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# Arterial stiffness and ischemic stroke in subjects with and without metabolic syndrome

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ABSTRACT

We conducted a study to evaluate arterial stiffness markers in subjects with acute ischemic stroke and metabolic syndrome and in relation to TOAST subtype of stroke. We enrolled 130 patients with acute ischemic stroke and metabolic syndrome, 127 patients with acute ischemic stroke without metabolic syndrome and 120 control subjects without acute stroke. Applanation tonometry to record pulse wave velocity (PWV). Stroke patients with metabolic syndrome, compared control subjects without stroke showed higher PWV. In subjects with ischemic stroke and metabolic syndrome, PWV was more significantly and positively correlated with body mass index, systolic blood pressure, hypertension, diabetes, glucose blood levels, LDL cholesterol levels, total cholesterol levels, micro-albuminuria, carotid plaque, previous brain infarct at neuro-imaging. Our findings underline important role of both small vessel disease and atherosclerosis on arterial stiffness pathogenesis in the clinical setting of metabolic syndrome.



## 1. Introduction

Metabolic syndrome (MetS) [1] and arterial stiffness [2] are recognized risk factors for ischemic stroke [3–5].

Nevertheless, no study has evaluated the relationship between arterial stiffness and ischemic stroke in patients with metabolic syndrome. On this basis we conducted a study to evaluate arterial stiffness markers in subjects with acute ischemic stroke and metabolic syndrome, and to evaluate the relationship between these indexes and other clinical and laboratory variables and each component of metabolic syndrome.

## 2. Materials and methods

### 2.1. Patient selection

Patients were considered as having metabolic syndrome on a basis of modification of the NCEP/ATP III [6].

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 2009 and January 2011. As controls, we used hospitalized patients with acute ischemic stroke without a diagnosis of metabolic syndrome, and hospitalized patients without a diagnosis of acute ischemic stroke, 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 [7].

Cardiovascular risk factors were evaluated for both cases and controls on the basis of the criteria as shown in Supplemental Material.

The type of acute ischemic stroke was classified according to the TOAST classification [8]:

1) Large Artery AtheroSclerosis (LAAS); 2) Cardio-Embolic Infarct (CEI); 3) LACunar infarct (LAC); 4) stroke of Other Determined Etiology (ODE); 5) stroke of UnDetermined Etiology.

### 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. 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

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**Table 1**
Premorbid cardiovascular risk factors, clinical characteristics and medication.

| Variable | Stroke pts with metabolic syndrome (*n*:130) | Stroke pts without metabolic syndrome (*n*:127) | Controls (*n*:109) | *P* |
|---|---|---|---|---|
| Age (years) | 64 (61–72.5) | 72 (69–83.5) | 69 (63–80) | **0.031** |
| M/F (*n*) | 69/61 | 60/67 | 54/55 | **0.027** |
| SBP/DBP (mm/Hg) | 152 ± 7.9/98 ± 6.2 | 147 ± 8.9/92 ± 3.2 | 141 ± 9.8/91 ± 2.2 | **<0.001** |
| diabetes (n/%) | 63 (48.46) | 39 (30%) | 47 (41.28%) | 0.263 |
| Hypertension (n/%) | 66 (50.79%) | 47 (37%) | 48 (44.03%) | 0.301 |
| Glucose blood levels (mg/dl) | 149.3 (97–186) | 129.1 (88–142) | 102 (81.5–133.5) | **<0.001** |
| Cholesterol blood levels (mg/dl) | 241 (189–270) | 222 (179–245) | 210 (167–225) | **<0.001** |
| Triglyceride blood levels (mg/dl) | 197.5 (149.75–210.75) | 157.5 (119.4–181.75) | 167.5 (139.4–192.1) | **0.004** |
| White blood cells (per $mm^3$) | 9100 (6200–11,000) | 8200 (7100–10,500) | 7400 (6500–9800) | **<0.001** |
| Stroke subtype | | | | |
| LAAS | 49 (37.69) | 52 (40.94) | | |
| Lacunar | 45 (34.61) | 37 (29.7) | | |
| CEI | 32 (24.61) | 35 (27.55) | | |
| ODE | 3 (2.3) | 2 (1.57) | | |
| UDE | 1 (0.76) | 1 (0.78) | | |
| AIx (%) | 105 ± 3.5 | 101 ± 4.1 | 89 ± 4.6 | **<0.001** |
| PWV (m/s) | 12.9 ± 3.3 | 11.2 ± 2.8 | 10.02 ± 2.29 | **<0.001** |
| SSS | 27.12 ± 16.21 | 29.35 ± 16.21 | 30 ± 16.21 | |
| NIHSS | 19.41 ± 10.06 | 21.21 ± 90.06 | – | |
| Ms-Rankin score at discharge | | | | |
| I | 25 (18.23) | 32 (25.19) | | |
| II | 23 (17.69) | 31 (24.40) | | |
| III | 32 (24.61) | 28 (22.04) | | |
| IV | 29 (22.30) | 23 (18.11) | | |
| V | 21 (16.15) | 13 (10.23) | | |
| Exitus (*n*/%) | 17 (13.07) | 11 (8.66) | – | **<0.001** |
| CAD (*n*/%) | 42 (32.23) | 37 (29.13) | 37 (36.27) | 0.44 |
| CHF (*n*/%) | 23 (17.69) | 20 (15.74) | 15 (14.70) | **0.065** |

