Superior mesenteric artery blood flow in systemic sclerosis patients

F. Quarto Di Palo, R. Rivolta¹, V. Berruti², M. Caronni², S. Bazzi² and R. Scorza²

Dipartimento di Scienze Radiologiche, IRCCS Ospedale Maggiore di Milano, ¹Servizio di Radiologia, Azienda Ospedaliera S. Carlo Borromeo, Milano and ²Immunologia Clinica e Allergologia Università di Milano-IRCCS Ospedale Maggiore di Milano, Italy

Abstract

Objective. Intestinal involvement is frequently observed in systemic sclerosis (SSc) and is associated with malnutrition and a decreased survival rate. Vascular lesions are claimed to underlie and precede these changes. The aim of this study was to establish whether a reduced mesenteric blood flow was present in SSc patients with no signs or symptoms of small bowel involvement.

Methods. Superior mesenteric artery (SMA) blood flow in the fasting state was measured by colour Doppler ultrasonography in 27 SSc patients and in 25 controls. The effect of a balanced liquid meal on mesenteric blood flow was measured in six matched patients and controls.

Results. In fasting SSc patients, there were reductions in mean SMA diameter (P < 0.001), blood flow (213 ± 92 vs 398 ± 125 ml/min in controls, P < 0.0001) and pulsatility index (3.49 ± 1.0 vs 4.13 ± 0.97 in controls, P < 0.07). In both groups, the meal increased basal flow values and the differences between controls and patients in the fasting state were not significant.

Conclusions. In the absence of symptoms of small bowel involvement, reversible SMA vasoconstriction is demonstrable in the fasting state in SSc patients.

KEY WORDS: Systemic sclerosis, Colour Doppler ultrasonography, Mesenteric artery, Mesenteric blood flow.

Systemic sclerosis (SSc) is a connective tissue disease [1] of unknown aetiology, affecting the skin and other internal organs, such as the kidneys [2–5], heart, lungs and alimentary tract [6]. The hallmark of the disease is vasomotor instability, which plays a pivotal role in microvascular damage and gives rise to blood flow reduction, tissue ischaemia, progressive dysfunction and fibrosis [7–9].

Among the connective tissue diseases, SSc is the condition in which lesions of the digestive tract are observed most frequently. When SSc affects the small intestine, motility is impaired [10, 11] and the normal peristaltic movements are lost, and this leads to stasis, bowel dilatation and bacterial overgrowth [12]. Patients with SSc and proven bacterial overgrowth have diarrhoea, steatorrhoea, malabsorption, weight loss and a decreased survival rate [13].

Gastrointestinal pathology is characterized by vasculopathy, resulting in tissue ischaemia [6]. Reductions in oesophageal blood flow and in the mucosal vascularization of the stomach and duodenum were demonstrated by laser Doppler [14]. A low oxygen content was also found in the gastric mucosa in scleroderma by means of an endoscopic electrode [15]. These vascular changes are claimed to precede clinical dysfunction and fibrosis of the digestive tract [6].

In previous work, we used colour Doppler ultrasonography (CDU) to demonstrate preclinical alterations in blood flow in the kidneys of SSc patients [5]. In this paper we investigated whether a reduction in blood flow might also be detectable in SSc patients at the level of the splanchnic arteries in the absence of clinical manifestations, in particular the absence of diarrhoea and malnutrition. We measured blood flow in the superior mesenteric artery (SMA), which is a large-calibre vessel that supplies the small intestine and the ascending colon. Blood flow in the SMA can be measured in a repeatable and non-invasive way by means of colour Doppler flowmetry [16–19]. This technique has been used extensively in the study of...
splanchnic flow in liver cirrhosis [20–22], Crohn’s disease [23] and coeliac disease [24].

