Increased popliteal circumferential wall tension induced by orthostatic body posture is associated with local atherosclerotic plaques

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ABSTRACT

Objective: Lower limb arteries are exposed to higher hemodynamic burden in erect posture. This study evaluated the effects of body posture on popliteal, carotid and brachial circumferential wall tension (CWT) and investigated the relationship between local CWT and atherosclerotic plaques in subjects with cardiovascular risk factors.

Methods: Two hundred and three subjects (118 women and 85 men) with cardiovascular risk factors (smoking, hypertension or diabetes mellitus) underwent clinical and laboratory analysis and had their blood pressure measured in the arm and calf in supine and orthostatic positions. Arteries were evaluated by ultrasound analysis, while CWT was calculated according to Laplace’s law.

Results: Among the enrolled participants, 47%, 29% and none presented popliteal, carotid and brachial plaques, respectively. Carotid CWT measurements were not associated with local plaques after adjustment for potential confounders. Conversely, general linear model and logistic regression analyses adjusted for potential confounders demonstrated that peak orthostatic CWT was the only local hemodynamic parameter showing significant relationship with popliteal plaques in the whole sample. In gender-specific analyses, although positively correlated with popliteal plaques in both genders, local peak orthostatic CWT exhibited an independent association with popliteal plaques after adjustment for potential confounders only in women.

Conclusion: Popliteal CWT measured in orthostatic posture, rather than in supine position, is associated with popliteal atherosclerotic plaques, particularly in women. These findings suggest that erectile posture might play a role in the atherogenesis of leg arteries by modifying local hemodynamic forces and that there may be gender differences in this regard.

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1. Introduction

Atherosclerosis is a systemic and inflammatory disease, caused or favored by systemic risk factors, that localizes in particular regions of the arterial tree, through interaction with local predisposing factors [1,2]. Among the local factors, hemodynamic forces generated by blood pressure are of greatest importance, given their ability to stimulate inflammatory response and remodeling of vascular cells [1,3,4]. Circumferential wall tension (CWT) is a hemodynamic force that leads to an extensional (dilating) effect on the vessel and has been directly related to atherosclerotic burden in human beings [5–7], supporting the notion that evaluation of this hemodynamic parameter might be useful to predict local development of atherosclerosis.

Peripheral artery disease is a manifestation of atherosclerosis and shares similar systemic risk factors with stroke and coronary heart disease [8]. Nevertheless, it typically occurs in arteries of the lower limbs [9], indicating that local stimuli play a major role in this process. Leg arteries are known to be exposed to greater hemodynamic stress than arm arteries, particularly in orthostatic posture [10,11], which might provide a potential explanation whereby atherosclerosis preferentially develops in these vessels. In agreement with this assumption, recent data from our group demonstrated that orthostatic CWT was a stronger hemodynamic predictor of popliteal intima-media thickness (IMT) than supine CWT in normotensive subjects without cardiovascular risk factors [11]. Nevertheless evaluation of IMT is an approach unable to discriminate between artery wall thickening caused by tunica
recognized to be a manifestation of atherosclerotic disease [13]. Therefore, the present study evaluated the influence of supine and orthostatic position on CWT measurements of popliteal, carotid and brachial arteries and determined whether these hemodynamic parameters were related to respective atherosclerotic plaques in a sample of subjects with cardiovascular risk factors for atherosclerosis.

2. Methods

2.1. Study participants

Two hundred and three subjects (118 women and 85 men) followed in outpatient clinics of a university hospital were included in the study from September 2008 to January 2011. Inclusion criteria were the presence of at least one of the following risk factors for peripheral artery disease: 1) current smoking; 2) hypertension (blood pressure ≥ 140/90 mmHg or use of antihypertensive medications) or 3) diabetes mellitus (fasting blood glucose ≥ 126 mg/dL or use of hypoglycemic medications). Exclusion criteria were age under 18 years, previous stroke and supine or standing systolic blood pressure > 220 or < 100 mmHg, respectively. Popliteal arteries displayed higher IMT and prevalence of atherosclerotic plaques, but lower luminal diameter compared to carotid arteries. All IMT measurements were made using an automatic border recognizer (Vivid 3 Pro IMT software analyzer) on stored images obtained during the sonographic scanning and were never taken at the level of a discrete plaque. End-diastolic and peak-systolic internal diameters were obtained by continuous tracing of the intimal–luminal interface of the near and far walls of the studied arteries in 3 cycles and averaged. Atherosclerotic plaques were defined as the presence of wall thickening ≥ 1.5 mm [17,18].

