2.1.5. Stroke of UnDetermined Etiology (UDE)

In some cases, the cause of a stroke cannot be determined with any degree of confidence. Some patients have no likely etiology determined despite an extensive evaluation. In others, no cause is found but the evaluation was cursory.

All the ischemic stroke patients underwent: medical history with recording of potential stroke risk factors, blood and coagulation tests, 12-lead ECG, 24 h electrocardiography monitoring, trans-thoracic echocardiography, carotid ultrasound, brain CT or MRI at admission (*repeated between the third and seventh days of stroke onset*).

Neurological deficit score on admission was evaluated by Scandinavian Stroke Scale (SSS). SSS assesses neurological deficit through an evaluation of consciousness level, eye movement, strength in arms, hands, and legs, orientation, language, facial weakness and gait, giving rise to a score ranging from 58 (*absence of deficit*) to 0 (*death*).

2.2. PWV measurement

Carotid-femoral PWV was measured in the supine position using the automatic device (SphygmoCor version 7.1) that measured the time delay between the rapid upstroke of the carotid and femoral artery pulse waves. The distance between the 2 arterial points was measured on the surface of the body using a tape measure. PWV

was calculated as the distance traveled by the arterial pulse wave (meters) divided by the time delay between the 2 arterial points (seconds), thus expressed as meters per second.

2.3. Pulse wave analysis

Applanation tonometry was used to record radial artery pressure waveform continuously, and mean values of ≥2 screens of pulse waves of good quality were used for analysis. On the basis of the collected data, an averaged radial pressure waveform was generated and a corresponding aortic pressure waveform and BP calculated by the validated transfer function (SphygmoCor version 7.1). The aortic pressure waveform was used to calculate the Aix (difference in height between the first and second systolic peaks expressed as a percentage of pulse pressure (PP)).

2.4. Laboratory evaluation

Blood samples were obtained in the non-fasting state. After 10 min of rest in the supine position, vital signs were recorded and blood samples were collected from the antecubital vein.

EDTA-anticoagulated peripheral blood was drawn from each patient within 12 h from symptom onset. Serum and plasma were immediately separated by centrifugation and stored in aliquots at −80 °C until analysis.

We evaluated plasma levels of C-reactive protein (CRP), interleukin-1beta (IL-1β), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-10 (IL-10), E-selectin, P-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), as markers of immune-inflammatory activation, von Willebrand Factor (vWF) plasma levels as a marker of endothelial dysfunction, tissue plasminogen activator (TPA) and plasminogen activator inhibitor-1 (PAI-1) as marker of thrombotic/fibrinolytic pathway.

IL-1β, TNF-α, IL-6 and IL-10 and VWF antigen were measured using a sandwich ELISA (*Human IL-1β, TNF-α, IL-6 and IL-10* Quantikine, R&D Systems (*VWF ELISA kitdurian, Instrumentation Laboratory, Milano, Italy*)); VCAM-1, ICAM-1, E-selectin, P-selectin, PAI-1 and TPA-antigen were measured by commercial bioimmunoassay (*Human sICAM-1, sVCAM-I, sE-selectin and sP-selectin Parameter*, Quantikine, R&D Systems, Gentaur AssayMax Human Plasminogen Activator Inhibitor-1 (PAI-1) ELISA Kit, Gentaur AssayMax Tissue Plasminogen Activator (TPA) ELISA Kit).

The minimum detectable concentrations for the diagnostic tests are: TNF alpha: 1.6 pg/ml; IL-1β: <1 pg/ml; IL-6: <0.70 pg/ml; IL-10: >3.9 pg/ml; ICAM-1: <0.35 ng/ml; VCAM-1: 0.6 ng/ml; E-selectin: <0.1 ng/ml; P-selectin: <0.5 ng/ml; vWF: 1.0%; TPA: 0.3 pg/ml; PAI-1: <50 pg/ml.

Intraassay and interassay coefficients of variation were: TNF alpha: 4.2% and 4.6%; IL-1β: 3.3% and 4.2%; IL-6: 1.6% and 3.3%; IL-10: 4.3% and 7.5%; ICAM-1: 4.8% and 6.1%; VCAM-1: 3.5% and 7.7%; E-selectin: 4.8% and 5.7%; P-selectin: 4.9% and 8.8%; vWF: 5% and 10%; TPA: 4.8% and 5%; PAI-1: 5.7% and 8.3%.

2.5. Statistical analysis

Results are expressed as mean ± SD for continuous variables and percentages for categorical data, with $P \geq 0.05$ considered significant. Analysis of normality was performed with the Shapiro–Wilk *W* test. Non-normally distributed data were logarithmically (Log 10) transformed before analysis.

