Association of Sarcoidosis With Endothelial Function, Arterial Wall Properties, and Biomarkers of Inflammation

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BACKGROUND
Sarcoidosis is an inflammatory disease, which may affect vascular function. The study was designed to assess the impact of sarcoidosis on endothelial function and arterial stiffness.

METHODS
Eighty-seven sarcoidosis patients and eighty-seven matched healthy subjects (CI) were included in the study. Sarcoidosis patients were divided into two groups. Group 1 included patients never treated and group 2 included patients receiving cortisone treatment. Endothelial function was evaluated by flow-mediated dilatation (FMD). Carotid-femoral pulse wave velocity (PWV) was measured as an index of aortic stiffness and augmentation index (AI75) as a measure of arterial wave reflections. Serum levels of soluble intercellular adhesion molecule-1 and tumor necrosis factor-α (TNF-α), were measured.

RESULTS
In the totality of the population, sarcoidosis patients had significantly lower FMD ($p < 0.01$) and significantly higher AI75 ($p < 0.05$). There was also a significant difference, between group 1, and CI in FMD and AI75, but there was no difference between group 2 and CI in FMD and AI75. AI75 values were significantly correlated with serum levels of intercellular adhesion molecule-1 (ICAM-1) ($r = 0.370, p < 0.01$) and TNF-α ($r = 0.219, p = 0.049$).

CONCLUSIONS
In the present study, we have shown that sarcoidosis patients have impaired endothelial function and increased arterial stiffness. Sarcoidosis patients on cortisone treatment had no differences compared to controls on the vascular parameters. Moreover, there was a significant correlation between inflammatory process and vascular function impairment. These findings indicate that sarcoidosis patients have impaired vascular function and increased inflammatory status, which may improve with cortisone treatment.

Keywords: arterial stiffness; blood pressure; endothelial dysfunction; hypertension; inflammation; sarcoidosis

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Recently, it has been found that parameters of vascular function and structure have important clinical impact. Endothelial function is usually quantified by flow-mediated dilatation (FMD) in the forearm, a common marker of increased cardiovascular risk. The FMD values in the forearm are correlated with the endothelial function of various arteries beds including coronaries arteries.1,2 Moreover, arterial stiffness and arterial wave reflections as they can be estimated noninvasively, with pulse wave velocity (PWV) and augmentation index (AIx) respectively, has an independent predictive value for cardiovascular events.3 Both, endothelial function and arterial stiffness are impaired in various inflammatory processes.4–7

Sarcoidosis is a systemic inflammatory disorder of unknown etiology, which is characterized by the formation of non-caseating granulomas. The term systemic implies that sarcoidosis can involve upon lungs and lymph nodes and many other organs such as heart, liver, eyes, nervous system etc.8 Sarcoidosis patients are also characterized by an increase in inflammatory mediators.9,10 The active phase of the disease is also associated with an increase in vasoactive substances such as endothelin-1.11 Growing evidence suggest that increase levels of various inflammatory and vasoactive substances in the active phase of the disease may affect the endothelial function and arterial wall properties.10–13 Recently, it was shown that sarcoidosis patients are characterized by reduced aortic distensibility,14 whereas the long-term effects of the disease on peripheral endothelial function and arterial stiffness and the associations between endothelial function, peripheral arterial stiffness, and inflammatory mediators are unknown.

In the present study, we hypothesized that sarcoidosis patients have impaired arterial wall properties, which are proportional...
to their inflammatory status. Furthermore as a secondary objective, we tested for differences in arterial wall properties between sarcoidosis group with different clinical characteristics.

