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Endothelial Function in Stroke Subtypes Using Endopat Technology.

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Abstract :

Background : Endothelial function is characterized by the vasodilator capacity of blood vessel smooth muscle cells mediated by nitric oxide. Some studies have shown an inverse association between the endothelial function and the carotid intima-media thickness (IMT). The relationship between endothelial dysfunction and stroke based on several studies has shown that is altered in all stroke subtypes especially lacunar strokes.

Methods : We aimed to investigate endothelial function by EndoPAT device in relation to stroke subtypes. We investigate too the correlations between endothelial function and IMT and we study possible interactions with age, sex, traditional risk factors and severity of stroke. Subsequent patients with acute ischemic stroke were enrolled. They were divided according with the etiological mechanism of stroke (TOAST classification). Endothelial function was assessed with finger plethysmography by the EndoPAT device that gave Reactive Hyperemia Index (RHI) and Augmentation Index (AI).

Results : Patients with a cardioembolic stroke had a RHI higher than atherotrombotic or lacunar stroke. There was a negative correlation between RHI and IMT and positive between AI and age.

Conclusions: The endothelial function is different between stroke subtypes with higher values of RHI in the cardioembolic respect to lacunar or atherotrombotic. The RHI is correlated with the atherosclerosis by the negative relationship with the IMT. The AI that shows the rigidity in the arteries increased with the age.

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Introduction :

Endothelial function is characterized by the vasodilator capacity of blood vessel smooth muscle cells mediated by nitric oxide [1]. In recent years, a number of experimental and clinical studies have established the role of endothelial dysfunction (ED) in the development of cerebrovascular diseases [2]. ED is an early event of atherosclerosis that precedes structural atherosclerotic changes in the vascular wall. As the major regulator of vascular homeostasis the endothelium maintains the balance between vasodilatation and vasoconstriction. Damage of the endothelium upsets this balance and initiates a number of events that promote or exacerbate atherosclerosis; these include increased endothelial permeability, platelet aggregation, leukocyte adhesion and generation of cytokines. Some studies have shown an inverse association between the endothelial function and the carotid intima-media thickness (IMT) [3,4].

There are different non-invasive methods for assess the endothelial function. Respect to brachial flow mediated dilatation (FMD), the peripheral arterial tonometry (PAT) has several unique qualities that improve its accuracy in assessing endothelial-mediated changes in vascular tone: The PAT signal is simultaneously recorded from both arms and the EndoPAT device enables assessment of occlusion and provocation quality. Comparing EndoPAT scores to intra-coronary assessment of endothelial function (considered as gold standard) yielded a sensitivity of 82% and a specificity of 77% [5].

The relationship between endothelial dysfunction and stroke based on several studies has shown that is altered in all stroke subtypes especially lacunar strokes. Chen et al. showed that overall stroke patients had impaired FMD, but only lacunar infarction had significantly impaired FMD versus controls [6]. Other studies have shown ED in large artery atheromatous stroke [7], cerebral atherosclerosis [8] and cardioembolic infarcts [1]. Chlumsky et al. showed that patients with atrial fibrillation had significantly better FMD results than patients without it [9].

We aimed to investigate endothelial function by EndoPAT device in relation to stroke subtypes according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification. We studied the correlations between endothelial function and IMT and study possible interactions with age, sex, traditional risk factors and severity of stroke.

Methods :

We studied patients consecutively admitted to our stroke unit between May 2012 and January 2013 with a clinical diagnosis of acute ischemic stroke (IS). The patients were enrolled within 48 hours and the examinations were completed within 4 days after the event. Stroke severity was assessed with the NIHSS score [10]. During the acute phase after stroke, all patients were on standard medical cardiovascular therapy in individual adjusted doses. . The patients only received sporadically Labetalol or Urapidil as treatment for release the arterial tension. Patients within the therapeutic window on admission for thrombolysis were treated with alteplase.

Acute IS was classified according to the TOAST classification: cardioembolic infarcts, large-artery atherosclerotic infarcts and lacunar infarcts. We obtained information about vascular risk factors: arterial hypertension (HTN), diabetes mellitus, hyperlipidemia and smoking.

Exclusion criteria were stroke of undetermined aetiology, poor participation with testing, amputation of one arm, hand or fingers, intercurrent acute illness, renal failure (glomerular filtration rate < 30), hemodynamic instability or use of vasoactive drugs.

Colour-coded duplex ultrasonography of the carotid arteries was performed in all patients. Carotid IMT was measured according to the Mannheim IMT consensus [11]. Local ethics committee approved the study, and all subjects gave their written informed consent.