The relationship between immune-inflammatory markers, PWV, Aix, and other parameters was analyzed using nonparametric methods (Spearman *P* correlations) after correction for age and gender.

According to sample size calculation a sample size of 100 patient-control pairs had 80% power at the 5% significance level to detect a 10% difference in selected biomarker plasma levels and arterial stiffness indexes between control subjects and patients and between each subtype of stroke.

3. Results

We enrolled 107 patients with acute ischemic stroke and 107 control subjects matched for age, sex, cardiovascular risk factors and previous cardiovascular morbidity.

According to the TOAST criteria, the etiology of stroke was large-artery atherosclerosis (LAAS) in 41 (38.31%) patients, cardioembolism (CEI) in 31 (28.97%) patients, lacunar stroke in 32 (29.92%) patients whereas 3 (2.80%) subjects were classified as ODE. Baseline patient characteristics are given in Table 1. Subjects with acute ischemic stroke showed significantly higher plasma levels of CRP, IL-1 β, IL-6 TNF α, E-selectin, P-selectin, I-CAM-1, V-CAM-1, VWF, TPA and PAI-1 (see Table 1). Baseline characteristic of subjects with ischemic stroke with regard of TOAST subtypes are given in Table 2.

PWV and Aix values in stroke patients and in each TOAST subtype are given in Table 1 and in Table 2. Subjects with acute ischemic stroke showed significantly higher levels of PWV and AIx (see Table 1) whereas in relation of stroke subtype lacunar subtype showed the highest value of both arterial stiffness indexes (see Table 2).

3.1. Relationship between PWV and immune-inflammatory variables

There was a significant positive relationship, corrected for age, and gender, between PWV and CRP ($r = 0.36$; $P < 0.001$), TNF-α ($r = 0.42$; $P < 0.001$), IL1β ($r = 0.35$; $P < 0.001$), VWF ($r = 0.46$; $P < 0.001$), and IL-6 ($r = 0.27$; $P < 0.05$) (see Table 3).

3.2. Relationship between Aix and immune-inflammatory variables

The Aix was significantly related, after correction for age and gender, to VWF ($r = 0.38$; $P < 0.0001$), but not to CRP ($r = 0.09$; $P = 0.37$), IL-6 ($r = 0.12$; $P < 0.08$), or TNF-α ($r = 0.14$; $P < 0.15$) levels (see Table 3).

3.3. Relationship between PWV and immune-inflammatory variables in relation to TOAST subtype

Among Lacunar subtype PWV, after correction for age and gender, was significantly and positively related to CRP, IL-1β, IL-6, TNF-α and vWF (see Table 4).

In subjects with stroke classified as LAAS, PWV was significantly and positively related to CRP, IL-1β, IL-6, TNF-α but not with vWF (see Table 4).

In CEI subtype, PWV was significantly and positively related to TNF-α and vWF but not with CRP, IL-6, IL-1β (see Table 4).

3.4. Relationship between Aix and immune-inflammatory variables in relation to TOAST subtype

Among Lacunar and CEI subtype Aix was positively and significantly related, after correction for age and gender, only to vWF; in LAAS subgroup this relationship was significantly weaker and only close to statistical significance (see Table 4).

Table 1
General characteristics and immuno-inflammatory variables of stroke patients and controls.