METHODS

Study population. Eighty-seven sarcoidosis patients (34 male and 53 female, mean age 49.3 ± 11.2 years) and eighty-seven (38 male and 49 female, mean age 49.0 ± 13.3 years) healthy subjects (CI), frequency matched for age and sex, were recruited from two collaborating hospitals. All measurements, in this study were made by the same observer who was unaware of the disease status and treatment condition of the participants. The sarcoidosis diagnosis, in all patients, was biopsy proved by the presence of noncaseating granulomas in various specimens such as lung, lymph nodes, skin, etc. Patients with sarcoidosis were divided in two groups according to treatment status. Group 1 consisted of 36 patients with mild form of the disease as it can be assessed by clinical signs and symptoms, biochemical measurements and imaging techniques.15 These patients did not suffer from breathlessness or respiratory failure, had no systemic symptomatic disease, had normal pulmonary function tests and they had never been treated with cortisone or other immune-modulate or immune-active drugs. Group 2 was consisted of 51 patients with aggressive form of the disease and threatened organ function. More precisely patients in this group had one or more of the following: bilateral hilar adenopathy with or without fibrosis in pulmonary parenchyma, persistent pulmonary infiltrates, progressive loss of lung function, symptoms of respiratory failure, abnormal pulmonary function tests with FEV1 <77%, FVC <74%, FEV1/FVC >89%, TLC <78%, and TLCO <71%, neurological or eye disease. These patients were under cortisone (5–60 mg of prednisone or its equivalents) treatment for at least 6 months.16 The median disease duration as it can be accessed from the time the diagnosis was biopsy proved, was 4.0 (1.1, 8.8) years. All patients were without clinical cardiac symptoms while patients with systemic disease, renal insufficiency (glomerular filtration rate <60.0 ml/min, calculated with MDRD formula17), diabetes mellitus, known or suspected neoplasm, hematological malignancies, immunosuppression, recent (within the previous 6 months) surgery, pregnancy and lactation, severe valvular disease, atrial fibrillation, and a history of myocardial infarction or stroke were excluded from the study. Based on medical history, physical examination, blood count and on specific serological tests we also excluded patients with other inflammatory or autoimmune disorders. CI were consecutive subjects recruited from the outpatient cardiology department, where they referred for preventive cardiology examination. Subjects who were recruited as CI were asymptomatic without medical treatment and had a normal physical examination, a normal resting electrocardiogram, normal blood pressure, normal blood count, and routine serological tests, and no history of cardiovascular or systemic diseases. We define as “smoker” the current smokers, who smoke at least one cigarette per day and as “no smoker” those who had never tried a cigarette in their lives or those who had stop smoking for at least 1 year.

The study (complied with the Declaration of Helsinki) was approved by the institutional ethics committee and an informed consent was given by each participant.

Evaluation of vascular function. Endothelial function was evaluated by estimating the flow-mediated dilation in the brachial artery, as previously described.18 Briefly, after 10 min rest, the right brachial artery was scanned in longitudinal section, 5 cm above the antecubital fossa using a linear array U/S transducer. A pneumatic cuff placed distal to the ultrasound probe was then inflated to suprasystolic pressure on the forearm for 5 min to induce reactive hyperemia. After the release of ischemia cuff, brachial artery diameter was measured every 15 s for 2 min, and FMD was defined as the %change of vessel diameter from rest to the diameter 60 s after cuff release. After 10-min rest, a further arterial diameter measurement was made between 2 and 5 min after a single sublingual spray of glyceryl trinitrate (400μg). Endothelium-independent dilation was defined as the %change of vessel diameter from rest to the maximum diameter postnitrate administration. The repeatability of the technique in our institution for determining FMD was determined according to the Bland–Altman method. The repeatability coefficient, which was calculated as defined by the British Standard Institution, that is, according to the formula: repeatability coefficient = $2 \times \sqrt{\frac{1}{N}(\sum d_i^2/N)}$ (where N is the sample size and di is the difference between the two measurements in a pair), was 5.0%.