Assessment of Endothelial Function

Quantitative determination of endothelial function was assessed using a finger plethysmograph (EndoPAT 2000; Itamar Medical, Caesarea, Israel). Endothelial function was based on PAT measurement of the index finger during reactive hyperemia of the forearm vascular bed. The post-occlusion reading is adjusted for the pre-occlusion baseline measurement PAT signal. To control for potential confounding stimuli during the recording, the signal is further adjusted for the spontaneous variations of the pulse pressure amplitude by simultaneous PAT assessment of the contralateral (nonocluded) arm. Pressure curves were recorded electronically and the reactive hyperemia index (RHI) as dimensionless ratio and the augmentation index (AI) as percentages were calculated using a computerized algorithm of the EndoPAT 2000 software system [12]. As this value changes with the heart rate, the device gives the normalized value at 75 bpm, the AI@75 [13].

All EndoPAT assessments were performed under standardized conditions with the patient in the supine position, in a quiet, air-conditioned and well-tempered room (23ºC). Pneumatic probes were placed on both index fingers. Baseline measurement was carried out for 10 minutes. Complete arterial occlusion for 5 minutes was induced by external compression with 50 mmHg above systolic blood pressure. In all subjects, the dominant arm was used for the occlusion protocol but in patients with arm paresis, the nonparetic arm was used.

Statistical Analysis

Continuous variables were expressed as mean ± SD or median and interquartile ranges, depending on whether they were normally distributed, and groups were compared using the Student t test or the Mann-Whitney test, as appropriate. Categorical variables were reported as percentage or absolute numbers. Proportions between groups were compared using the chi-squared test, and Fisher exact test as appropriate.

One-way analysis of variance test followed by Bonferroni multiple comparison tests was used to compare the differences among different stroke subtypes. The relationship between variables was analyzed by linear regression analysis. Statistical analysis was performed with SPSS-13.0 program for Windows. $p < 0,05$ was considered statistically significant.

Results :

The study included 74 patients with a mean age of 68.1 ± 12.2 years, 39.2% were women. Stroke aetiology was: cardioembolic in 28.4%, large-artery atherosclerosis in 33.8% and small-vessel occlusion in 37.8% of patients. Mean RHI was 1.83 ± 0.65, median AI was 19% [IQR=-3

30] and AI@75 was 16% [7-26]. The main clinical characteristics are summarized in table 1.

The differences in the RHI, AI and AI@75 between demographic, clinical, risk factors and stroke subtypes are shown in table 2. There were differences in the RHI between subtype strokes (p=0.036) as shows the figure 1, but not in the AI (p=0.163) or AI@75 (p=0.258). The Bonferroni multiple comparison showed that RHI was lower in lacunar and large-artery atherosclerosis infarcts compared with cardioembolic strokes (p=0.003). Differences continued spite of stratification by risk factors.

Patients with HTN have an AI and AI@75 higher than not hypertensive patients (p=0.043 and p=0.006, respectively). There were differences in the AI@75 between males and females, so the last had higher values (p=0.042)

Linear regression analysis between continuous variables is summarized in table 3. There is a negative correlation between RHI and carotid IMT. There was a negative correlation between AI and AI@75 with NIHSS scores but positively between AI and AI@75 with age. There was not a correlation between RHI and AI or AI@75.

Discussion:

The main results of this study are that the patients with cardioembolic strokes had higher values in the endothelial function assesses by RHI than the lacunar and large-artery atherosclerotic strokes. Patients with history of HTN had an AI and AI@75 higher than non hypertensive patients.

Despite widespread use in clinical research, the methods used for the assessment of endothelial function are not adequately standardized. The non-invasive EndoPAT technology was used for evaluating peripheral ED. This method was applied previously in other clinical studies [14-15]. The third-generation Framingham Heart Study tested an association between peripheral vascular function determined by fingertip peripheral tonometry device and cardiovascular risk factors [16]. Notably, the RHI signal recorded by Endo-PAT is not limited to endothelium-dependent vasodilation but also includes endothelium-independent signals induced by ischemia.

Table 3. Lineal regression analysis between continuous variables.