Variable	Stroke pts (*n*: 107)	Controls (*n*: 102)	*P*
Age (years)	71 (63–80.5)	68 (63–80)	0.79
M/F (*n*)	66/41	57/55	0.022
SBP/DBP (mm/Hg)	151 ± 8.9/96 ± 4.2	141 ± 9.8/91 ± 2.2	<0.001
MAP (mm/Hg)	114.33 ± 9.4	107.6 ± 8.4	<0.005
Diabetes (*n*/%)	44 (41.12)	41 (40.19%)	0.263
Hypertension (*n*/%)	50 (45.72%)	46 (45.09%)	0.301
Age (years)	71 (63–80.5)	68 (63–80)	0.79
Glucose blood levels (mg/dl)	148.5 (97–213)	109 (81.5–163.5)	<0.001
Cholesterol blood levels (mg/dl)	231 (189–250)	220 (168–215)	<0.001
Triglycerids blood levels (mg/dl)	177.5 (130.75–201.75)	141 (96–205)	0.004
White blood cells (per mm^3)	9200 (6000–13,000)	7400 (6500–9800)	<0.001
Neutrophils (%)	6180 (5071–9000)	4040 (3200–5800)	<0.001
Diabetes (*n*/%)	44 (41.12)	41 (40.19%)	0.263
Hypertension (*n*/%)	50 (45.72%)	46 (45.09%)	0.301
Aix (%)	103 ± 3.5	89 ± 4.6	<0.001
PWV (m/s)	11.8 ± 3.3	10.02 ± 2.29	<0.001
SSS	30.22 ± 16.21	–	
NIHSS	19.41 ± 10.06	–	
msRankin score at discharge			
I	20 (18.69)		
II	22 (20.56)		
III	20 (18.69)		
IV	24 (22.45)		
V	21 (19.62)		
Death (*n*/%)	7 (6.5)	–	<0.001
CAD (*n*/%)	38 (35.51)	37 (36.27)	0.44
CHF (*n*/%)	21 (19.62)	15 (14.70)	0.065
Previous TIA (*n*/%)	40 (37.38)	11 (10.87)	<0.001
Previous stroke (*n*/%)	33 (30.84)	7 (6.82)	<0.001
Microalbuminuria (*n*/%)	41 (38.31)	18 (17.64)	<0.001
Carotid plaque (*n*/%)	61 (57)	33 (32.35)I	<0.001
LVH (*n*/%)	45 (42.05)	21 (20.58)	<0.001
Previous brain infarct at neuroimage (*n*/%)	40 (37.38)	19 (18.62)	<0.001
WMHLS (*n*/%)	27 (25.23)	18 (17.64)	0.024
CRP (mg/dl)	3.8 ± 2.2	1.9 ± 0.9	<0.05
IL-1-β (pg/ml)	8 (5–10)	4 (2–5)	<0.001
IL-6 (pg/ml)	10 (6–28)	8 (3.1–12)	<0.001
TNF-α (pg/ml)	30.5 (10.25–46)	5.1 (1.1–4.3)	<0.001
E-selectin (ng/ml)	2.05 (1.0–3.8)	2 (1–2)	<0.001
P-selectin (ng/ml)	4.5 (2–6.8)	3.1 (2.1–4)	0.004
VICAM (ng/ml)	16 (10.1–20)	10 (7–15)	<0.001
ICAM (ng/ml)	18.8 (12.2–20)	10.9 (12–16.1)	<0.001
IL-10 (pg/ml)	3.95 (2–7)	4 (2–10)	0.233
vWF (ng/ml)	11 (6–15)	4 (3–9)	0.0001
PAI-1 (pg/ml)	137 (99.5–155)	23 (11–24)	<0.001
TPA (pg/ml)	21 (10.55–39)	55 (29–88)	<0.001
Premorbid antithrombotics			
Antiplatelets (*n*/%)	41 (38.31)	34 (33.33)	0.74
Anticoagulants (*n*/%)	33 (30.84)	27 (26.47)	0.54
Premorbid cardiovascular drugs			
Ace-inhibitors (*n*/%)	39 (36.44)	30 (29.41)	0.041
ARBs (*n*/%)	28 (26.18)	21 (20.58)	0.40
Statins (*n*/%)	42 (39.25)	32 (31.37)	0.35
Antidiabetic drugs (*n*/%)	21 (19.62)	22 (21.50)	0.21
Biguanids (*n*/%)	12 (11.21)	14 (13.72)	0.35
Sulphonilureas (*n*/%)	9 (8.41)	8 (7.8)	0.67
Thiazolidinediones (*n*/%)	–	–	
Insulin (*n*/%)	23 (21.49)	19	0.28

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; Aix: augmentation index; PWV: pulse wave velocity; SSS: Scandinavian Stroke Scale score; NIHSS: National Institutes of Health Stroke Scale; Angiotensin II receptor blockers (ARBs); CAD: coronary artery disease; CHF: congestive heart failure; LVH: left ventricular hypertrophy; WMHLS: white matter hyperintensity lesions; TIA: transitory ischemic attack; CRP: C-reactive protein; TNF-α: tumor necrosis factor α; IL-1β: interleukin-1-β; IL-6: interleukin-6; IL-10: interleukin 10; ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1; vWF: von Willebrand Factor; TPA: tissue plasminogen activator; PAI-1: plasminogen activator inhibitor-1.
Immuno-inflammatory and thrombotic-fibrinolytic variables are expressed as median and interquartile (lower and upper quartile).
Demographic and anamnestic data are expressed as no. (percentage).

4. Discussion

The main our findings were that patients with acute ischemic stroke had both increased inflammatory markers and arterial stiffness markers compared to control subjects without acute ischemic stroke.