Carotid-femoral PWV, which is considered to be an index of aortic stiffness,19,20 was calculated from measurements of pulse transit time and the distance traveled between two recording sites (PWV = distance in meters divided by transit time in seconds) by using a well-validated noninvasive device (SphygmoCor; AtCor Medical, Sydney, Australia)21 as previously described.22

AIx of the central (aortic) pressure waveform was measured as an index of wave reflection.23 AIx is a composite measure of the magnitude of wave reflection and arterial stiffness, which affects timing of wave reflection. Large values of AIx indicate increased wave reflection from the periphery and/or earlier return of the reflected wave as a result of increased PWV (owing to increased arterial stiffness) and vice versa. Because AIx is influenced by changes in heart rate, it was also corrected accordingly (corrected for a steady heart rate of 75 beats/min-AIx75).24 AIx75 was measured with a validated, commercially available system (SphygmoCor; AtCor Medical) that uses the principle of applanation tonometry and appropriate acquisition and analysis software for noninvasive recording and analysis of the arterial pulse, as previously described.25,26 Waveforms of radial pressure were calibrated according to sphygmomanometric systolic and diastolic pressure measured in the brachial artery.

Biochemical measurements. Venous blood samples were centrifuged at 3,000 route/min and serum/plasma was collected and stored at −80°C until assayed. Serum levels of soluble intercellular adhesion molecule and tumor necrosis factor-α (TNF-α) were measured in the sarcoidosis population, as well-estab-
lished inflammatory markers, by commercially available ELISA kits (R&D Systems, Minneapolis, MN). B-type natriuretic peptide was measured as a marker of left ventricular dysfunction using the Triage Cardio ProfilER panel method (fluorescence immunoassay; Biosite, San Diego, CA). The mean ± s.d. inter- and intra-assay variability ranged from 7.2 to 8.0 ± 1.5 pg/ml. Biochemical measurements including lipids and glucose levels were measured by using commercially enzymatic method.

**Statistical analysis.** All variables were tested for normal distribution of the data. The values of soluble intercellular adhesion molecule-1 and TNF-α were skewed and they were log-transformed to improve normality. Normally distributed data were expressed as means ± s.d. and otherwise as median and first and third quartile. A Student’s t-test was used for normally distributed continuous data, otherwise Mann–Whitney test was perform. A χ²-test was used for categorical variables. Bivariate analysis was performed to examine the relationship between AI75, PWV, and FMD values of sarcoidosis patients with other variables examined in the study. Multiple linear regression analysis was used to test for independent associations after adjustment for several confounders. The selection of the confounders such as age, mean arterial pressure, and heart rate was based on bibliography data. 3 For normally distributed