Peak and mean CWT were calculated according to Laplace’s law (3, 4): peak CWT (dyne/cm) = systolic blood pressure × peak-systolic internal diameter/2; mean CWT (dyne/cm) = mean blood pressure × end-diastolic internal diameter/2. Brachial blood pressure was used to calculate brachial and carotid CWT while popliteal blood pressure was used to calculate popliteal CWT.

To test the reproducibility of measurements, they were repeated weekly for 2 weeks in 20 subjects. The variation coefficients averaged 2% and 3% for peak-systolic internal diameter and end-diastolic internal diameter; 5% for systolic blood pressure and 5% for diastolic blood pressure; 4% for peak CWT and 3% for mean CWT; 4% for carotid IMT, 3% for popliteal IMT and 3% for brachial IMT; 1% for carotid atherosclerotic plaques and 2% for popliteal atherosclerotic plaques.

2.5. Statistical analysis

Continuous parametric and non-parametric variables are presented as mean ± standard error and median (25–75th percentile), respectively. The Kolmogorov–Smirnov test was used to test for normal distribution of the variables. Differences in continuous parametric variables were evaluated by unpaired t-test and one-way ANOVA followed by the Tukey test for pairwise comparisons. Differences between continuous non-parametric variables were evaluated by Mann–Whitney test. χ² was used to compare categorical variables. Bivariate correlation analysis between atherosclerotic plaques and local CWT measurements were carried out using the Spearman’s method. General linear models were used to evaluate the relationship between carotid/popliteal plaques and local CWT and blood pressure measurements adjusted for potential confounding factors. Logistic regression analysis was used to evaluate the independent predictors of popliteal plaques. The median was used as the cut-off point of continuous independent variables included in logistic regression models. A p-value of less than 0.05 was considered significant.

3. Results

Table 1 summarizes the clinical features of studied subjects in the whole sample and according to gender. No differences in the clinical features were detected between the genders. Vascular and hemodynamic characteristics in the whole sample and according to gender are shown in Table 2 and Supplementary Table 1, respectively. Popliteal arteries displayed higher IMT and prevalence of atherosclerotic plaques, but lower luminal diameter compared to carotid arteries. Brachial arteries presented no plaques and exhibited lower IMT and luminal diameter than the other studied arteries. Changing from supine to standing was associated with increased peak CWT in carotid and popliteal arteries and with higher mean CWT only in popliteal vessels (Table 2). In addition, similar vascular and hemodynamic features were observed in both genders, except for higher carotid, popliteal and brachial diameters and CWT measurements in men (Supplementary Table 1).
Unpaired t-test analysis and χ² evaluated the clinical features of enrolled participants according to the presence or not of popliteal and carotid plaques in order to identify potential confounding factors (Supplementary Tables 2 and 3). Considering the whole sample, subjects with popliteal plaques exhibited higher local IMT, age, low-density-lipoprotein-cholesterol, prevalence of hypertension and use of angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers than subjects without plaques. Women with popliteal plaques presented higher prevalence of diabetes mellitus and hypertension and use of angiotensin-converting-enzyme inhibitors while men with popliteal plaques exhibited higher local IMT, age, low-density-lipoprotein-cholesterol, glycemia, prevalence of diabetes mellitus and use of statins than those without plaques (Supplementary Table 2). Regarding the whole sample, subjects with carotid plaques exhibited higher age, local IMT, low-density-lipoprotein-cholesterol, glycemia, triglycerides, prevalence of diabetes mellitus and hypertension and use of angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers and statins than individuals without plaques. Women with carotid plaques exhibited higher age, local IMT, prevalence of menopause and hypertension and use of angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers, while men with carotid plaques presented higher local IMT, age, low-density-lipoprotein-cholesterol, triglycerides, glycemia, prevalence of diabetes mellitus and hypertension and use of statins than those without plaques (Supplementary Table 3).