This is the first study to show in patients with acute ischemic stroke that circulating levels of some immune-inflammatory markers such as CRP, IL-6, IL-1β, TNF-α and VWF are related to PWV and wave reflection.

Large artery stiffness is now recognized as a modifiable, independent predictor of cardiovascular risk [26,27]. Structural

Table 2
Premorbid cardiovascular risk factors, clinical characteristics and antithrombotic medication by ischemic stroke subtype.

Variable	Lacunar	LAAS	CEI	ODE	*P*
Number	32	41	31	3	
Age (years)	76.31 ± 7.37	72.17 ± 6.83	76.00 ± 8.79	49.00 ± 45.50	<0.001
Sex (M/F)	19/12	29/12	23/8	4/0	<0.001
Diabetes (*n*/%)	17 (56.25)	18 (43.90)	9 (29.03)	0	<0.001
Hypertension (*n*/%)	18 (56.2)	17 (41.46)	14 (45.16)	1 (33.33)	0.25
Hypercholesterolaemia (*n*/%)	7 (21.87)	16 (39.02)	9 (29.03)	0	<0.05
Atrial fibrillation (*n*/%)	3 (9.3)	5 (12.19)	24 (77.41)	0	<0.001
Previous TIA (*n*/%)	5 (15.6)	13 (31.07)	10 (32.2)	1 (33.3%)	<0.001
Previous stroke (*n*/%)	7 (21.8)	8 (19.5)	7 (22.05)	2 (66.66)	0.038
Glucose blood levels (mg/dl)	169.12 ± 74.06	117.00 ± 53.44	102.29 ± 7.68	92.29 ± 17.68	<0.001
Total cholesterol blood levels (mg/dl)	179.56 ± 40.07	175.02 ± 46.42	165.71 ± 30.64	169.00 ± 49.46	<0.05
LDL cholesterol (mg/dl)	95.62 ± 38.65	103.247 ± 28.9	84.67 ± 33.99	99.20 ± 32.81	<0.05
Trygliceride blood levels (mg/dl)	170.16 ± 82.40	190.82 ± 162.12	112.35 ± 32.36	148.00 ± 83.439	<0.05
WBC (per mm^3)	10041.37 ± 4167.31	11742.82 ± 9267.20	16282.41 ± 2556.64	10785.00 ± 5437.65	<0.05
Neutrophile (%)	7384.51 ± 3769.68	7803.87 ± 4303.00	6996.13 ± 3107.86	8418.00 ± 7481.19	<0.05
HCT (%)	39.20 ± 3.9	40.70 ± 4.24	41.386 ± 3.196	38.25 ± 9.54	0.041
SB P/DBP (mm/Hg)	153 ± 9.5/96 ± 4.2	151 ± 6.5/95 ± 4.2	149 ± 9.8/93 ± 2.2	145 ± 5.8/91 ± 2.5	<0.05
MAP (mm/Hg)	115 ± 9.7	113.6 ± 10.1	111.6 ± 8.2	109 ± 6.7	<0.05
Aix (%)	112 ± 5.5	108 ± 3.5	99 ± 3.5	101 ± 3.5	<0.05
PWV (m/s)	12.04 ± 1.54	11.98 ± 2.445	10.40 ± 2.445	11.48 ± 1.345	<0.05
NIHSS	14.65 ± 14.59	20.51 ± 16.06	15.64 ± 8.73	19.00 ± 12.72	<0.05
msRankin score at discharge (*n*/%)					
I	8 (25)	7 (17.07)	4 (12.90)	1 (25)	
