Differentiation of Primary and Secondary Raynaud’s Disease by Carotid Arterial Stiffness


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Introduction: primary Raynaud’s disease may be difficult to differentiate clinically from the secondary form with an underlying connective tissue, haematological, neurovascular or drug-induced disorder. We undertook a study to determine the elastic carotid and muscular femoral arterial biomechanical properties and intima-media thickness (IMT) in subjects with primary and secondary Raynaud’s disease, to assess whether these parameters could differentiate the two conditions.

Methods: twenty patients with primary Raynaud’s disease and 53 subjects with secondary Raynaud’s associated with scleroderma (systemic sclerosis, SSc) had measurements of their carotid and femoral wall mechanics with a duplex scanner coupled to a Wall Track system. Their age, gender, body mass index, heart rate, systolic and diastolic blood pressures, presumed cardiovascular load, plasma creatinine, fasting cholesterol, triglyceride and glucose concentrations were also measured.

Results: the carotid elastic properties [mean (SD): elastic modulus: 560 (180) vs 1204 (558) mmHg, $p < 0.001$ and stiffness index: 5.69 (1.35) vs 11.92 (6.4), $p < 0.001$ for primary and secondary Raynaud’s respectively] were significantly impaired in patients with secondary Raynaud’s disease even after adjustment for potentially influencing physiological and biochemical variables. There were no statistical differences in the femoral elastic properties or the carotid and femoral IMTs between the two groups.

Conclusion: Duplex determination of the carotid elasticity or stiffness is different in primary Raynaud’s phenomenon compared with secondary Raynaud’s associated with SSc. This may be a useful non-invasive tool, in addition to autoantibody markers and nail-fold capillaroscopy, to differentiate between the two forms of Raynaud’s phenomenon.

Key Words: Raynaud’s; Scleroderma; Carotid artery; Compliance; Stiffness.

Introduction

Raynaud’s syndrome was first described in 1862 by the French physician, Maurice Raynaud. It is characterized by spasm of the small arteries of the fingers and toes, causing the skin to turn pale and dusky blue. Estimates of its prevalence range from 5 to 30% of the population. It is five times commoner in women, particularly between the ages of 18 and 30 years. It is thought that 25-30% of cases occur in healthy women.

Primary Raynaud’s disease has no known cause. However, a multi-centre observation study has shown that 48% of primary Raynaud’s showed one or more clinical features, indicating a high risk of evolving into scleroderma (systemic sclerosis, SSc). Secondary Raynaud’s is associated with an underlying connective tissue, neurovascular, haematological or drug-induced disorder. The same study has shown that secondary Raynaud’s was most frequently associated with SSc and was often the first presenting symptom of SSc, often preceding the connective tissue disorder by months to years.

It is sometimes difficult to distinguish primary Raynaud’s disease from the secondary form. Nailfold capillaroscopy may be able to diagnose Raynaud’s secondary to SSc. As SSc is a generalized connective tissue disease affecting other organs of the body apart from the skin, we may expect to see changes in the connective tissue matrix and hence, the wall mechanics of large arteries. There has been no study we could find in the literature looking at the carotid and femoral
wall mechanics in primary and secondary Raynaud’s disease.

The aim of this study is to determine the elastic carotid and muscular femoral biomechanical properties and intima-media thickness (IMT) in subjects with primary and secondary Raynaud’s disease to assess whether we could use these parameters to differentiate the two forms.

Methods

Elastic indices

The arterial biomechanical properties are well described.2-5 In this study, we use the diametrical compliance (C), Petersen’s elastic modulus (Ep) and stiffness index (β) to assess the common carotid and femoral wall mechanics to avoid bias towards any of the parameters. Both C and Ep are dependent on blood pressure but β is claimed by some authors to be less pressure dependent.6

Subjects

A total of 73 subjects were recruited prospectively in this study, which has been approved by the local hospital Ethics Committee and conformed to the principles of the Declaration of Helsinki. Twenty had primary Raynaud’s disease and 53 had thermographically confirmed secondary Raynaud’s disease associated with SSc.

Raynaud’s disease was diagnosed by the classical colour changes, which occurred in the digits of the hands or/and feet. Primary Raynaud’s was defined by the Allen and Brown’s criteria of negative nail-fold capillaroscopy and normal serological study (sera screened on Hep 2 cells at 1:100). SSc was diagnosed clinically by an experienced rheumatologist and broadly followed the classification criteria of the American College of Rheumatology. Ninety-five percentage of cases carried antinuclear antibodies and in 70% these included a hallmark SSc associated reactivity. Patients were recruited consecutively from the rheumatology and general surgical clinics. No other exclusion criteria were applied.

Measurements

The age, gender, body mass index (BMI), heart rate, systolic and diastolic blood pressures were recorded for all subjects. In addition, the plasma creatinine, fasting cholesterol, triglyceride and glucose were measured.