<p>| Table 1 | Baseline characteristics in the sarcoidosis groups |</p>
<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1 (no cortisone treatment)</th>
<th>Group 2 (cortisone treatment)</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical and demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects number</td>
<td>36</td>
<td>51</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>2.0 (0.1, 5.5)b</td>
<td>5.0 (2.5, 9.0)b</td>
<td>—</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.4 ± 10.6</td>
<td>50.6 ± 11.3</td>
<td>49.0 ± 13.3</td>
<td>0.48</td>
</tr>
<tr>
<td>Male%</td>
<td>36</td>
<td>41</td>
<td>44</td>
<td>0.74</td>
</tr>
<tr>
<td>Body mass index (kg·m−2)</td>
<td>26.3 ± 4.0</td>
<td>26.8 ± 4.3</td>
<td>26.5 ± 4.1</td>
<td>0.83</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>126 ± 15</td>
<td>120 ± 11</td>
<td>121 ± 15</td>
<td>0.12</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>84 ± 10</td>
<td>82 ± 10</td>
<td>80 ± 11</td>
<td>0.15</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>41 ± 10</td>
<td>38 ± 9</td>
<td>41 ± 11</td>
<td>0.23</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>74 ± 9</td>
<td>70 ± 12</td>
<td>69 ± 12</td>
<td>0.11</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (ml/min)</td>
<td>92 ± 14</td>
<td>95 ± 16</td>
<td>92 ± 14</td>
<td>0.35</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>17</td>
<td>16</td>
<td>11</td>
<td>0.60</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>28</td>
<td>26</td>
<td>20</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Arterial wall properties measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMD (%)</td>
<td>5.0 ± 3.0c</td>
<td>6.4 ± 2.5</td>
<td>7.5 ± 3.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EID (%)</td>
<td>13.2 ± 4.3</td>
<td>14.4 ± 4.5</td>
<td>14.7 ± 3.4</td>
<td>0.65</td>
</tr>
<tr>
<td>AI75 (%)</td>
<td>25.4 ± 5.9c</td>
<td>21.3 ± 10.1</td>
<td>20.5 ± 10.5</td>
<td>0.04</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>7.6 ± 1.6</td>
<td>7.2 ± 1.7</td>
<td>7.1 ± 1.6</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Biochemical measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose levels (mg/dl)</td>
<td>92 ± 14</td>
<td>95 ± 16</td>
<td>90 ± 11</td>
<td>0.92</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>211 ± 29</td>
<td>210 ± 44</td>
<td>199 ± 55</td>
<td>0.34</td>
</tr>
<tr>
<td>Low density lipoprotein (mg/dl)</td>
<td>126 ± 38</td>
<td>132 ± 30</td>
<td>133 ± 39</td>
<td>0.63</td>
</tr>
<tr>
<td>High density lipoprotein (mg/dl)</td>
<td>49 ± 16</td>
<td>56 ± 15</td>
<td>49 ± 15</td>
<td>0.09</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>123 (88, 197)b</td>
<td>109 (94, 132)b</td>
<td>105 (80, 135)b</td>
<td>0.08d</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>0.44 ± 0.26</td>
<td>0.21 ± 0.27</td>
<td>—</td>
<td>0.02</td>
</tr>
<tr>
<td>sICAM-1 (ng/ml)</td>
<td>2.46 ± 0.26</td>
<td>2.40 ± 0.31</td>
<td>—</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Treatment characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins use (%)</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>0.23</td>
</tr>
<tr>
<td>Antihypertensive treatment (%)</td>
<td>23</td>
<td>29</td>
<td>12</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± s.d. or median (25–75 percentiles) or numbers of subjects or valid percentages. Percentages are rounded to integers and P values are rounded to two decimal places. Differences between group 1 and group 2 were tested with t-test for normally distributed continuous data or with Mann–Whitney test otherwise. Differences of normally distributed continuous data between group 1, group 2, and control group were tested with ANOVA or Kruskall–Wallis test for nonparametric data. χ² was used for the comparison between categorical variables.

AI75, augmentation index at 75 beats/min; EID, endothelium-independent dilation; FMD, flow-mediated dilation; PWV, pulse wave velocity; sICAM, soluble intercellular adhesion molecule-1; TNF-α, tumor necrosis factor-α.

a P value based on Mann–Whitney test. bValues are expressed as median (25–75 percentiles). cANOVA post hoc with Bonferroni correction revealed statistical significant difference between group 1 and control. d P values based on Kruskall–Wallis test.
data analysis of variance was performed to examine for inter-group differences, otherwise Kruskal–Wallis test was used. Differences in values between study subgroups were tested by using post hoc analysis after Bonferroni correction. P values of <0.05 were considered to indicate statistical significance. All statistical calculations were performed using SPSS software (version 13.0; SPSS, Chicago, IL).

The sample size of our study was calculated according to the applied a priori power analysis based on mean values of FMD and AI75 (t-test) collected from pilot data. Accordingly a total sample size of ~170 participants (divided into two almost equal groups), was adequate to reveal an effect size of 0.44, achieving the desirable statistical power of >80%, at a prefixed 0.05 type I error. Concerning PWV taking into account the sample size calculated from the above-mentioned data, a type I error of 0.05 and an effect size of 0.34 calculated from the pilot study the power was assessed at 60%.

**RESULTS**
There was no difference between the two groups (CI and sarcoidosis) in the basic demographic and clinical characteristics such as age, sex, and cardiovascular risk factors. The demographic and clinical characteristics of the control group and the two sarcoidosis groups are listed in Table 1 along with biochemical and arterial wall measurements.