II	13 (18.75)	6 (14.63)	3 (9.6)	–	
III	6 (40.62)	9 (21.95)	5 (16.19)	2 (50)	
IV	3 (9.37)	10 (24.39)	10 (32.22)	1 (25)	
V	2 (6.25)	9 (21.95)	9 (29.03)	–	
Death (*n*/%)	–	2 (4.8)	5 (16.12)	–	
CAD (*n*/%)	13 (40.6)	18 (43.91)	7 (22.58)	0	
CHF (*n*/%)	4 (12.5)	5 (12.19)	11 (35.48)	1 (33.33)	
Microalbuminuria (*n*/%)	24 (75%)	11 (26.82)	6 (19.35)	0	<0.001
Carotid plaque (*n*/%)	22 (68.7)	27 (65.85)	14 (45.16)	0	<0.05
LVH (*n*/%)	18 (56.25)	17 (41.46)	10 (32.25)	0	<0.05
Previous brain infarct at neuroimaging (*n*/%)	13 (40.62)	15 (36.58)	10 (32.2)	2 (66.66)	0.65
WMHLS (*n*/%)	13 (40.6)	8 (25.80)	5 (16.1)	1 (66.66)	<0.05
CRP (mg/dl)	2.8 ± 2.1	3.9±	3.1 ± 1.7	1.8 ± 0.9	0.041
IL-1-β (pg/ml)	5 (4–9)	8 (6–11)	11 (6–12)	7 (5–11)	<0.05
IL-6 (pg/ml)	8 (6–21)	10 (5–25)	12 (6–29)	10 (6–28)	<0.05
TNF-α (pg/ml)	22.5 (8.5–26)	30.5 (11.25–40)	39.5 (24–55)	32.5 (10.25–46)	<0.05
E-selectin (ng/ml)	3.05 (1.5–3.7)	2.45 (1.6–3.9)	3.05 (2.0–4.0)	2.05 (1.0–3.8)	0.035
P-selectin (ng/ml)	3.5 (2–4.8)	4.4 (2–6.0)	4.6 (2–6.9)	4.5 (2–6.8)	0.71
VICAM (ng/ml)	16 (9.1–18)	14 (10.2–21)	17 (10.1–22)	16 (10.51–20)	0.67
ICAM (ng/ml)	16.8 (11.2–18)	17.9 (10.2–210)	20.6 (11.2–24)	17.8 (13.2–21)	0.041
IL-10 (pg/ml)	3.55 (2–6)	3.96 (2–8)	3.2 (2–9)	3.95 (2–7)	0.65
vWF (ng/ml)	10 (4–17)	12 (5–13)	14 (6–18)	11 (7–116)	0.021
PAI-1 (pg/ml)	139 (90.5–143)	138 (91.5–135)	139 (99.0–145)	137 (99.5–155)	0.34
TPA (pg/ml)	23 (10.15–37)	23 (10.45–41)	24 (12.1–47)	22 (10.55–39)	0.81
Premorbid antithrombotics					
Antiplatelets (*n*/%)	11 (38.31)	20 (48.78)	10 (32.22)	–	<0.05
Anticoagulants (*n*/%)	4 (12.5)	7 (17.07)	21 (67.74)	1	<0.001
Premorbid cardiovascular drugs					
Ace-inhibitors (*n*/%)	18 (56.25)	11 (26.82)	10 (32.25)	–	<0.05
ARBs (*n*/%)	10 (31.25)	11 (26.82)	7 (22.58)	–	0.041
Statins (*n*/%)	15 (46.87)	20 (48.78)	7 (22.58)		0.031
Antidiabetic drugs (*n*/%)					
Biguanids (*n*/%)	10 (31.25)	7 (17.07)	4 (12.9)	–	<0.05
Sulphonilureas (*n*/%)	6 (18.75)	3 (7.31)	2 (6.45)		<0.05
Thiazolidinediones (*n*/%)	4 (12.5)	4 (9.7)	2 (6.45)		<0.025
Insulin (*n*/%)	11 (34.37)	6 (14.63)	6 (19.35)	–	<0.05