The presumed cardiovascular load assessed on the basis of a cumulative total vascular risk score (TVRS) was calculated for all subjects.5,7 This was based on Lehmann’s study, which showed a significant inverse relation between the aortic compliance and the number of cardiovascular risk factors.7 We believed that this was a significant finding and has modified the TVRS to include hypercholesterolaemia, peripheral vascular disease and renal impairment.5 These risk factors and events were as follows: (1) current cigarette smoking or ex-smoker within the last 12 months; (2) history of hypertension on medication; (3) history of hypercholesterolaemia on medication; (4) history of diabetes mellitus; (5) history of ischaemic heart disease; (6) history of stroke, transient ischaemic attack or known carotid stenosis >50%; (7) known renal impairment and (8) peripheral vascular disease. Although we have not formally assessed the modified scoring system, we believed that this is one method, which allowed equal adjustment of the cardiovascular load in our groups of subjects.

The subjects were rested for 10 min in the supine position to allow resting pulse rate and blood pressure to be achieved before any form of measurement was performed. Heart rate and blood pressure were recorded non-invasively from the right brachial artery using an automated pressure monitor (Dynamap Compact TS, Johnson & Johnson Medical, Newport, U.K.). Real-time B-mode and M-mode images of the arterial wall motion and IMT were recorded using a 7.5 MHz linear array probe in the sagittal plane at 90° to the long axis of the artery using a specially adapted duplex scanning system (Pie 350, Pie Medical Systems, Maastricht, The Netherlands) with signal output to a high-resolution, echo-locked Wall Track system (Wall Track, Pie Medical Systems, Maastricht, The Netherlands).5,8-11 This system tracked the anterior and posterior walls of the vessel over a cardiac cycle. Each recording was programmed to last for 2 s in order to catch at least one R wave-trigger reading and also not to distort the results by prolonged tracking of the specific part of the vessel. It also automatically measured the far wall IMT of the vessel. The far wall was chosen because it has been shown to be more accurate than the near wall IMT.12,13 The IMT was recognized by the double line pattern corresponding to the lumen-intima and media-adenitia interfaces.12 The distance between these two interfaces is the IMT.12,14,15

The side of the recording was chosen such that it was the asymptomatic side or the side with the lowest degree of stenosis. The site was chosen such that no
visible atheroma could be visualized on the duplex scanner. Measurements were taken within 3 cm proximal to the bifurcation of the common carotid or common femoral artery. Vessel wall motion and IMT were each recorded for three times from the common carotid and common femoral arteries. Vessel wall motion and IMT were each recorded for three times from the common carotid and common femoral arteries. The average of three recordings of the vessel distension was taken as the mean diastolic and systolic luminal diameters. The average of three IMT recordings was used as the mean IMT. The elastic indices were subsequently calculated from the given equations.\(^5\)

### Data analysis and statistical methods

The chi-squared test was used to compare the gender ratio between the two groups. The remaining physiological and biochemical variables were compared between the two groups using unpaired (independent) \(t\)-test. A general linear model was applied to estimate differences in means in the carotid and femoral elastic indices and IMT between the two groups of subjects, after adjusting for potentially influential variables, including age, BMI, heart rate, systolic and diastolic pressures, TVRS, plasma creatinine, fasting cholesterol, triglyceride and glucose concentrations.

The intra-observer variations were quantified from the three readings using the intra-class correlation coefficients (ICCs):

\[
\text{ICC} = \frac{V_b}{V_b + V_w}
\]

where \(V_b\) is the between subject variance and \(V_w\) is the within subject variance.

The inter-observer errors in our unit has been determined from our previous study with the ICCs between 0.88 and 0.91 for carotid and femoral distensions and 0.89 for carotid and femoral IMT measurements.\(^5\)

All statistical tests were performed with SPSS version 10.05 for Windows.

### Results

The physiological and biochemical parameters between primary and secondary Raynaud’s are shown in Table 1. Patients with secondary Raynaud’s were significantly older and had significantly higher heart rate and systolic blood pressure than those with primary Raynaud’s. Both primary and secondary Raynaud’s were commoner in female subjects.

Patients with secondary Raynaud’s disease caused by SSC have significantly impaired carotid elastic properties \[\text{mean (SD): C: } 9.5 (3.01) \text{ vs } 19.54 (5.71) \text{ mmHg}^{-1}10^{-2}, p < 0.001; \text{ Ep: } 1204 (558) \text{ vs } 560 (180) \text{ mmHg; } \beta: 11.92 (6.4) \text{ vs } 5.69 (1.35) \text{ for secondary and primary Raynaud’s respectively}\] (Table 2). This highly significant finding exists even after adjustment for potentially influencing physiological and biochemical variables (Table 3). There are no statistical differences in terms of the femoral elastic indices, the carotid and the femoral IMTs between the two groups (Table 3).