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; TIA: transitory ischemic attack; LVH: left ventricular hypertrophy; WMHLS: white matter hypertension lesions.
Demographic and history data are expressed as *n* (percentage).
In bold are expressed values of $p < 0.05$.

meters per second. Three data collection runs were performed, each obtaining a minimum of 10 pairs of simultaneously recorded flow waves. The "distance between the 2 arterial points" was measured using the total distance between the carotid and femoral sites of measurement.

### 2.3. Pulse wave analysis

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 PP).

### 2.4. Statistical analysis

Data are expressed as the mean ± SD. All data were analyzed using the SAS 9.1 statistical program. Clinical characteristics were compared among the four groups using a one-way ANOVA. Pearson's correlation coefficients were calculated to evaluate the relationship of PWV with cardiovascular risk factors in all stroke patients and in each TOAST subtype. Significance was defined at the 0.05 confidence level.

## 3. Results

We enrolled 130 patients with acute ischemic stroke and metabolic syndrome, 127 patients with acute ischemic stroke without metabolic syndrome and 120 control subjects matched for age, sex, cardiovascular risk factors and previous cardiovascular morbidity.

Baseline characteristics in stroke patients and in relation to each TOAST subtype are given in Tables 1 and 2.

Stroke patients with metabolic syndrome, compared to subjects without metabolic syndrome and with stroke, and compared to control subjects without stroke showed a higher mean PWV (12.9 ± 3.3 m/s vs. 11.2 ± 2.8 m/s vs. 10.02 ± 2.29 m/s; $p < 0.001$).

PWV values in lacunar subjects with metabolic syndrome were significantly higher compared to values observed in subjects with lacunar stroke without metabolic syndrome (14.45 ± 2.6 m/s vs. 12.81 ± 2.1 m/s). PWV in subjects with LAAS and metabolic syndrome were significantly higher compared to values observed in subjects with LAAS stroke without metabolic syndrome (11.2 ± 2.31 m/s vs. 10.4 ± 2.22 m/s) and PWV in subjects with CEI subtype and metabolic syndrome were significantly higher compared to values observed in subjects with CEI subtype without metabolic syndrome (11.48 ± 1.98 m/s vs. 10.7 ± 3.5).

### 3.1. Relationship between PWV and clinical and laboratory variables in stroke patients

In subjects with ischemic stroke and metabolic syndrome, compared to those with ischemic stroke and without metabolic syndrome, pulse wave velocity (PWV) was more significantly and positively correlated with body mass index (BMI) ($r = 0.44$ vs 0.39; $p = 0.021$), SBP ($r = 0.42$ vs 0.38; $p = 0.040$), hypertension ($r = 0.42$ vs 0.36; $p < 0.05$), diabetes ($r = 0.44$ vs 0.38; <0.05), glucose blood levels($r = 0.44$ vs 0.31; $p < 0.05$), LDL cholesterol levels($r = 0.36$ vs 0.30; $p = 0.011$), total cholesterol levels ($r = 0.38$ vs 0.31; $p = 0.010$), CAD ($r = 0.37$ vs 0. 29; $p = 0.022$), micro-albuminuria($r = 0.40$ vs 0.30; $p < 0.05$), carotid plaque ($r = 0.35$ vs 0.29; $p = 0.030$), previous brain infarct at neuro-imaging($r = 0.33$ vs 0.28; $p = 0.040$), WMHLS($r = 0.32$ vs 0.24; $p < 0.05$).