**Flow-mediated dilatation**
The FMD was significantly lower in overall sarcoidosis group (N = 87) compared to control (N = 87) (5.77 ± 2.80% vs. 7.49 ± 3.55%, P < 0.01) whereas there was no difference in endothelium-independent dilatation and endothelium-independent dilatation (13.96 ± 3.76% vs. 14.67 ± 3.38%, P = 0.25) (Table 1). One-way analysis of variance showed significant differences between CI subjects, group 2 of sarcoidosis patients and group 1 (F(2,161) = 5.44, P < 0.01). Subgroups analysis revealed that although there was a significant difference in FMD between group 1 of sarcoidosis patients and CI (5.03 ± 3.01% vs. 7.50 ± 3.56%, P < 0.01), there was no significant difference between group 2 of sarcoidosis patients and CI (6.37 ± 2.51% vs. 7.50 ± 3.56%, P = 0.25) for the same variables (Figure 1). Bivariate analysis in sarcoidosis group showed that FMD was negatively correlated with age (r = −220, P = 0.05) and body mass index (r = −234, P = 0.05), whereas there was no correlation between disease duration and FMD (r = 0.177, P = 0.397).

**AI75 and PWV**
Patients with sarcoidosis compared to healthy subjects had significantly higher AI75 (23.77 ± 8.85% vs. 20.51 ± 10.47%, P < 0.05) and higher PWV (7.47 ± 1.65 m/s vs. 7.07 ± 1.56 m/s, P = 0.11). Furthermore, bivariate correlations in sarcoidosis patients revealed that PWV was correlated with age (r = 0.583, P < 0.01), body mass index (r = 0.224, P < 0.05), and mean arterial pressure (r = 0.284, P < 0.01). AI75 was correlated with age (r = 0.523, P < 0.01), soluble intercellular adhesion molecule-1 (r = 0.370, P < 0.01), TNF-α (r = 0.219, P = 0.049), and mean arterial pressure (r = 0.196, P = 0.05). Neither PWV (r = 0.165, P = 0.15), nor AI75 (r = 0.179, P = 0.12) had a correlation with disease duration.

The difference in AI75 between the overall sarcoidosis group and the control group remained significant after adjustment for age and mean arterial pressure (B = 2.481, 95% confidence interval (0.082, 4.879), P = 0.04). By contrast, the difference in PWV between the CI group and overall sarcoidosis group was no longer significant after adjustment for age, mean arterial pressure, and heart rate (B = 0.240, 95% confidence interval (−0.181, 0.661), P = 0.26) (Figure 2). Regression analysis, after adjustment for age and mean arterial pressure showed significant differences in AI75 values between CI subjects, group 2 of sarcoidosis patients and group 1 (F(2, 158) = 3.06, P = 0.049). More precisely regression analysis revealed that although group 1 of sarcoidosis patients compared to CI had greater
In the present study, we have demonstrated that arterial wall properties were impaired in sarcoidosis patients compared to controls. Interestingly, sarcoidosis patients on cortisone treatment had no differences compared to controls on the vascular parameters. Moreover, inflammatory status was correlated with vascular function impairment in this population.

**Vascular function and sarcoidosis**
Cardiovascular risk factors have a significant role in the development of endothelial dysfunction. Studies have shown that impaired endothelial function is associated with adverse cardiovascular events, and that endothelial function is a key regulator of the elastic properties of large vessels. Moreover, large-artery stiffness and wave reflections are important determinants of left ventricular function, coronary blood flow, and mechanical integrity of arteries and have been identified as markers of cardiovascular disease and independent prognostic markers of cardiovascular risk.

