Predictive value of ankle brachial index in patients with acute ischaemic stroke

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Background: The ankle brachial index (ABI) is a known measure of lower-limb peripheral artery disease (PAD), as well as a marker for other cardiovascular disease events. Objective: Our goal was to compare the prevalence of abnormal ABI scores (ABI ≤ 0.9) between: consecutive patients with acute ischaemic stroke (IS), primary care patients with refractory hypertension (rHT), and patients at intermediate cardiovascular risk (ICVR). Also, to determine the prognostic value of abnormal ABI for stroke recurrence in patients with IS.

Methods: We compared 116 consecutive patients with IS with 190 rHT and 150 ICVR patients. Clinical data and ultrasonographic findings were recorded. Stroke recurrence and risk of new vascular events were assessed after 18 months of follow-up.

Results: Low ABI was more frequent in rHT (35.8%) than in the IS (24.1%) and ICVR (24.7%) groups (P = 0.031). Amongst patients with IS, ABI ≤ 0.9 was associated with vascular risk factors (VRF) ≥ 3 (33.8% vs. 7.1%, P = 0.001) and large-artery atherosclerosis (LAA) (43.5% vs. 19.4%, P = 0.015). Multivariate analyses (logistic regression) only identified VRF > 3 as independently associated with low ABI (OR: 6.46; 1.81-23.02; P = 0.004). Abnormal ABI was associated with stroke recurrence (32.1% vs. 13.6%, P = 0.027) and the appearance of any major vascular event (50.0% vs. 17.0%, P < 0.001). In the logistic regression analysis, adjusted for VRF, age, and LAA, ABI remained as an independent predictor of vascular events (HR 3.99; 1.90-8.41 P < 0.001).

Conclusion: Abnormal ABI was associated with classical risk factors, especially hypertension. The measurement of ABI amongst patients with IS appeared to be useful to identify high-risk patients and plan adequate prevention therapies.

Introduction

The ankle brachial index (ABI) is an inexpensive, easy, and reliable tool to identify patients with subclinical peripheral arterial disease (PAD) [1]. Our group [2], consistent with previous publications in the literature [3,4], has recently described the existence of a high percentage of elevated ABI scores in patients who have suffered from ischaemic stroke (IS). The determination of ABI is based on a simple and increasingly available sonography test. In patients with IS, PAD is associated with large-artery atherosclerosis (LAA) [2,4] and vascular risk factors (VRF) [2]. Pathological ABI values are associated with greater risk of a vascular event (VE) [5–10]. There are few studies in patients with IS that have proposed a predictive role for ABI [3,10]. Detection of subclinical PAD can constitute a useful prognostic tool for selecting patients at increased risk of suffering a VE after an IS.

In the current study, we investigate the predictive value (risk of IS recurrence and appearance of any type of VE) of a PAD diagnosis based on the determination of ABI in patients who are suffered from IS. We also compare the incidence of pathological ABI in a control group of patients with VRF who had not suffered from VE.
Methods

Population

We included 116 consecutive patients admitted to the Neurology Department of the Hospital Universitari Arnau de Vilanova (Lleida, Spain), with a diagnosis of IS between March 2006 and November 2006, in a prospective study. The cohort of patients with IS was compared with two other cohorts studied in the Detection and Treatment Unit of Atherothrombotic Diseases. The first was a group of 190 subjects studied for primary arterial hypertension (rHT) taking ≥2 antihypertensive medications. The second cohort was constituted of 150 subjects from primary-care centers with the common characteristic of having a cardiovascular risk score (Score, low prevalence of cardiovascular diseases) equal to or below five [11]. Moreover, we matched patients with IS with patients from the other groups according to gender and age.

Variables

Patients with IS underwent a systematic study during their hospital stay [2]. All patients underwent routine blood biochemistry, electrocardiography (ECG), cervical duplex ultrasonography and transcranial doppler (TCD), computed tomography (CT), and cranial MRI with DWI sequences. Transthoracic echocardiography, Holter ECG, and right-to-left shunt detection were achieved when indicated.