**Table 2**
Laboratory and clinical variables and arterial stiffness markers by ischemic stroke subtype in subjects with ischemic stroke and metabolic syndrome and in patients with acute ischemic stroke without metabolic syndrome.

| Variable | Lacunar | | *p* | LAAS | | *p* | CEI | | *p* |
|---|---|---|---|---|---|---|---|---|---|
| Number | With metabolic syndrome (*n*:49) | Without metabolic syndrome (*n*:52) | | With metabolic syndrome (*n*:45) | Without metabolic syndrome (*n*:37) | | With metabolic syndrome (*n*:32) | Without metabolic syndrome (*n*:35) | |
| SBP/DBP (mm/Hg) | 148 ± 6.5/ 94 ± 4.5 | 144 ± 45/9235 | **0.020** | 146 ± 3.4 / 93 ± 4.5 | 1455/91 ± 2.9 | 0.89 | 144 ± 3.8/ 90 ± 3.1 | 143 ± 2.8/ 90 ± 4.1 | 07 |
| Diabetes (*n*/%) | 27 (55.10) | 22 (42.30) | **0.025** | 19 (42.22) | 17 (45.94) | 0.71 | 9 (28.13) | 10 (28.57) | 0.51 |
| Hypertension (*n*/%) | 29 (59.18) | 28 (53.84) | **0.040** | 19 (41.30) | 20 (54.05) | **0.013** | 14 (43.75) | 12 (34.28) | **0.011** |
| Previous stroke (*n*/%) | 19 (38.77) | 14 (26.92) | **0.010** | 16 (34.78) | 10 (27.02) | **0.041** | 11 (34.37) | 9 (25.71) | **0.027** |
| AIx (%) | 116. 3.5 | 112 ± 2.8 | **0.030** | 111 ± 3.7 | 108 ± 2.9 | **0.031** | 108 ± 4.4 | 107 ± 3.5 | **0.021** |
| PWV (m/s) | 14.45 ± 2.6 | 12.81 ± 2.1 | **0.030** | 11.2 ± 2.31 | 10.4 ± 2.22 | **0.030** | 11.48 ± 1.98 | 11.25 ± 2.65 | **0.030** |
| NIHSS | 17.65 ± 14.59 | 15.64 ± 8.73 | **0.021** | 22.51 ± 16.06 | 19.00 ± 12.72 | **0.034** | 25.23 ± 8.78 | 22.23 ± 8.78 | **0.023** |
| CAD (*n*/%) | 18 (36.73) | 14 (26.92) | **0.011** | 16 (35.5) | 12 (32.43) | 0.71 | 8 (25) | 8 (20) | 0.07 |
| Micro-albuminuria (*n* /%) | 21 (42.85) | 17 (32.76) | **0.02** | 17 (37.77) | 9 (24.37) | **0.03** | 9 (28.12) | 7 (20) | **0.045** |
| Carotid plaque (*n*/%) | 14 (28.57) | 9 (17.30) | **0.031** | 16 (35.55) | 11 (29.79) | **0.023** | 7 (21.87) | 5 (14.28) | **0.02** |
| LVH (*n*/%) | 11 (22.44) | 14 (26.92) | **0.021** | 9 (20) | 6 (16.27) | **0.011** | 10 (31.25) | 9 (25.71) | **0.03** |
| Previous brain infarct at neuro-imaging | 18 (36.73) | 12 (23.07) | **0.011** | 14 (30.43) | 9 (24.32) | **0.021** | 9 (28.12) | 7 (20) | **0.02** |
| WMHLS (*n*/%) | 19 (38.77) | 14 (26.92) | **0.0210** | 13 (28.26) | 8 (21.62) | **0.032** | 11 (34.37) | 8 (22.85) | **0.021** |

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; AIx: augmentation index; PWV: puls; CAD: coronary artere wave velocity; SSS: Scandinavian Stroke Scale score; NIHSS: National Institutes of Health Stroke Scale; Angiotensin II receptor blockers (ARBs)y disease; CHF: congestive heart failure; LVH: left ventricular hypertrophy; WMHLS: white matter hypertension lesions.
Demographic and history data are expressed as *n* (percentage).
In bold are expressed values of $p < 0.05$.

### 3.2. Relationship between PWV and clinical and laboratory variables in stroke patients in relation to each TOAST subtype

Among subjects with Lacunar subtype, those with metabolic syndrome, compared to those without metabolic syndrome, showed a more significant positive correlation between PWV and Age ($r = 0.40$ vs 0.33; $p = 0.025$), SBP($r = 0.37$ vs 0.29; $p = 0.022$), hypertension ($r = 0.42$ vs 0.34; $p < 0.05$), diabetes($r = 0.43$ vs 0.34; $p < 0.05$), previous stroke ($r = 0.37$ vs 0.29; $p = 0.022$), glucose blood levels ($r = 0.38$ vs 0.31; $p = 0.021$), micro-albuminuria ($r = 0.39$ vs 0.29; $p < 0.05$), carotid plaque ($r = 0.41$ vs 0.34; $p = 0.031$), LVH ($r = 0.35$ vs 0.29; $p = 0.033$), and previous brain infarct at neuro-imaging ($r = 0.35$ vs 0.28; $p = 0.027$), WMHLS ($r = 0.35$ vs 0.24; $p = 0.025$).