Patients and methods

Patient selection

Twenty-seven female SSC patients without diarrhoea or malnutrition, attending our out-patient clinic, were included in this study. All patients satisfied the classification criteria of the American College of Rheumatology [25]. At disease onset, 12 patients were classified as having diffuse scleroderma and 15 had the diagnosis of limited scleroderma. Their mean age was 51 ± 12 yr and mean disease duration 7.3 ± 5.9 yr (Table 1). Haemoglobin concentration, haematocrit and serum albumin and transferrin levels were within normal ranges. Oesophageal involvement was present in 23 and constipation in 12 of the 27 SSC patients. Patients with oesophageal hypo- or aperistalsis were being treated chronically with cisapride (30 mg/day orally). All the patients were receiving chronic treatment with slow-release nifedipine (40 mg/day orally) and aspirin (100 mg/day orally) and had optimal control of Raynaud’s phenomenon. Patients with pulmonary hypertension were not included in this study because we judged it unethical to stop vasodilators in order to do the test. None of the patients was being treated with steroids or immunosuppressive drugs. Drugs were withdrawn 24 h before the Doppler examination. Twenty-five healthy women (healthy volunteers, nurses or female medical personnel), who were matched for age and weight [SMA blood flow and pulsatility index (PI) are dependent on body size] and had a mean age of 49 ± 11 yr, served as a control group. Demographic data for the study groups are shown in Table 1. All subjects gave informed consent to participation in the study.

Study design

The SMA behaves as a muscular vessel. At rest or in the fasting state, blood flow in this vessel is low and impedance is high. During muscular effort or in the digestive phase, vascular resistance decreases and diastolic blood flow increases. The study was divided into two parts. In the first part, the SMA blood flow was measured by CDU, at 12 noon, 1 h after last meal (i.e. in the fasting state) and at least 36 h after the last medication. Before the CDU examination, all the subjects were allowed to rest for 1 h in the supine position in a suitable environment (20–23°C) to obtain basal conditions; brachial arterial pressure was then measured and mean arterial pressure was calculated. Body weight and height were measured to determine body surface area and body mass index. In the second part of the study, we evaluated the effect of a meal on SMA circulation [22, 26–28] in six healthy controls and six SSC patients. After an overnight fast of 15 h, at mid-day a basal CDU scan of the SMA was performed. At the end of the basal test, a standardized balanced mixed liquid meal (355 kcal, Ensure plus; Abbott Laboratories, North Chicago, IL, USA) was given and new SMA measurements were obtained 30 min later [22, 28].

Assessment of blood flow and impedance of SMA

The CDU examination of SMA blood flow was performed with an Ultramark-9 HDI scanner (ATL, Bothell, WA, USA), using a 2–4 MHz broadband convex probe. This probe shows an axial and lateral resolution of 0.8 and 1.5 mm respectively at a depth of 6 cm. The same sonologist (RR) performed all the Doppler examinations. Respiration was suspended for up to 10 s during Doppler measurements.

The outcome variables of SMA were vessel internal diameter, flow mean velocity (V mean), blood flow and PI. Doppler measurements were taken just distal to the point at which the vessel changes course from an anterior to a caudal direction. If a distinct angle was not present in the SMA, blood flow was measured 2 cm from its origin. SMA blood flow was determined from the time-averaged mean velocity of the Doppler spectrum and vessel diameter. When the desired measurement site was identified (by colour Doppler), the position of the transducer was adjusted to afford an angle of less than 60°, the sample volume was adjusted to include the entire inner diameter of the vessel and the measurement was subsequently taken in the grey scale. Every measurement represented the mean of five sequential determinations. The PI was used to measure vascular impedance, and was determined from the spectral waveform by taking the average value for five waveforms of the expression (peak systolic frequency shift—lowest diastolic frequency shift)/mean blood flow velocity. Doppler waveforms were produced at the lowest possible pulse repetition frequency to avoid artefacts. This maximized the size of the Doppler spectrum and decreased the percentage error in the measurements.