Variables	R	p
RHI – Age	+0.153	0.194
RHI – carotid IMT	- 0.411	0.000
RHI – AI	-0.071	0.549
RHI – AI@75	-0.017	0.885
RHI – NIHSS score	-0.061	0.605
AI – Age	+0.243	0.037
AI – carotid IMT	+0.085	0.437
AI – NIHSS score	-0.270	0.020
AI@75 – Age	+0.309	0.007
AI@75 – carotid IMT	+0.029	0.808
AI@75 – NIHSS score	-0.238	0.041

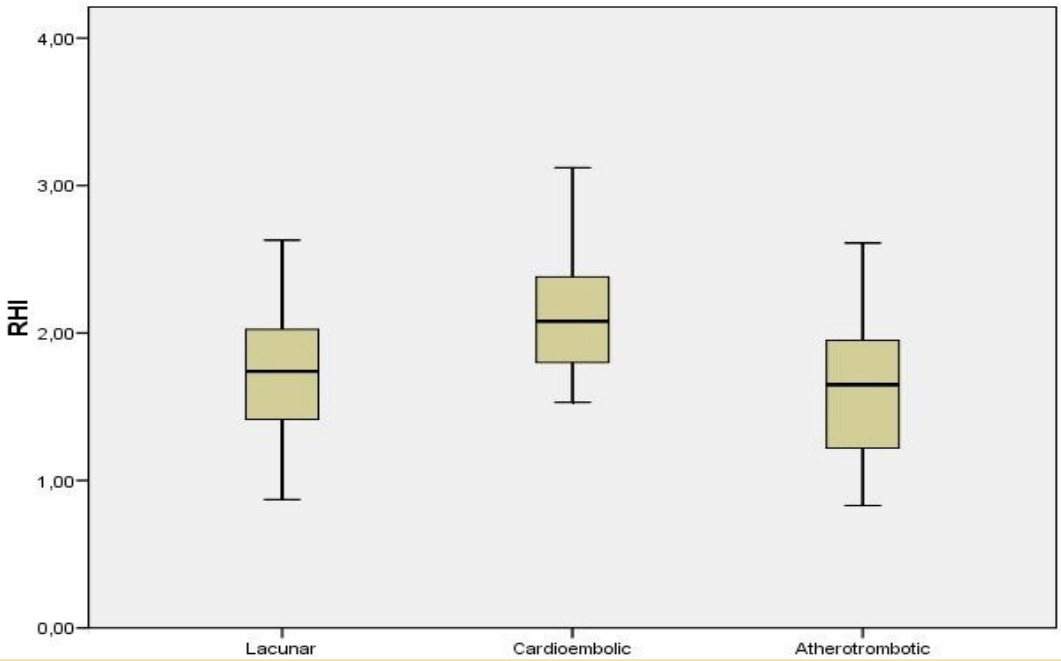

Figure 1. Blox plot showing differences in the RHI between stroke subtypes: Cardioembolic infarcts have a RHI value higher than lacunar and atherotrombotic infarcts (p:0,003).

Table 1. Clinical and demographic characteristics of patients with acute ischemic stroke (subgroups according to TOAST classification) enrolled in the study, n=74.

Variable	n	Percentage or Mean ± SD or Median ± IQR
Age	74	68.1 ± 12.2
Men	45	60.8%
Hypertension arterial	41	55.4%
Diabetes mellitus	20	27.0%
Hypercholesterolemia	30	40.5%
Current smoking	19	35.6%
Right Carotid IMT	74	0.84 ± 0.25
Left Carotid IMT	74	0.86 ± 0.25
RHI	74	1.83 ± 0.65
AI	74	19 [8-30]
AI@75	74	16 [7-26]
NIHSS score	74	4.55 ± 5.41
Cardioembolic	21	28.4%
Large-artery atherosclerosis	25	33.8%
Small-vessel occlusion	28	37.8%

Table 2. Studies comparing the variables RHI, AI and AI@75 between patients with or without risk factors and stroke subtypes.

