RESEARCH LETTER

Increased pulse wave velocity in pulmonary sarcoidosis: a preliminary study

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Introduction Sarcoidosis is a systemic inflammatory disease of unknown etiology, characterized by tissue infiltration of mononuclear phagocytes/antigen presenting cells (APCs) and lymphocytes with the subsequent noncaseating granuloma formation.[1] On the basis of the modified Matzinger's model of immune response and the results of our studies as well as those of other investigators, human heat shock proteins (HSPs) as main "danger signals" or microbial HSPs as pathogen-associated molecular patterns recognized by pattern recognition receptors on altered APCs may induce inflammation in sarcoidosis by both noninfectious and infectious factors in a genetically differently predisposed host.[2]

The disease typically affects the lungs and mediastinal lymph nodes, but it may also occur in other organs such as the liver, eyes, skin, and heart.[3] Moreover, sarcoidosis may also affect vascular structure and function, altering vascular stiffness.[4-6] Arterial stiffness is one of the most potent prognostic factors of cardiovascular morbidity and mortality. The measurement of pulse wave velocity (PWV) by applanation tonometry is generally accepted as the most simple, noninvasive, well-validated, and reproducible method to determine arterial stiffness. Carotid-femoral PWV is a direct measurement, which corresponds to the widely accepted propagative model of the arterial system.[7,8]

To the best of our knowledge, there has been 1 study that revealed increased arterial stiffness while indirectly measuring the augmentation index corrected to a heart rate of 75 bpm (AI75) in sarcoidosis.[6] Other 2 reports detected reduced aortic elasticity in sarcoidosis using transthoracic echocardiography.[4,5]

Therefore, the main objective of the present study was to assess the specific effect of sarcoidosis on PWV measured by applanation tonometry.

Patients and methods We enrolled healthy subjects and patients with chronic pulmonary sarcoidosis recruited from the University Hospital in Gdańsk, Poland. All participants were over 18 years of age and were enrolled between October 2012 and September 2014. A diagnosis of sarcoidosis was based on histological (scalenobiopsy of the lymph nodes), clinical, and radiological evidence. High-resolution computed tomography was used to diagnose sarcoidosis stage II (bilateral hilar lymphadenopathy and diffuse pulmonary infiltrations, 12 patients) and stage III (diffuse pulmonary infiltrations, 11 patients).

None of the patients had Löfgren syndrome. Microbiological and cytological examinations of the lymph nodes and sputum samples revealed no acid-fast bacilli (polymerase chain reaction, culture of the *M. tuberculosis* strain), fungi, or atypical cells. All patients had negative cardiovascular history and cardiac stress test results. No abnormalities were found on echocardiography or in lung function tests. Arterial blood gases were normal. None of the patients received corticosteroids.

The control group consisted of unrelated healthy volunteers. All individuals showed normal results of chest radiography and blood and serum analysis. In addition, there were no acid-fast bacilli in sputum smears or in the sputum culture of the *M. tuberculosis* strain. None of the healthy subjects had any chronic disease or received ongoing treatment. None of the participants were infected with HIV. Finally, none of the control or sarcoidosis patients had a familial history of tuberculosis, sarcoidosis, or autoimmune disease.

The study conformed to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Independent Ethics Committee at the Medical University of Gdansk, Gdańsk, Poland. All subjects gave written informed consent to participate in the study.

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Conflict of interest: none declared.
Received: April 3, 2015.
Revision accepted: May 19, 2015.
Published online: May 22, 2015.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2015; 125 (6): 475-477

PWV was calculated from the measurements of pulse transit time and the distance between the 2 recording sites (distance in meters divided by transit time in seconds) by using an applanation tonometry device (SphygmoCor; AtCor Medical, Sydney, Australia). PWV was assessed in subjects in the supine position after 15 minutes of the acclimatization period. Pulse sensors were placed at points where the pulse was the best palpable. Measurements were performed above the right common carotid artery and the right femoral artery.