In our experience, the mean intra-examination coefficient of variation (CV) of Doppler measurements is 3.3% for SMA diameter, 4.4% for SMA V mean, 4.36% for SMA blood flow and 4.1% for PI. The results obtained in healthy controls were fully comparable with the measures reported by other authors [16–21].
Statistical analysis

The data were analysed with SPSS software [SPSS, Chicago, IL, USA (1990)]. One-way analysis of variance was used to examine variables among groups. Tukey’s multiple comparison procedure was used when appropriate, with alpha error corrected according to Bonferroni’s method, to select significantly different groups.

Linear regression analysis was used to assess the effects of age, disease duration, type of disease (diffuse or limited) and the relationships with oesophageal motility for the variables that were examined. Data are shown as mean \( \pm \) s.d. unless otherwise indicated. \( P < 0.05 \) was considered significant.

Results

Table 1 lists the relevant epidemiological and physical data for the subjects of this study. No statistical differences were found between SSc patients and healthy controls for the following variables: mean body weight, height, body surface area and body mass index.

In the fasting state, the shape of the Doppler wave was different in the two groups of subjects: in the SSc patients, the negative diastolic component seen in the normal SMA ultrasound spectrum was absent (Fig. 1).

As shown in Table 2, the mean SMA diameter was significantly lower in the patients than in the healthy controls (\( P < 0.001 \)). In the two groups, mean blood velocity (\( V_{\text{mean}} \)) was not significantly different between the two groups, whereas mean SMA blood flow was significantly lower in SSc patients than in controls (\( P < 0.0001 \)). This difference was also evident when values were related to the body weight of the subject (\( P < 0.0001 \)).

The mean PI was lower in SSc patients than in controls but the difference was not significant. The results were not influenced by the patient’s age, by the duration and type (cutaneous limited or diffuse) of the disease (Table 2), by the degree of impairment of oesophageal motility or by therapy; in particular, no significant difference was observed between patients treated and not treated with cisapride (data not shown).

The effects of a standardized balanced liquid meal on SMA blood flow are reported in Table 3. In the

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\begin{array}{cccc}
\text{Healthy controls} & \text{lcSSc patients} & \text{dcSSc patients} & P^a \\
\hline
\text{No. of subjects} & 25 & 12 & 15 \\
\text{Diameter (cm)} & 0.48 \pm 0.07 & 0.36 \pm 0.09^* & 0.37 \pm 0.03 & 0.001 \\
\text{Mean velocity (cm/s)} & 35.8 \pm 12.6 & 37.6 \pm 20.4 & 33.6 \pm 14 & 0.45 \\
\text{Blood flow (ml/min)} & 398 \pm 125 & 222 \pm 106^{**} & 199 \pm 74^{**} & 0.0001 \\
\text{Flow/weight (ml/kg)} & 6.4 \pm 1.9 & 4.3 \pm 2.1^{**} & 3.5 \pm 1.4^{**} & 0.0001 \\
\text{PI} & 4.13 \pm 0.97 & 3.51 \pm 0.95 & 3.48 \pm 1.12 & 0.07 \\
\end{array}
\]

lcSSc, limited cutaneous SSc; dcSSc, diffuse cutaneous SSc; n.s., not significant.

\(^a\)One-way analysis of variance.

\(^* P < 0.05; ^{**} P < 0.01 \) vs healthy controls (Tukey’s test). Differences between limited and diffuse SSc were not significant.
In both the SSc and the control group, the meal significantly increased SMA blood flow and no statistical difference between the groups was found, although mean SMA blood flow was slightly lower in patients than in controls. These observations suggest that, for SSc patients, the difference in flow rate reported in the fasting state was of functional rather than any anatomical significance, i.e. it was a consequence of vascular vasoconstriction of the SMA that disappeared under the effect of stimulation by the meal. In the presence of an anatomical lesion, the differences observed in the fasting condition should become more evident after a meal [27, 28]. Our results therefore suggest the existence in SSc patients of increased vascular sympathetic tone, at least in the first tract of the SMA, where the measurements were taken. The sensitivity of transabdominal Doppler ultrasonography does not allow the demonstration of changes in arterial wall thickness or abnormalities of the bowel arterioles or capillaries; these are the vessels that are mostly responsible for resistance to blood flow and are probably involved by the disease. The involvement of these vascular structures in our patients is also suggested by the small amount of variation in PI in comparison with SMA blood flow in the fasting state; this supports reduced vascular impedance downstream.