Bivariate correlation and general linear model analyses evaluated the relationship between atherosclerotic plaques and local CWT measurements. Popliteal plaques significantly correlated with all CWT measurements in the whole sample and in both genders, particularly with peak orthostatic CWT (Table 3). General linear model analysis adjusted for potential confounders revealed that in the whole sample and in women popliteal plaques were associated with all local CWT measurements, but most notably with peak orthostatic CWT (p = 0.004 in the whole sample and p < 0.001 in women). Conversely, no CWT measurement showed significant association with popliteal plaques after adjustment for potential confounding factors in men (Table 3). Carotid plaques significantly correlated with all CWT measurements in the whole sample and in both genders, but after adjustment for the potential confounders presented in Supplementary Table 3, no significant relationship between carotid plaques and local CWT measurements was detected neither in the whole sample nor in the genders. In addition, general linear model analyses showed no significant relationship between carotid/popliteal plaques and local blood pressure measurements.

Logistic regression analysis was then performed to evaluate which CWT measurements and clinical variables were independently related to popliteal plaques. Peak orthostatic CWT was the only hemodynamic variable that presented a significant association with popliteal plaques in the whole sample and in women (Table 4), while no CWT measurement was significantly associated with popliteal plaques in men (data not shown).

4. Discussion

Hemodynamic forces acting on the arterial wall participate in atherosclerosis as local factors [13]. Lower limb arteries are exposed to higher hemodynamic burden in erectile posture [10,11], which might contribute to explain the preferential development of peripheral artery disease in these vessels. In the present report, we evaluated the effects of body posture on popliteal, carotid and brachial CWT and investigated the relationship between local CWT and atherosclerotic plaques in subjects with cardiovascular risk factors. Noticeably, we found that: 1) popliteal arteries were subjected to the highest local CWT levels among the studied vascular territories, which were detected in orthostatic posture; 2) popliteal arteries exhibited higher prevalence of atherosclerotic plaques in comparison to carotid arteries, while brachial arteries showed no atherosclerotic plaques; 3) orthostatic CWT, rather than supine CWT, was the only hemodynamic variable independently associated with the presence of popliteal plaques, particularly in women. Taken together, these findings suggest that erectile posture might play a role in the atherogenesis of leg arteries by modifying local hemodynamic forces and that there may be gender differences in this regard.

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole sample (n = 203)</th>
<th>Women (n = 118)</th>
<th>Men (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>51.4 ± 0.7</td>
<td>50.7 ± 0.9</td>
<td>52.5 ± 1.0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.4 ± 0.3</td>
<td>26.2 ± 0.4</td>
<td>26.7 ± 0.5</td>
</tr>
<tr>
<td>Low-density-lipoprotein-cholesterol, mg/dL</td>
<td>121.8 ± 2.4</td>
<td>120.7 ± 3.0</td>
<td>123.3 ± 3.7</td>
</tr>
<tr>
<td>High-density-lipoprotein-cholesterol, mg/dL</td>
<td>43.3 ± 0.6</td>
<td>43.0 ± 0.7</td>
<td>43.7 ± 0.9</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>135 (68)</td>
<td>136 (68)</td>
<td>131 (78)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>99.6 ± 2.1</td>
<td>98.2 ± 2.7</td>
<td>101.7 ± 3.4</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>175 (86)</td>
<td>102 (86)</td>
<td>73 (86)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>81 (40)</td>
<td>45 (38)</td>
<td>36 (42)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>41 (20)</td>
<td>22 (19)</td>
<td>19 (22)</td>
</tr>
<tr>
<td>Menopause, n (%)</td>
<td>88 (43)</td>
<td>88 (75)</td>
<td>—</td>
</tr>
<tr>
<td>ACEI or ARB, n (%)</td>
<td>61 (30)</td>
<td>32 (26)</td>
<td>29 (34)</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>16 (8)</td>
<td>10 (9)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>10 (5)</td>
<td>5 (4)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Calcium-channel blockers, n (%)</td>
<td>6 (3)</td>
<td>3 (3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Statis, n (%)</td>
<td>41 (20)</td>
<td>26 (21)</td>
<td>15 (18)</td>
</tr>
</tbody>
</table>

ACEI or ARB - angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers.