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; Aix: augmentation index; PWV: pulse wave velocity; SSS: Scandinavian Stroke Scale score; NIHSS: National Institutes of Health Stroke Scale; Angiotensin II receptor blockers (ARBs); CAD: coronary artery disease; CHF: congestive heart failure; LVH: left ventricular hypertrophy; WMHLS: white matter hyperintensity lesions; CRP: C-reactive protein; TNF-α: tumor necrosis factor α; IL-1β: interleukin-1-β; IL-6: interleukin-6; IL-10: interleukin 10; ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1; vWF: von Willebrand Factor; TPA: tissue plasminogen activator; PAI-1: PAI-1: plasminogen activator inhibitor-1.
Immuno-inflammatory and thrombotic-fibrinolytic variables are expressed as median and interquartile (lower and upper quartile).
Demographic and anamnestic data are expressed as no. (percentage).
Significative *R* and *P* are in bold.

components within the arterial wall, mainly collagen and elastin, together with transmural pressure, are key determinants of large vessel stiffness. However, smooth muscle tone also influences the stiffness of elastic and muscular arteries, suggesting functional regulation of stiffness by local and/or circulating vasoactive substances [28–30]. Interestingly, acute systemic inflammation has recently been associated with endothelial dysfunction in vivo [31–33].

Our findings show that both aortic stiffness and wave reflection are related to the degree of systemic inflammation in stroke subjects, suggesting that circulating inflammation mediators such

Table 3
Correlations of pulse wave velocity (PWV) and augmentation index (Aix) with immuno-inflammatory variables in stroke patients.

Variable	Pulse wave velocity		Augmentation index (Aix)	
	R	*P*-values	*R*	*P*-values
CRP	**0.36**	**<0.001**	0.09	0.37
IL-1-β	**0.35**	**<0.001**	0.10	0.22
IL-6	**0.27**	**<0.05**	0.12	0.35
TNF-α	**0.42**	**<0.001**	0.14	0.15
E-selectin	0.13	0.42	0.12	0.22
P-selectin	0.11	0.56	0.12	0.35
VICAM-1	0.08	0.37	0.08	0.37
ICAM-1	0.10	0.7	0.10	0.7
IL-10	0.11	0.81	0.10	0.77
vWF	**0.46**	**<0.001**	**0.38**	**<0.0001**
PAI-1	0.12	0.42	0.13	0.32
TPA	0.15	0.42	0.14	0.36

Coefficients (*R*) and *P*-values are calculated by the Pearson correlation mode.
CRP: C-reactive protein; TNF-α: tumor necrosis factor α; IL-1β: interleukin-1-β; IL-6: interleukin-6; IL-10: interleukin 10; ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1; vWF: von Willebrand Factor; TPA: tissue plasminogen activator; PAI-1: PAI-1: plasminogen activator inhibitor-1.
Significative *R* and *P* are in bold.

as CRP and some pro-inflammatory cytokines can influence the stiffness of vessels distant to those involved in the disease process itself.

Previous studies in healthy subjects have shown a positive relationship between either PWV or Aix with CRP but not with both [9,10], whereas Mahmud and Feely [22] showed in hypertensive patients a relationship between augmentation index to IL-6 and TNF-α.

PWV is a classic marker of aortic stiffness, whereas Aix is far more complex and is composed of the magnitude of arterial wave reflection, PWV, and pattern of left ventricular ejection. Also, the determinants of these indices differ. Aix is influenced to a greater extent by the level of heart rate, BP, gender, age, and height, whereas PWV is predominantly determined by age and BP [25].

Aix and PWV represent not only large artery stiffness but, very importantly, the vascular smooth muscle tone in the peripheral medium-sized muscular arteries, emphasizing the systemic nature of the inflammatory response encompassing biochemical and hemodynamic parameters. Cytokine plasma levels in its turn also influences vascular vulnerability to the inflammatory response and decreased production of the endogenous vasodilator nitric oxide (NO) [34]. Inhibition of basal NO synthesis increases aortic Aix and velocity in vivo [35].

An immune-inflammatory cascade occurs after an acute ischemic stroke [5,6] so on this basis cytokine levels that we reported and measured 72 h from symptom onset express an acute rise of these inflammatory markers.

Our group [3,4] recently showed some differences in acute immune-inflammatory activation with regard of plasma levels of inflammatory markers between each diagnostic subtype of stroke.

We also evaluated the predictive value of a series of candidate serum immuno-inflammatory and thrombotic/fibrinolitic molecules towards diagnosis of acute ischemic stroke showing that TNF-α, PAI-1 and TPA on bivariate logistic regression were highly correlated to stroke diagnosis [7].

Furthermore [8] we recently reported that patients with acute ischemic stroke in comparison with patients without stroke show higher arterial stiffness index values and that among stroke patients, lacunar subtype has the highest arterial stiffness indexes.

On this basis it's possible to hypothesize a possible relationship between acute immuno-inflammatory cascade and acute arterial stiffness increase in patients with acute ischemic stroke and our findings concerning a relationship between some cytokines plasma levels and PWV and Aix may represent a possible confirmation of this association.

What is the relationship between acute high levels of cytokines and arterial stiffness indexes in stroke patients? Does a hyper-acute inflammatory state after ischemic stroke directly cause increase of arterial stiffness? Or in stroke-prone patients with a chronic inflammatory activation exacerbated by acute stressor events such an acute cerebrovascular event, does it represent the pathogenetic basis of high arterial stiffness?

It's difficult to answer; nevertheless, it's possible to obtain an answer to the question about the relationship between inflammation markers and arterial stiffness indexes in acute ischemic stroke by evaluating our findings of some significant correlations at intra-group analysis in each TOAST subtype between arterial stiffness indexes and immune-inflammatory markers.

For instance, only in lacunar subtype we observed a strong correlation between PWV and IL6, IL-1β, TNF-α and vWF, whereas in LAAS we did not report any correlation with vWF and in the CEI group we reported only a positive relation with TNF-α and vWF.