Impaired endothelial function has been described in several connective tissue diseases such as, temporal arteritis, systemic sclerosis, ankylosing spondylitis, systemic vasculitis and polyarteritis nodosa, rheumatoid arthritis, and Adamantiades–Behçet’s disease. It is also known that inflammatory diseases are associated with enhanced atherosclerosis and an increased in cardiovascular events. To our knowledge there are no studies evaluating the endothelial function and arterial wall properties of sarcoidosis patients.

In this study, it was demonstrated that sarcoidosis patients had significantly impaired endothelial function, as it can be expressed with FMD values, compared to control group. Endothelial dysfunction is probably responsible for the increase in arterial wave reflections of sarcoidosis patients. Indeed, we found that sarcoidosis patients, even after adjustment for age and mean arterial pressure, have increased AI75 compared to healthy subjects. These findings imply that endothelial dysfunction in sarcoidosis patients can probably induce arteriosclerosis and highlight the need to further evaluate the atherosclerotic status of this population.

More specifically, it was found that although sarcoidosis patients with mild form of the disease (group 1) had impaired endothelial function and increased AI75, patients with aggressive form of the disease (group 2) had no significant changes in arterial wall properties, compared to CI subjects. In accordance with our findings, there are data showing that patients with active form of Behçet’s disease on cortisone treatment have FMD values comparable of control subjects whereas patients not treated with cortisone had lower FMD than control individuals. The different trend in arterial wall properties between groups 1 and 2 does not seem to be the result of disease duration, because patients with sorter disease duration have worse endothelial function and increased arterial stiffness. Changes in arterial wall properties may be attributed at the inappropriate function of immune system in this population, which is associated with increased inflammatory status. Thus, we cannot exclude the possibility that the discrepancy in arterial wall properties between the two sarcoidosis groups is a consequence of the difference in the inflammatory status. Previous, studies have shown that sarcoidosis is associated

**Table 2 | Univariate and multivariable linear regression analysis of AI75 (%)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.47 (0.36, 0.57)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>0.22 (0.09, 0.34)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Group 1</td>
<td>4.92 (0.07, 8.76)</td>
<td>0.01</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.83 (−2.59, 4.25)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Reference category: Control group. AI75, augmentation index at 75 beats/min; B, linear regression coefficient; CI, confidence interval; Group 1, sarcoidosis patients never treated with cortisone; Group 2, sarcoidosis patients on cortisone treatment.

**Figure 3 | Box-plots of augmentation index at 75 beats/min (AI75) adjusted values for age and mean arterial pressure in group 1, group 2, and in healthy subjects. Group 1 consisted of sarcoidosis patients without cortisone treatment and group 2 of sarcoidosis patients on cortisone treatment. AI75, there was no difference between group 2 of sarcoidosis patients and CI for the same variables (Table 2) (Figure 3).**

**Inflammatory markers**
Group 1, compared to group 2 of sarcoidosis patients, had significantly increased values of logTNF-α (0.44 ± 0.26 pg/ml vs. 0.21 ± 0.27 pg/ml, *P* = 0.02) whereas there was no difference in values of log intercellular adhesion molecule-1 (ICAM-1) (2.46 ± 0.26 ng/ml vs. 2.40 ± 0.31 ng/ml, *P* = 0.72). There were also, significant correlations between arterial stiffness, as it is expressed with values of AI75, and serum levels of log ICAM-1 (*r* = 0.287, *P* = 0.048) and logTNF-α (*r* = 0.228, *P* = 0.049). Moreover, we found that sarcoidosis patient in the lower quartile of ICAM-1 level have significantly increased FMD compared to those in the upper quartile (6.70 ± 2.52% vs. 4.54 ± 2.96%, *P* = 0.03). Serum levels of B-type natriuretic peptide were not correlated with FMD (*r* = −0.211, *P* = 0.23), AI75 (*r* = 0.178, *P* = 0.30), and PWV (*r* = −0.073, *P* = 0.67).