Measurement of ankle brachial index

The ABI measure was obtained using a hand-held Doppler scanning probe with a Minidop ES-100X. Systolic arterial pressure was measured once in both brachial arteries, dorsalis pedis arteries, and posterior tibial arteries. After, the patient had rested supine for at least 5 min. ABI was calculated as indicated by McDermott [12], dividing the lower extremity arterial pressure by the brachial arterial pressure. Patients were classified as a function of ABI values: ≤0.90 (abnormal) and > 0.90 [13]. In patients with IS, the ABI measurement was obtained during the hospital stay. Five subjects were not measured during the inclusion period because of death secondary to IS during their hospital stay.

Ultrasound protocol

TCD studies were carried out using a Multi-DopT/TCD (DWL Elektronische Systeme GmbH) on admission. Intracranial stenosis was diagnosed if the mean blood flow velocity at a circumscribed insonation depth was > 80 cm/s, with side-to-side differences > 30 cm/s and signs of disturbed flow [14]. Baseline cervical internal carotid artery (ICA) atherosclerosis was categorized using an Eco Doppler Micromaxx device (Sonosite) as follows: absent; mild, if one or both ICAs had < 50% stenoses; moderate, when any of the ICA presented 50–70% stenoses; and severe, if any ICA had > 70% stenosis, according to Society of Radiologists in Ultrasound Consensus Conference criteria [15].

The arteriothrombotic etiology was established in all patients in which it was possible to demonstrate symptomatic intracranial or extracranial arterial stenosis leading to the clinical condition; in the case of extracranial stenoses, these should have been > 50% [16].

Vascular episodes

The recurrence of IS, the risk of new episodes of myocardial ischaemia, and the development of symptomatic PAD were evaluated in all patients after 18 months of follow-up. Patients were followed up by face-to-face interview every 6 months.

Statistical analysis

Analyses were performed using the srsr statistical package, version 12.0. Comparisons between categorical variables were performed using the Pearson $\chi^2$ test and the Fisher’s exact test. Statistical significance for intergroup differences was assessed by the $\chi^2$ test for categorical variables and the Student’s $t$, ANOVA, and Mann–Whitney $U$-tests for continuous variables. Univariate analysis was performed to detect variables associated with pathological ABI and the occurrence of VE. We carried out a multivariate analysis Cox proportional modeling analysis, adjusted for variables associated with pathological ABI and the risk of VE, respectively. The Kaplan–Meier method was used to compare survival curves with the log-rank test. A $P < 0.05$ was considered statistically significant in all comparisons.

The study was approved by our local ethics committee, “Comité d’Ética i Investigació Clínica de l’Hospital Universitari Arnau de Vilanova de Lleida”. The patients gave informed consent.

Results

A total of 456 subjects were included in our study: 116 patients with IS, 190 patients with rHT and 150 patients with ICVR. The baseline characteristics of the initial cohorts and the effect of matching between groups are presented in Table 1. In the whole study population, mean age was $61.2 \pm 11.5$ years, and 66.2% were male.
Ankle brachial index in patients with stroke

Table 1 Baseline characteristics and ABI value

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with stroke (n = 116)</th>
<th>rHTA (n = 190)</th>
<th>ICVR (n = 150)</th>
<th>P</th>
<th>Matched Stroke patients (n = 68)</th>
<th>Matched controls (n = 90)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>70.4 ± 12.2</td>
<td>58.0 ± 9.1</td>
<td>58.2 ± 9.8</td>
<td>&lt;0.001</td>
<td>63.1 ± 8.6</td>
<td>65.5 ± 9.9</td>
<td>0.106</td>
</tr>
<tr>
<td>Hypertension</td>
<td>81 (69.8%)</td>
<td>190 (100%)</td>
<td>30 (20.0%)</td>
<td>&lt;0.001</td>
<td>45 (66.2%)</td>
<td>68 (75.6%)</td>
<td>0.216</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>38 (32.8%)</td>
<td>44 (23.2%)</td>
<td>26 (17.3%)</td>
<td>0.013</td>
<td>22 (24.4%)</td>
<td>22 (32.4%)</td>
<td>0.287</td>
</tr>
<tr>
<td>Smokers</td>
<td>22 (19.0%)</td>
<td>44 (23.2%)</td>
<td>82 (54.7%)</td>
<td>0.131</td>
<td>6 (10.7%)</td>
<td>10 (11.0%)</td>
<td>0.959</td>
</tr>
<tr>
<td>Male</td>
<td>86 (74.1%)</td>
<td>127 (66.8%)</td>
<td>89 (59.3%)</td>
<td>0.039</td>
<td>53 (77.9%)</td>
<td>72 (80.0%)</td>
<td>0.753</td>
</tr>
<tr>
<td>Dyslipemia</td>
<td>33 (28.4%)</td>
<td>52 (28.0%)</td>
<td>65 (43.3%)</td>
<td>0.006</td>
<td>18 (26.5%)</td>
<td>22 (24.4%)</td>
<td>0.835</td>
</tr>
<tr>
<td>ABI ≤ 0.9</td>
<td>28 (24.1%)</td>
<td>68 (35.8%)</td>
<td>37 (24.7%)</td>
<td>0.031</td>
<td>13 (19.1%)</td>
<td>26 (28.9%)</td>
<td>0.158</td>
</tr>
</tbody>
</table>