Among LAAS subtype, stroke patients with metabolic syndrome compared to those without metabolic syndrome, showed a more significant positive correlation between PWV and SBP ($r = 0.38$ vs 0.27; $p = 0.040$), hypertension ($r = 0.40$ vs 0.34; $p = 0.023$), LDL cholesterol plasma levels ($r = 0.40$ vs 0.30; $p < 0.05$), total cholesterol plasma levels ($r = 0.39$ vs 0.30 $p = 0.012$), CAD ($r = 0.29$ vs 0.23; $p = 0.040$), CHF ($r = 0.21$ vs 0.19; $p = 0.022$), carotid plaque ($r = 0.38$ vs 0.32; $p = 0.028$), LVH ($r = 0.37$ vs 0.29; $p = 0.022$), and previous brain infarct at neuro-imaging ($r = 0.37$ vs 0.30; $p = 0.037$).

Among CEI subjects, stroke patients with metabolic syndrome compared to those without metabolic syndrome, showed a more significant positive correlation between PWV and age ($r = 0.44$ vs 0.36; $p = 0.020$), hypertension ($r = 0.35$ vs 0.31; $p = 0.044$), atrial fibrillation ($r = 0.41$ vs 0.31; $p < 0.05$), previous stroke ($r = 0.37$ vs 0.21; $p = 0.023$), glucose blood levels ($r = 0.38$ vs 0.33; $p = 0.023$), LDL cholesterol plasma levels ($r = 0.47$ vs 0.34; $p = 0.012$), total cholesterol plasma levels ($r = 0.36$ vs 0.30; $p = 0.022$), CAD ($r = 0.29$ vs 0.23; $p = 0.042$), CHF($r = 0.34$ vs 0.26; $p = 0.039$), and LVH ($r = 0.36$ vs 0.29; $p = 0.021$).

## 4. Discussion

Our study shows that patients with ischemic stroke and metabolic syndrome have higher values of indexes of arterial stiffness in relation to age, sex and cardiovascular risk factor compared to control subjects without stroke and also compared to stroke subjects without metabolic syndrome.

Metabolic syndrome represents a determinant of progressive arterial stiffening [2,9,10].

At intergroup analysis our findings show a significant difference among TOAST diagnostic subtypes with regard to arterial stiffness indexes in subjects with or without metabolic syndrome. We report that subjects with lacunar subtype and metabolic syndrome show higher values of PWV and AIx compared to subjects with lacunar syndrome and without metabolic syndrome. Furthermore subjects with metabolic syndrome other stroke subtypes (LAAS and CI) also showed higher values of arterial stiffness indexes compared to subjects without metabolic syndrome.

Our findings are consistent with the hypothesis that cerebral small-vessel disease results from abnormal flow pulsations into the brain microcirculation as an exposure to highly pulsate pressure and augmented flow, which exist in the carotid and vertebral arteries as a result of arterial stiffening, may thus lead to microvascular damage and eventually to stroke [11].

Ischemic stroke is not a homogenous disease and some studies [12,13] indicate that its patho-physiology differs among the subtypes of stroke. Moreover, different potentially modifiable vascular risk factor profiles were identified for each subtype of ischemic stroke, particularly hypertension (and more recently diabetes) in the case of lacunar infarction. Our study confirms

previous data regarding the strict association between hypertension and diabetes and lacunar subtype of stroke, showing a higher percentage of hypertensive and diabetic subjects in the lacunar group compared to other subtypes.

So it's possible that the high prevalence of hypertension in lacunar stroke subjects may explain the higher values of arterial stiffness indexes observed in these subjects.

In our patients with acute ischemic stroke and metabolic syndrome we observed a more significant correlation between hypertension and diabetes and arterial stiffness, particularly in subjects with lacunar stroke.

On this basis it's possible to hypothesize that the major determinants of arterial stiffness and stroke risk in subjects with metabolic syndrome are hypertension and diabetes. It's also possible that the high prevalence of hypertension and diabetes in lacunar stroke subjects with metabolic syndrome may explain the higher values of arterial stiffness indexes observed in these subjects.

It is also plausible that some differences in the relationship between arterial stiffness indexes and acute ischemia in relation to the presence of metabolic syndrome could be related to differences in immune-inflammatory activation of the acute phase of acute ischemia and to each TOAST diagnostic subtype. This is a very interesting issue and future studies should address this question.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2012.08.027.

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