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Carotid</th>
<th>Orthostatic</th>
<th>Popliteal</th>
<th>Orthostatic</th>
<th>Brachial</th>
<th>Orthostatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intima-media thickness, mm</td>
<td>0.80 ± 0.01&lt;sup&gt;*&lt;/sup&gt;</td>
<td>—</td>
<td>0.91 ± 0.01&lt;sup&gt;†&lt;/sup&gt;</td>
<td>—</td>
<td>0.40 ± 0.01</td>
<td>—</td>
</tr>
<tr>
<td>Systolic internal diameter, mm</td>
<td>6.09 ± 0.04&lt;sup&gt;†&lt;/sup&gt;</td>
<td>6.88 ± 0.05&lt;sup&gt;†&lt;/sup&gt;</td>
<td>5.54 ± 0.04&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>5.33 ± 0.05&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>3.85 ± 0.04</td>
<td>3.86 ± 0.04</td>
</tr>
<tr>
<td>Diastolic internal diameter, mm</td>
<td>6.43 ± 0.04&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>6.63 ± 0.05&lt;sup&gt;†&lt;/sup&gt;</td>
<td>5.30 ± 0.04&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>5.11 ± 0.05&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>3.66 ± 0.04</td>
<td>3.67 ± 0.04</td>
</tr>
<tr>
<td>Atherosclerotic plaque, n (%)</td>
<td>59 (29)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>—</td>
<td>35 (47)</td>
<td>—</td>
<td>0.00</td>
<td>—</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>130.0 ± 0.9</td>
<td>134.2 ± 0.9&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>131.4 ± 0.9&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>194.4 ± 0.9&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>130.0 ± 0.9</td>
<td>134.2 ± 0.9&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>84.1 ± 0.6</td>
<td>83.9 ± 0.6&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>84.0 ± 0.6</td>
<td>99.3 ± 0.7&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>84.1 ± 0.6</td>
<td>83.9 ± 0.6&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>45.9 ± 0.4</td>
<td>50.4 ± 0.4&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>47.1 ± 0.4</td>
<td>95.2 ± 0.6&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>45.9 ± 0.4</td>
<td>50.4 ± 0.4&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Peak CWT, 10&lt;sup&gt;2&lt;/sup&gt; dyn/cm</td>
<td>5.81 ± 0.006&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>6.18 ± 0.006&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>4.86 ± 0.005&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>6.92 ± 0.006&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>3.33 ± 0.04</td>
<td>3.43 ± 0.05</td>
</tr>
<tr>
<td>Mean CWT, 10&lt;sup&gt;2&lt;/sup&gt; dyn/cm</td>
<td>4.27 ± 0.005&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>4.46 ± 0.005&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>3.53 ± 0.004&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>4.44 ± 0.004&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>2.42 ± 0.03</td>
<td>2.44 ± 0.03</td>
</tr>
</tbody>
</table>

CWT – Circumferential wall tension. *p at least <0.01 in comparison to respective popliteal measurement; †p at least <0.01 in comparison to respective brachial measurement; ‡p at least <0.05 in comparison to respective supine measurement.
A recent paper of our group demonstrated that orthostatic CWT was a stronger predictor of popliteal IMT than supine CWT in normotensive subjects without cardiovascular risk factors [11]. Those results raised the assumption that erectile posture might be a potential risk factor for popliteal atherosclerosis by increasing local hemodynamic burden. Nevertheless that report exhibited some limitations that are worth mentioning. First, vascular remodeling was assessed by measuring IMT. Although considered a measure of diffuse or early atherosclerosis [19], IMT may also increase as a consequence of medial hypertrophy, related to hypertension, but not to atherosclerosis [12]. Given that popliteal arteries are muscular arteries, therefore with prominent medial layer, and are usually subjected to higher local blood pressure, particularly in standing position [10,11], it is possible that IMT might not be a suitable surrogate of atherosclerosis in this vessel. Second, a sample with very low cardiovascular risk was included, which could not be adequate to evaluate the predictors of peripheral artery disease. In order to overcome these limitations, the present study was designed to assess the presence of focal plaques, which are considered a manifestation of atherosclerosis [13], and enrolled a sample with risk factors for peripheral artery disease. In this regard, results from general linear model analysis adjusted for potential confounders revealed that peak orthostatic CWT was the variable exhibiting the most significant relationship with popliteal plaques among all orthostatic and supine CWT measurements. In addition logistic regression analysis including peak orthostatic and mean supine CWT as independent variables revealed that only orthostatic CWT was independently associated with popliteal plaques. To our knowledge, the present results provide the first evidence confirming a link between leg hemodynamic alterations consequent to body posture changes and the presence of focal plaques, which are unequivocal markers of atherosclerosis, and therefore, of peripheral artery disease.