Percentage values provided in parentheses.

Mean ABI was 0.99 ± 0.20. Although patients with stroke were older, the incidence of abnormal ABI was higher in the rHT group. The univariate analysis revealed that hypertension (33.2% vs. 21.3%, P = 0.008) and diabetes (36.1% vs. 27.0%, P = 0.069) were associated with ABI < 0.9.

In univariate analyses of the cohort of patients with stroke (Table 2), the presence of three or more accumulated VRF, LAA, and extracranial stenosis >50% were associated with pathological ABI score, P < 0.05. In multivariate analysis, only accumulated VRF remained an independent predictor of pathological ABI score (HR 6.46; 1.81-23.02, P = 0.004).

Factors associated with the appearance of new VE

After 18 months of follow-up, 21 (16.5%; 95% CI: 9.5–23.5) patients suffered from recurrence of IS, three (2.7%, 95% CI: 0.2–6.2) suffered from intraparenchymatous hemorrhage, eight (6.5%, 95% CI: 1.9–11.1) suffered from episode of ischaemic cardiopathy, three (4.6%, 95% CI: 0–13.2) developed clinical PAD, and six (5.5%, 95% CI: 0–14.5) died because of non-vascular causes. The variables associated with the recurrence of IS and the appearance of any type of VE (Table 3) were age, LAA, and pathological ABI (P < 0.05). The presence of three or more VRF was associated only with the appearance of any VE (P = 0.045).

The Cox proportional modeling analysis – adjusted for age, VRF, and LAA – showed that the detection of a pathological ABI behaves as an independent prognostic factor for any VE (HR: 3.99; 95% CI: 1.90–8.41; P < 0.001), but not for the recurrence of IS (HR: 1.76; 95% CI: 0.64–4.89; P = 0.276). LAA becomes the single independent prognostic factor for IS recurrence (RR 3.86; 95% CI: 1.55–8.74; P = 0.003).

The Kaplan–Meier survival curves shown in Fig. 1 make clear the poor evolution of patients with PAD detected by ABI.

Discussion

This study confirms previously published data on the elevated prevalence of pathological ABI values in patients with IS [2–4,10] and their association with the accumulation of vascular risk factors [2]. The original aspect of this research is that it shows that the existence of a pathological ABI score is an independent prognostic factor for the appearance of new vascular episodes in this group of patients.

Nakano et al. [4] were the first to examine the incidence of subclinical PAD in patients with IS, obtaining results with incidences similar to those observed in our

Table 2 Variables associated with abnormal ABI amongst patients with stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>&gt;0.9 (88) n (%)</th>
<th>≤0.9 (28) n (%)</th>
<th>All cases n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>69.4 ± 12.5</td>
<td>73.3 ± 11.1</td>
<td>70.4 ± 12.2</td>
<td>0.143</td>
</tr>
<tr>
<td>Male sex</td>
<td>62 (70.5)</td>
<td>24 (85.7)</td>
<td>86 (74.1)</td>
<td>0.108</td>
</tr>
<tr>
<td>Association of &gt;2 risk factors</td>
<td>49 (55.7)</td>
<td>25 (89.3)</td>
<td>74 (63.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Extracranial stenosis &gt;50%</td>
<td>7 (8.0)</td>
<td>6 (21.4)</td>
<td>13 (11.2)</td>
<td>0.049</td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>13 (14.8)</td>
<td>10 (35.7)</td>
<td>23 (19.8)</td>
<td>0.015</td>
</tr>
<tr>
<td>Intracranial stenosis</td>
<td>6 (6.8)</td>
<td>4 (14.3)</td>
<td>10 (8.6)</td>
<td>0.220</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>24 (27.3)</td>
<td>5 (17.9)</td>
<td>29 (25.0)</td>
<td>0.316</td>
</tr>
<tr>
<td>Cardioembolic disease</td>
<td>19 (21.6)</td>
<td>3 (10.7)</td>
<td>22 (18.9)</td>
<td>1</td>
</tr>
<tr>
<td>Undetermined etiology</td>
<td>32 (36.4)</td>
<td>8 (28.6)</td>
<td>40 (34.5)</td>
<td>0.450</td>
</tr>
</tbody>
</table>