**DISCUSSION**
In the present study, we have demonstrated that arterial wall properties were impaired in sarcoidosis patients compared to
with subclinical vasculitis which may be responsible for the impairment of arterial wall properties. Moreover, other studies suggest that sarcoidosis patients have autoantibodies against endothelial cells which may cause further endothelial dysfunction.

Cortisone has unfavorable results in vascular properties and in endothelial function by inhibiting endothelial nitric oxide synthetase and by reducing nitric oxide levels. Moreover, in healthy normotensive subjects cortisone administration results in an increased arterial pressure and in an increased vasoconstriction response to noradrenaline. Nevertheless, in inflammatory diseases, cortisone treatment reduces inflammatory process and prevents or suppresses the development of the manifestations of inflammation, by inhibiting the release from different cell sources of mediators of inflammation, such as arachidonic acid and its metabolites (prostaglandins and leukotrienes), platelet-activating factor, TNF, interleukin-1 (IL-1), and plasminogen activator. In addition to the above, the anti-inflammatory action of corticosteroids may also be attributed to their ability to inhibit the platelet-derived growth factor-induced transcription of vascular endothelial growth factor mRNA and secretion of vascular endothelial growth factor protein. The preserved endothelial function in group 2 of sarcoidosis patients can partially attributed to the favorable effects of cortisone treatment in the inflammatory status.

Inflammatory markers and sarcoidosis

Previous studies have shown that inflammation plays a key role in the development of atherosclerosis. It is also known that inflammatory diseases are associated with increased cardiovascular events. Moreover, it has been demonstrated that increased circulating levels of inflammatory mediators such as TNF-α, IL-1β, IL-6, IL-10 are constantly found in patients with sarcoidosis. These cytokines promote the production of metalloproteinases, which degrade collagen and elastin content of the large arteries intima and are responsible for impaired function of the arteries wall.

In the present study, we found that serum levels of TNF-α were increased in group 1 of sarcoidosis patients compared to group 2. This finding is not totally unexpected because in previous studies levels of inflammatory markers were not able to define the aggressiveness of the disease. Moreover, the reduced levels of TNF-α in the sarcoidosis patients with the aggressive form of the disease (group 2) can be attributed to the immune-modulatory effect of cortisone. This is in accordance with previous studies demonstrated that the expression of inflammatory markers such as TNF-α and IL-1 were greatly reduced in inflammatory diseases after cortisone treatment.

Although, acute systemic inflammation causes a decrease in waves reflections, chronic low grade inflammation is associated with an increase in reflected waves. In accordance, there are data in patients with Behçet’s disease showing that patients in the acute phase of the disease had decreased reflected waves compared to patients in the chronic phase of the disease. Increased AI75 has also been described in inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus. In this study, it was found that serum levels of ICAM-1 and TNF-α were correlated with AI75 in sarcoidosis patients. Furthermore, lower values of ICAM-1 were associated with improved endothelial function.

These findings imply that inflammation is a causative mechanism of endothelial dysfunction and increased arterial wave reflections in this population. However, further studies are needed to elucidate if specific or broad-spectrum anti-inflammatory treatments can improve arterial wall properties, endothelial function and reduce cardiovascular events in sarcoidosis patients.

The patient population was heterogenous concerning treatment status and disease duration and the sample size was relatively small. Consequently, the study had adequate power to reveal differences between control subjects and sarcoidosis patients as well as between control subjects and group 1, but the power of the study was inadequate to reveal intergroup differences between group 2 and group 1 and CI subjects. Moreover, inflammatory indices were not measured in the control group and consequently it was impossible to estimate the inflammatory impairment in the sarcoidosis group.

In the present study, we have demonstrated that endothelial function was impaired and wave reflections were significantly increased in sarcoidosis patients compared to controls. Sarcoidosis patients on cortisone treatment showed no differences when compared to controls on the vascular parameters. Moreover, inflammatory status was correlated with vascular function impairment in this population. These findings demonstrate the importance of assessing the vascular function in sarcoidosis patients, which may have significant clinical implications.

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Sarcoidosis and Arterial Wall Impairment