Although bivariate correlation analysis showed a direct relationship between popliteal plaques and local CWT measurements in men and in women, results of general linear model and logistic regression analysis adjusted for potential confounding factors disclosed significant associations between popliteal plaques and local CWT only in women. These findings suggest that popliteal arteries of women might be more susceptible to atherogenesis related to hemodynamic load. The reasons for such gender differences are not apparent, but may include variation in sexual hormone profile. Given that the majority of enrolled women were postmenopausal, it is possible that the lack of endogenous estrogen favored the association between popliteal plaques and local CWT in this gender. However, our results showing no differences in the prevalence of menopause between women with and without popliteal plaques seem to weaken this assumption. Therefore further studies are necessary to unveil the precise mechanisms by which gender influences the relationship between hemodynamic forces and atherosclerosis in popliteal arteries.

Some aspects of the present report deserve further comments. First, we detected a higher prevalence of atherosclerotic plaques in popliteal arteries than in carotid ones. These results agree with data from other groups showing higher atherosclerotic burden in lower limb arteries than in carotid arteries [20,21], and could be explained by the increased hemodynamic stress imposed to popliteal arteries, particularly in orthostatic posture. Second, no plaques were detected in brachial arteries, a finding that was previously reported either in subjects with or without cardiovascular risk factors [22], thus strengthening the notion that the brachial artery does not seem a good model to study atherosclerosis by ultrasound measurements. Third, only individuals with supine leg/brachial systolic blood pressure ratio >0.9 and <1.2 were enrolled in our protocol. Subjects with a ratio <0.9 are considered to present peripheral artery occlusive disease [23,24], while values >1.2 can be falsely elevated because of heavily calcified or non-compressible arteries [14,25]. Given that these vascular abnormalities could artificially alter popliteal blood pressure measurements, and therefore CWT values, we preferred not to include subjects with ratios <0.9 and >1.2 in our study.

Previous studies demonstrated that local CWT was associated with subclinical atherosclerosis in common carotid arteries. For instance, CWT was independently related to carotid IMT in subjects with and without cardiovascular risk factors [5,6,11]. In addition local CWT was reported to be an independent predictor of carotid atherosclerotic plaque burden in hypertensive subjects [7]. However, our results revealed that after adjustment for potential confounding factors, carotid plaques were not independently related to any CWT measurement. The reasons for these discrepancies are not clear, but it is possible that clinical differences among the samples played a role in this regard. In addition, it was
noteworthy that blood pressure values used to calculate CWT in carotid arteries were recorded at the brachial artery. Although this procedure has been extensively used in studies evaluating carotid hemodynamics [5,6,26], it may overestimate carotid peak CWT, especially in those of younger age with tall stature [27], which might have influenced our results.

Some potential limitations of this study should be acknowledged. First, the cross-sectional design may limit our ability to infer a causal relationship between popliteal plaques and local orthostatic CWT. Second, part of enrolled subjects was using antihypertensive medications or statins, which could be potential confounding factors, given the inflammatory nature of atherosclerosis [2].

In conclusion, the present report showed that popliteal CWT measured in orthostatic posture, rather than in supine position, was independently associated with local atherosclerotic plaques, particularly in women. This finding suggests that erectile posture might play a role in the atherogenesis of leg arteries by modifying local hemodynamic forces. Further studies are necessary to evaluate whether orthostatic body posture may be risk factor for the development of peripheral artery occlusive disease, especially in women.

Conflict of interest

None.

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Appendix A. Supplementary material

Supplementary material related to this article can be found online at http://dx.doi.org/10.1016/j.atherosclerosis.2012.06.069.

References