A statistical analysis was performed using IBM SPSS Statistics v. 21 (Chicago, Illinois, United States). The results were tested for normality of distribution using the Shapiro–Wilk test. Differences between the groups were assessed using the *t* test. A 1-way analysis of variance was performed. Data were presented as mean ± standard deviation. A *P* value of 0.05 or less was considered statistically significant.

Results Twenty-three patients with sarcoidosis (15 men and 8 women; mean age, 47.6 ±11.7 years; mean body mass index [BMI], 26 ±3.6 kg/m^2) were enrolled to this study. In patients with sarcoidosis, systolic and diastolic arterial blood pressure was 122 ±18 and 78 ±10 mmHg, respectively. The control group consisted of 22 healthy subjects matched to sarcoidosis patients for sex, age, and BMI (13 men and 9 women; mean age, 45.3 ±11.6 years; BMI, 25 ±3.2 kg/m^2). In controls, systolic and diastolic arterial blood pressures were 122 ±19 and 76 ±11 mmHg, respectively. The values of total cholesterol and low-density lipoprotein cholesterol did not differ between the groups. There was no difference in age between healthy subjects and sarcoidosis patients (P = 0.569). Mean PWV values were significantly higher in patients with sarcoidosis than in healthy controls (8.6 ±1.6 m/s vs 6.3 ±1.2 m/s, P = 0.02). A 1-way analysis of variance was performed using age, systolic blood pressure, and BMI as covariates. PWV remained higher in patients with sarcoidosis (P <0.001) using this model, with age being the only variable associated with PWV in this model (P = 0.001).

Discussion In the present study, we demonstrated that patients with chronic pulmonary sarcoidosis had significantly higher carotid-femoral PWV values than healthy subjects. Indeed, we found that sarcoidosis patients, even after adjustment for age and systolic blood pressure, had increased PWV compared with healthy subjects.

In line with our results, Siaos et al.[6] also revealed increased arterial stiffness in patients with sarcoidosis compared with healthy controls, evaluating the AI75. However, in contrast to our study, PWV values were not significantly different in the study groups. Interestingly, patients with sarcoidosis receiving corticosteroid treatment showed no differences in vascular parameters compared with controls. Using echocardiography, Moyssakis et al.[4] showed reduced aortic distensibility, an index of aortic elasticity, in patients with systemic sarcoidosis compared with control subjects. Moreover, they revealed that the presence and severity of sarcoidosis were associated with reduced aortic distensibility, irrespective of the disease duration, pulmonary artery pressure, and lung function. Similarly, Ardic et al.[5] used transthoracic echocardiography to evaluate the aortic stiffness index, aortic strain, and aortic distensibility and reported impaired aortic elastic properties in sarcoidosis.

The pathogenesis of increased arterial stiffness in sarcoidosis is unknown. However, Siaos et al.[6] showed that patients on cortisone treatment have the same vascular parameters as healthy controls. Therefore, the increased PWV in our patients may result from systemic intimal and medial infiltration of the vasculature by a noncaseating granuloma.[9,10] Moreover, vascular cell proliferation and vascular reactivity depending either on the sympathetic nervous system or endothelial function (eg, reduced nitric oxide, increased endothelin 1, increased intracellular Ca^{2+}) or the renin–angiotensin system may be considered as the cause of changes in arterial distensibility in sarcoidosis.[11] It should be noted that Siaos et al.[6] detected impaired endothelial function in sarcoidosis patients and revealed a significant correlation of AI75 values with the serum levels of intercellular adhesion molecule 1 and tumor necrosis factor α, which play the main role in the pathogenesis of sarcoidosis.[1,2] Normal pulmonary arterial pressures with normal lung function and arterial blood gases, like in our sarcoidosis patients, may also suggest the presence of an intrinsic sarcoid vasculopathy.[9]

In conclusion, increased PWV values in patients with pulmonary sarcoidosis suggest disturbances in arterial compliance and elasticity in those patients. Moreover, applanation tonometry can be useful for a noninvasive detection of vascular changes and for therapy monitoring in this patient group. To confirm our preliminary findings, we are currently conducting a larger, more complex study on arterial elastic properties in patients with sarcoidosis.

Acknowledgments This study was supported by an ST-98 grant from the Medical University of Gdansk.

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