Moreover evidence has shown that platelet reactivity is higher in patients following ischemic stroke [34,36]. The correlation between vWF and arterial stiffness markers does not indicate a direct biological background although the possible inflammatory role recently demonstrated for vWF [35,37], could explain the relationship with arterial stiffness indexes.

Table 4
Correlations of pulse wave velocity (PWv) and augmentation index (Aix) with immuno-inflammatory variables in stroke patients in relation of TOAST stroke subtype.

Variables	Lacunar				LAAS				CEI			
	PWV		Aix		PWV		Aix		PWV		Aix	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*
CRP	**0.37**	**<0.001**	0.022	0.19	**0.35**	**<0.001**	0.33	0.022	0.22	0.06	0.12	0.78
IL-1-β	**0.272**	**<0.05**	0.25	0.121	**0.32**	**<0.05**	0.11	0.27	0.20	0.07	0.18	0.980
IL-6	**0.27**	**<0.05**	0.12	0.10	**0.29**	**<0.05**	0.12	0.022	0.19	0.567	0.12	0.78
TNF-α	**0.36**	**<0.001**	0.11	0.121	**0.35**	**<0.001**	0.10	0.27	**0.34**	**<0.001**	0.18	0.980
E-selectin	0.022	0.19	0.08	0.11	0.15	0.27	0.13	0.10	0.16	0.267	0.12	0.78
P-selectin	0.25	0.121	0.09	0.12	0.12	0.022	0.12	0.11	0.18	0.98	0.18	0.980
VICAM	0.10	0.19	0.70	0.07	0.15	0.27	0.12	011	0.18	0.98	0.14	0.68
ICAM	0.09	0.10	0.014	0.19	0.14	0.48	0.33	0.022	0.0367	0.12	0.10	0.788
IL-10	0.11	0.121	0.12	0.121	0.25	**<0.05**	0.19	0.27	0.19	0.32	0.12	0.78
vWF	**0.39**	**<0.001**	**0.38**	**<0.001**	0.21	0.065	**0.20**	**0.06**	**0.39**	**<0.001**	**0.37**	**<0.001**
PAI-1	0.11	0.19	0.12	0.20	0.13	0.21	0.08	0.78	0.022	0.19	0.12	0.78
TPA	0.12	0.20	0.13	0.21	0.14	0.22	0.12	0.20	0.11	0.19	0.132	0.980

Coefficients (*R*) and *P*-values are calculated by the Pearson correlation mode.
CRP: C-reactive protein; TNF-α: tumor necrosis factor α; IL-1β: interleukin-1-β; IL-6: interleukin-6; IL-10: interleukin 10; ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1; vWF: von Willebrand Factor; TPA: tissue plasminogen activator; PAI-1: PAI-1: plasminogen activator inhibitor-1.
Significative *R* and *P* are in bold.

On this basis it is possible that observed differences with regard to the relationship between arterial stiffness indexes and inflammatory markers could be related to differences in immune-inflammatory activation of the acute phase of each TOAST diagnostic subtype.

Cardioembolic stroke could appear as the "less atherosclerotic" among each diagnostic subtype of stroke and this finding could explain the correlation only with CRP and vWF, although our group recently demonstrated that this subtype of acute ischemic stroke is characterized by the highest degree of immune-inflammatory activation of the acute phase [38].

Our finding concerning some differences in the observed correlation between immune-inflammatory markers and arterial stiffness indexes in relation to each TOAST subtype of stroke might also indicate a different degree of vascular anatomy impairment or a different distribution of certain risk factors already reported as related to the inflammation markers, such as hypertension and diabetes. In fact our patients with lacunar stroke, in which both CRP, IL-6, IL-1β, TNF-α and vWF are related to PWV, have an higher frequency of both hypertension and diabetes and this finding allow it to represent, in some ways the prototype of the acute cerebrovascular event in diabetic or hypertensive subjects. Furthermore the molecular events associated with remodelling of the large and medium to small arteries also have been well characterized and involve the combinatorial influences of adhesion molecules, integrins, metallo-proteinases, the renin-angiotensin axis, and inflammation on the cellular constituents (endothelial cells, vascular smooth cells, fibroblasts, and matrix components) of the vasculature [39,40,42].