In our study group, the blood flow differences observed in SSc patients were not related to the type of disease (limited or diffuse), the duration of disease or to the patient’s age. This lack of correlation might be related to the small number of cases examined or to polymorphism in the expression of the disease.

In conclusion, this research showed the existence of fasting SSc patients of a change in basal haemodynamics caused by vasoconstriction of the SMA, which was demonstrable before the appearance of clinical symptoms of small bowel involvement.

Discussion

Fasting SMA blood flow is related to body size. For this reason our study included only female subjects, whose body size and body mass index were homogeneous. Therefore, we did not find any correlation between body mass index and either body surface area or SMA blood flow.

The selected SSc patients included in this study did not present any sign or symptom of small bowel dysfunction, diarrhoea or malnutrition. Indeed, in these cases, an important reduction in fasting SMA blood flow was frequently found, mainly because the internal diameter of the SMA was low in these patients. Patients but not controls were receiving chronic treatment with a slow-release nifedipine preparation. However, this did not account for the differences we observed. In fact, patients were asked to stop the drug the day before the examination; thus, there was an interval of 36 h or longer between the last drug consumption and the CDU examination. Furthermore, residual vasodilation caused by nifedipine should reduce rather than amplify the difference between groups.

Table 3. Effect of a standard balanced liquid meal (350 kcal) on SMA blood flow in normal controls and SSc patients (mean ± s.d.)

<table>
<thead>
<tr>
<th></th>
<th>Healthy subjects</th>
<th>SSc patients</th>
<th>p&lt;0.01</th>
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<tbody>
<tr>
<td></td>
<td>(n = 6)</td>
<td>(n = 6)</td>
<td></td>
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<tr>
<td><strong>Fasting</strong></td>
<td></td>
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<tr>
<td>SMA diameter (cm)</td>
<td>0.47 ± 0.05</td>
<td>0.35 ± 0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>V&lt;sub&gt;mean&lt;/sub&gt; (cm/s)</td>
<td>28.8 ± 9.7</td>
<td>32.9 ± 18.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>SMA flow (ml/min)</td>
<td>338 ± 93</td>
<td>171 ± 57</td>
<td>0.01</td>
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<tr>
<td>SMA flow/weight (ml/min/kg)</td>
<td>5.7 ± 1.3</td>
<td>2.8 ± 0.9</td>
<td>0.01</td>
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<tr>
<td>PI</td>
<td>4.4 ± 0.43</td>
<td>3.8 ± 1.3</td>
<td>0.01</td>
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<tr>
<td><strong>After meal (30 min)</strong></td>
<td></td>
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<tr>
<td>SMA diameter (cm)</td>
<td>0.49 ± 0.07</td>
<td>0.41 ± 0.06</td>
<td>n.s.</td>
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<tr>
<td>V&lt;sub&gt;mean&lt;/sub&gt; (cm/s)</td>
<td>53.5 ± 21.5b</td>
<td>60.5 ± 14.2b</td>
<td>n.s.</td>
</tr>
<tr>
<td>SMA flow (ml/min)</td>
<td>582 ± 135&lt;sup&gt;a&lt;/sup&gt;</td>
<td>480 ± 127&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n.s.</td>
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<tr>
<td>SMA flow/weight (ml/min/kg)</td>
<td>10.1 ± 1.9&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>7.9 ± 3.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n.s.</td>
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<tr>
<td>PI</td>
<td>1.8 ± 0.51</td>
<td>1.5 ± 0.20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n.s.</td>
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</table>

<sup>a</sup>Ensure plus (Abbott Laboratories, North Chicago, IL, USA).

<sup>b</sup>Two-factor analysis of variance.

*P < 0.05; **P < 0.01; n.s., not significant (meal vs fasting).

References