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**Table 1. Physiological and biochemical parameters between primary and secondary Raynaud’s.**

<table>
<thead>
<tr>
<th></th>
<th>Primary Raynaud’s</th>
<th>Secondary Raynaud’s</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>M:F</td>
<td>4:16</td>
<td>10:43</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.75 (15.58)</td>
<td>55.43 (11.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>23.65 (3.35)</td>
<td>23.82 (3.71)</td>
<td>0.85</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>79.60 (6.60)</td>
<td>83.51 (7.83)</td>
<td>0.04</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>119.50 (15.60)</td>
<td>139.58 (17.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>78.15 (12.86)</td>
<td>76.7 (11.38)</td>
<td>0.64</td>
</tr>
<tr>
<td>TVRS (number)</td>
<td>0.35 (0.75)</td>
<td>0.57 (0.8)</td>
<td>0.3</td>
</tr>
<tr>
<td>Creatinine ((\mu)mol/l)</td>
<td>71.00 (10.86)</td>
<td>93.83 (59.27)</td>
<td>0.11</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.77 (1.26)</td>
<td>5.01 (1.02)</td>
<td>0.55</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.89 (1.02)</td>
<td>1.78 (0.79)</td>
<td>0.73</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.02 (2.62)</td>
<td>4.87 (1.83)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Data are mean (SD). M denotes male and F denotes female. BMI is the body mass index. TVRS is the total vascular risk score.

**Table 2. The elastic indices and IMT of primary and secondary Raynaud’s subjects.**

<table>
<thead>
<tr>
<th></th>
<th>Primary Raynaud’s</th>
<th>Secondary Raynaud’s</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid C (% mmHg (10^{-2}))</td>
<td>19.54 (5.71)</td>
<td>9.50 (3.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid Ep (mmHg)</td>
<td>559.50 (180.56)</td>
<td>1204.07 (558.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid (\beta) (dimensionless)</td>
<td>5.69 (1.35)</td>
<td>11.92 (6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Femoral C (% mmHg (10^{-2}))</td>
<td>6.35 (4.29)</td>
<td>5.55 (3.93)</td>
<td>0.49</td>
</tr>
<tr>
<td>Femoral Ep (mmHg)</td>
<td>2095.36 (993.82)</td>
<td>2549.17 (1386.89)</td>
<td>0.23</td>
</tr>
<tr>
<td>Femoral (\beta) (dimensionless)</td>
<td>21.34 (9.85)</td>
<td>24.38 (13.21)</td>
<td>0.4</td>
</tr>
<tr>
<td>Carotid IMT (mm)</td>
<td>0.63 (0.19)</td>
<td>0.65 (0.24)</td>
<td>0.74</td>
</tr>
<tr>
<td>Femoral IMT (mm)</td>
<td>0.64 (0.19)</td>
<td>0.74 (0.31)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Data in mean (SD). C denotes diametrical compliance, Ep the Petersen’s elastic modulus and \(\beta\) is the stiffness index.
The intra-observer ICCs for the carotid and femoral distension and IMT measurements varied from 0.92 to 0.96, indicating a high level of reproducibility.

Discussion

The theoretical accuracy of the Wall-Track system is in the region of three microns for distension and ten microns for arterial diameter. The reproducibility of the duplex-Wall Track system is good with errors of between 8 and 12% for the carotid compliance and well below 20% for the IMT. Our study has shown that the augmentation phenomenon also increases so that the augmentation phenomenon also increases.

In the pulse pressure between central and peripheral arteries, we could therefore assume that the brachial pressure is used because it is more accessible than either the carotid or femoral arteries. It is a muscular rather than an elastic artery. It is hypertensive crisis and pulmonary hypertension.

The femoral artery is not similarly affected because it is a muscular rather than an elastic artery. It is hypertensive crisis and pulmonary hypertension.

Abnormalities in uninvolved skin fibroblasts are consistent with a genetically based alteration in fibrillin biochemistry in SSc. Another explanation is the result of increased vascular tone secondary to repeated reperfusion injury associated with the severe form of digital vasospasm seen in secondary Raynaud’s. The last explanation may be due to increased cardiovascular load in subjects with secondary Raynaud’s. The carotid elastic properties are recognized as good markers of cardiovascular risk and events. Indeed, subjects with secondary Raynaud’s caused by SSc have higher risk of hypertensive crisis and pulmonary hypertension. The femoral artery is not similarly affected because it is a muscular rather than an elastic artery. It is interesting that fibrillin-1 regulates elastin fibre assembly and elastin is expressed most commonly in the elastic arteries. Ultrasonic measurement of the carotid elastic properties is an invaluable clinical tool in the assessment of Raynaud’s disease and provides further complementary information in addition to tests such as antinuclear antibodies and nail-fold capillary microscopy. This method is non-invasive, accurate and reproducible. It is quick and easy to perform by a trained vascular technican with the available hardware and software and should be readily available in a vascular unit with easily accessible vascular laboratory.

References


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