Percentage values provided in parentheses.
cohort. They observed a relationship between pathological ABI and the existence of LAA pathology [4]. This circumstance supports the hypothesis that the atheromatous phenomenon is universal and dynamic, affecting all of the arterial tree.

Recently, Weimar et al. [10], in a multicentric German study, have obtained similar results, observing a greater risk of stroke recurrence or death from vascular causes in patients with stroke with pathological ABI scores.

Despite the existence of age differences between the patients with IS and the control group with VRF, there were no differences detected with respect to the incidence of pathological ABI. These data are in agreement with those seen in previous studies, in which the association of VRF has a determinant role in the development of PAD [17,18]. Returning to the concept of the universality of the atherosclerotic process, the detection of subclinical atherosclerotic disease using ultrasound exploration of the extracranial and intracranial vessels and the ABI could be beneficial to all patients with VRF.

The prognostic role of pathological ABI can be important in the management of patients with IS, especially with the goal of avoiding extracranial vascular episodes. In patients with IS and pathological ABI, diagnostic protocols could be established to detect coronary or intra-abdominal atherosclerotic pathology. In the same vein, the presence of subclinical PAD can determine the best choice of anti-aggregant, taking into account that not all anti-platelet medications have the same efficacy for PAD [17]. Clopidogrel, compared to acetylsalicylic acid, reduces the appearance of vascular episodes, especially in patients with symptomatic PAD [19].

The number of patients is the principal limitation of the present study. A larger study would more accurately demonstrate the prognostic value of ABI in different etiological subtypes of stroke.

In summary, the determination of ABI is a simple technique that detects the presence of subclinical PAD in a considerable percentage of cases, especially in patients with LAA and associated VRF. The calculation of the ABI may facilitate the detection of patients

| Table 3 Variables associated with new cerebral ischaemic event or any vascular event |
|---------------------------------|---------------------------------|-----------------|
| Cerebral ischaemic event        | Any vascular event              |
| No (95) N (%)                  | Yes (21) N (%)                  |
| Age, mean ± SD, y              | 69.4 ± 13.0a                    | 74.9 ± 6.3      |
| Male sex                       | 70 (73.7)                       | 16 (76.2)       |
| Association of >2 risk factors | 59 (62.1)                       | 15 (71.4)       |
| Extracranial stenosis >50%     | 9 (9.5)                         | 4 (19.0)        |
| Large-artery atherosclerosis   | 14 (14.7%)                      | 9 (42.9 %)      |
| Intracranial stenosis          | 5 (5.3)                         | 23 (28.6)       |
| Small vessel disease           | 19 (20.0)                       | 3 (14.3)        |
| Cardioembolic disease          | 21 (22.1)                       | 3 (14.3)        |
| Undetermined etiology          | 41 (43.2)                       | 6 (28.6)        |
| ABI ≤ 0.9                      | 19 (20.0)                       | 9 (42.9 %)      |

Percentage values provided in parentheses.

The Kaplan–Meier estimates the proportion of patients free of new cerebral episodes ($P = 0.017$; log-rank test). The continuous line represents patients with ABI values within the normal range, whilst the dotted line represents patients with abnormal ABI values. (b) The Kaplan–Meier estimates the proportion of patients free of new cerebral episodes ($P < 0.001$; log-rank test). The continuous line represents patients with ABI values within the normal range, whilst the dotted line represents patients with abnormal ABI values.
with greater vascular risk, for whom optimized treatment and secondary prevention can improve the natural evolution of their condition.

Conflicts of Interest
The authors have reported no conflicts of interest.

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