EndoPAT values	Variable		Mean	SD	p
RHI	Sex	Male	1.86	0.73	0.676
		Female	1.93	0.46	
	Hypertension arterial	Yes	1.76	0.50	0.065
		No	2.04	0.76	
	Diabetes Mellitus	Yes	1.97	0.95	0.623
		No	1.86	0.45	
	Hypercholesterolemia	Yes	1.92	0.80	0.766
		No	1.87	0.51	
	Current Smoking	Yes	1.71	0.63	0.158
		No	1.95	0.63	
	Stroke Subtypes	Lacunar	1.87	0.76	0.036
		Cardioembolic	2.16	0.47	
		Atherotrombotic	1.68	0.54	
AI	Sex	Male	15.16	21.53	0.124
		Female	23.76	24.10	
	Hypertension arterial	Yes	23.15	25.47	0.043
		No	12.79	17.71	
	Diabetes Mellitus	Yes	18.15	28.87	0.941
		No	18.67	20.62	
	Hypercholesterolemia	Yes	23.90	22.62	0.094
		No	14.86	22.62	
	Current Smoking	Yes	13.84	16.70	0.219
		No	20.15	24.49	
	Stroke Subtypes	Lacunar	19.5	15.9	0.102
		Cardioembolic	11.0	29.8	
		Atherothrombotic	23.7	21.8	
AI@75	Sex	Male	12.76	15.90	0.042
		Female	22.17	20.68	
	Hypertension arterial	Yes	21.41	20.12	0.006
		No	10.27	13.92	
	Diabetes Mellitus	Yes	17.75	21.92	0.744
		No	15.96	17.09	
	Hypercholesterolemia	Yes	20.50	18.81	0.123
		No	13.68	17.76	
	Current Smoking	Yes	11.32	10.39	0.061
		No	18.22	20.20	
	Stroke Subtypes	Lacunar	15.18	13.91	0.258
		Cardioembolic	12.52	24.65	
		Atherothrombotic	21.16	16.29	

ED is an important link between risk factors and atherosclerosis. It is considered to be an integral component of atherosclerotic vascular disease and its presence is a risk factor for the development of clinical event. Decreased endothelial function may reduce vascular compliance, which is related to increased arterial stiffness and correlates with cardiovascular events [17]. Thus, increased arterial stiffness may be a mechanism by which ED predisposes to complications of atherosclerosis [18].

A systematic review of endothelial function in stroke have shown than ED is present in patients with lacunar stroke but may simply reflect exposure to vascular risk factors and having a stroke, because a similar degree of dysfunction is found in large-artery atherosclerotic strokes [7]. Large-artery atherosclerotic infarcts are also associated with ED [19].

Chlumsky et al. [9] measured carotid IMT and FMD in patients with ischemic strokes and evaluated if there was a relationship between these measurements and the presence of atrial fibrillation. Patients with atrial fibrillation had lower IMT values compared with patients without atrial fibrillation and better FMD results. Compliance increased in patients with atrial fibrillation compared with patients without atrial fibrillation. They concluded that measuring IMT, compliance and FMD might be helpful in the differentiation between stroke of embolic and thrombotic aetiology. Our data show than endothelial function too is different between aterothrombotic and cardioembolic aetiologies, but the arterial stiffness is similar. A systematic review of ED in lacunar strokes revealed that ED might be involved in the pathogenesis of lacunar stroke, especially in those patients with concomitant silent lacunar infarcts and ischemic white matter lesions [20].

ED assessed by FMD has been proposed as an independent predictor for a new-onset vascular event after first-ever ischemic stroke [21]. Another study measured with FMD showed that ED is similar in patients with recent acute and stable cerebrovascular disease [22]. Rundek et al. [4] found a significant association between endothelial dysfunction and presence of carotid plaque in a population-based cohort.

Noon et al. [23] showed by applanation tonometry that women had a higher degree of arterial stiffness than men of a similar age. The majority of women were over 40 years, providing the possibility of postmenopausal effects on arterial compliance. These data are congruent with us results. Mitchell et al. [24] studied in a healthy sample with no evidence of cardiovascular disease and low burden of risk factors, an age-related increase in arterial stiffness. We have found similar results with an increase of arterial stiffness with age.

Treatment with Atorvastatin has shown an improvement of FMD values in patients with lacunar infarcts and patients with risk factors but without stroke [25]. One study showed than endothelial nitric oxide synthase gene is a modifier of the cerebral response to ischemia [26] and in obese patients the endothelial function is related with thrombolysis [27]. There are no physiopatological reasons for think that the administration of Alteplase could change the results in endothelial reactivity.

Our study has some limitations: Firstly, the small sample size and the fact that our study was not a control group mean that our conclusions must be treated with caution.

Secondly, we were unable to withdraw some medications for more than five half-lives before the stroke. The beneficial effects on vasoreactivity of these medications might be confounding. And finally, we did not study the underlying mechanisms of endothelial dysfunction as analysis of endothelin or other substances as circulating endothelial cells [28].

In conclusion, this study demonstrates that in the acute phase of ischemic cerebrovascular diseases the endothelial function assessed by EndoPAT technology is different between the stroke subtypes with higher values in cardioembolic infarcts and patients with arterial hypertension had higher values of arterial stiffness than non hypertensive patients.

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