Biomarkers of inflammation like CRP, interleukin-6, and tumor necrosis factor-α have been associated positively with both indirect (e.g. brachial artery pulse pressure) [41] and direct measures of arterial stiffness in previous studies in apparently healthy individuals, [9] in specific patient groups (e.g. patients with hypertension) [22], and in community-based samples [43–45]. Most of these studies had modest sample sizes, but no study evaluated the relationship between stiffness indexes and immune-inflammatory markers in patients with acute ischemic stroke or other acute cardiovascular event, so our findings appear novel.

A number of possible confounding factors (including additional cardiovascular risk factors, smoking, and other clinical variables as well as pharmacological and non pharmacological treatments) might negatively confound our observed findings. Nevertheless, we compared our patients with acute ischemic stroke patients with matched controls for cardiovascular risk factor. Moreover, we observed no significant difference between case and controls with regard of treatment with ace-inhibitors, ARBs, statins and antidiabetic drugs, potentially able to interfere with vascular inflammation and arterial stiffness markers.

Only one study examined the relationship between arterial stiffness markers and an inflammation marker in subjects with acute ischemic stroke [23].

These authors studied the relationship of arterial stiffness, measured by carotid-femoral pulse wave velocity and inflammation, measured by serum erythrocyte sedimentation rate among 334 ischemic stroke patients. There was a significant correlation between carotid-femoral pulse wave velocity and erythrocyte sedimentation rate ($P = 0.001$), a relationship independent of age, hypertension, diabetes and smoking.

The same authors examined the relationship also investigated the role of inflammation measured by serum erythrocyte sedimentation rate (ESR) in the metabolic syndrome-arterial stiffness relationship amongst 229 prospectively recruited acute ischemic stroke patients, we measured carotid-femoral PWV using applanation tonometry and the inflammatory marker serum ESR. They showed that Carotid-femoral PWV was significantly higher amongst patients with MetS (P, increased waist circumference, raised blood pressure and abnormal glycemia and increased with the number of MetS components).

Our study is the first study that analyzed in patients with acute cerebrovascular events, the relationship between markers of immuno-inflammatory activation such as plasma levels of pro-inflammatory cytokines and both markers of arterial stiffness such as pulse wave velocity (PWV) and augmentation index (Aix) and thus providing a possible explanation for increased arterial stiffness in patients with acute ischemic stroke [46].

Possible limitations of our study are that our findings corroborate previous observational data showing an association between arterial stiffness and inflammatory markers but it does not provide an explanatory causative link for these associations. Previous studies have shown that exogenously administered cytokines (specifically IL-1β) cause a NO-mediated basal vasodilation in human veins by inducing the constitutively expressed endothelial nitric oxide (NO)-synthase [45]. Nevertheless in acute ischemic stroke excitotoxic or ischemic conditions excessively activate nNOS, resulting in concentrations of NO that are toxic to surrounding neurons [47]. But what are extra-cerebral large artery levels of NO in ischemic stroke subjects? No study to our knowledge analyzed this issue.

Another possible limitation because of technical limitations with regard of Aix evaluation is that we recruited in patients with cardioembolic subtype of stroke patients subjects with atrial fibrillation. However, other studies that have assessed the markers of arterial stiffness in patients with atrial fibrillation, have evaluated both PWV and Aix [48,49].

Maybe an acute NO depletion role is not directly presumable to explain an acute rise in arterial stiffness in acute stroke patients. For this series of limitations whether our findings can be extended to a chronic situation is a matter of discussion that future studies should be clarify evaluating arterial stiffness indexes change in subjects at cerebrovascular risk before and after an acute ischemic cerebrovascular event.

The arterial changes have a multitude of potential interconnected causes including endothelial dysfunction, oxidative stress, inflammation, atherosclerosis and vascular calcification. The role and contribution of the biochemical changes to arterial stiffness in the acute phase ischemic stroke is not known, but it's likely that immune-inflammatory activation, acute hyperglycemia, endothelial dysfunction and other toxic effects could be responsible of a acute increase of arterial stiffness after ischemic stroke.

This finding may have potential therapeutic applications aimed to reducing arterial stiffness by interfering with these biochemical changes of acute phase after ischemic stroke by means neuroprotective agents like anti-inflammatory or anti-oxidizing agents or cardiovascular drug with potential pleiotropic actions such as statins.

In conclusion we reported that both aortic stiffness and wave reflection are related to the degree of systemic inflammation in stroke subjects, showing a significant relationship between immuno-inflammatory marker and PWV in LAAS and lacunar subtype of stroke and suggesting that circulating inflammation mediators after acute ischemic stroke can influence the stiffness of vessels distant to those involved in the disease process itself.

Conflict of interest

All the authors state that they have no conflicts to disclose.

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