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Arterial Stiffness in Patients with Sarcoidosis and Obstructive Sleep Apnea

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Abstract: Background: Obstructive sleep apnea (OSA) and sarcoidosis have both been implied to be risk factors for increased arterial stiffness. However, it is unclear whether an elevated apnea–hypopnea index (AHI) in sarcoidosis patients increases arterial stiffness and thus the cardiovascular risk. Methods: We performed non-invasive applanation tonometry in 57 adults with sarcoidosis. The participants underwent SphygmoCor to assess arterial stiffness using an aortic augmentation index with a heart rate of 75/min (AIx) and level-3 respiratory polygraphy. An AHI of ≥5/h, ≥15/h, and ≥30/h defined mild, moderate, and severe OSA, respectively. Multivariate regression analysis was used to investigate the association between AIx and AHI, adjusted for prespecified risk factors for AIx. Results: 23 (40%) sarcoidosis patients had at least mild OSA (AHI ≥ 5), while 7 (12%) patients showed AHI ≥ 15/h. AHI was significantly associated with AIx (coef. (95%CI) of 0.31 (0.09/0.52), $p = 0.006$) even after adjustment for known risk factors of arterial stiffness. While severe OSA was positively associated with increased AIx, mild and moderate OSA were not associated with increased AIx after adjusting for known risk factors. Conclusions: Increased AHI is independently associated with increased arterial stiffness in sarcoidosis patients. Further investigations are needed to underline the association between OSA severity and the magnitude of arterial stiffness.

Keywords: sarcoidosis; arterial stiffness; augmentation index; cardiovascular risk; obstructive sleep apnea

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1. Introduction

Cardiovascular disease (CVD) is one of the leading causes of death worldwide. Beside traditional risk factors such as diabetes, hypertension, and smoking, chronic inflammation has increasingly been recognized as a non-traditional risk factor for CVD. Several studies have described an increased incidence of atherosclerosis and cardiovascular risk in patients with inflammatory diseases, such as ankylosing spondylitis, vasculitis, and sarcoidosis [1–4]. Sarcoidosis is a granulomatous disease of an unknown etiology that typically affects the lungs, but can involve virtually any other organ [5]. Beside lymphadenopathy and the formation of non-ceasing granulomas, systemic inflammation is a hallmark of the disease [6]. Non-invasive assessment techniques such as the measurement of arterial stiffness, endothelial function, and carotid-intima media thickness have been investigated to improve the early detection of vascular dysfunction before it becomes clinically overt in the form of cardiovascular events [7]. Arterial stiffness assessed by pulse wave velocity (PWV) and the augmentation index (AIx) is a strong predictor of cardiovascular events and all-cause mortality in the general population [8]. There is growing proof that patients with sarcoidosis might be at higher risk for endothelial dysfunction and increased arterial stiffness [9]. Higher AIx values have been described in sarcoidosis patients with ocular and cardiac sarcoidosis, thereby supporting the hypothesis that AIx not only predicts cardiovascular risk in sarcoidosis patients, but also extra pulmonary

involvement [10]. Hence, the understanding of the pathomechansim of increased arterial stiffness in sarcoidosis is of great importance. While disease-specific risk factors such as increased inflammation cytokines, direct granulomatous involvement of the vessels, and medication side effects have been under intense investigation, little is known about the role of classical risk factors in the development of arterial stiffness in this patient group [9,11]. We recently described an increased prevalence of obstructive sleep apnea (OSA) in sarcoidosis patients [12]. OSA is considered to be an independent cardiovascular risk factor in the general population [13]. It is the most common form of sleep-related breathing disorder (SDB) and is characterized by repetitive breathing cessation due to narrowing of the upper airways. Kohler et al. [14] reported that even patients with minimally symptomatic OSA show endothelial dysfunction and increased arterial stiffness. Several potential mechanisms have been discussed in the literature. Aside from arterial wall shear stress caused by rising blood pressure during apneic events, the suppression of endothelial nitric oxide (NO) synthase (due to increased oxidative stress), increased endothelial cell apoptosis, increased levels of coagulation factors, and cholesterol might orchestrate endothelial dysfunction and increased arterial stiffness in OSA patients [15–18].

Whether OSA is associated with an additional increase in arterial stiffness in sarcoidosis patients has so far not been investigated. This information would be of great interest as therapeutic options such as continuous positive airway therapy (CPAP) might be able to reverse pathological vascular changes in OSA patients [19]. The intent of this study was to assess the association between the apnea–hypopnea index (AHI) and arterial stiffness in patients with sarcoidosis.

2. Materials and Methods

2.1. Study Design and Participants

This study was part of a prospective cross-sectional study at the University Hospital Zurich, which our group conducted to assess the prevalence of OSA in sarcoidosis patients. For this purpose, 71 adult patients with sarcoidosis were matched one-to-one to 71 adult controls according to sex, age, and Body mass index (BMI). The study procedures included structured interviews, level-3 respiratory polygraphy, and arterial tonometry in all sarcoidosis patients.

Sarcoidosis patients were recruited via (1) visits to the University Hospital Zurich and (2) the sarcoidosis database of the University Hospital Zurich. Only sarcoidosis patients diagnosed according to international American thoracic society (ATS)/European respiratory society (ERS)/World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) guidelines were included [20]. All of the inclusion and exclusion criteria can be viewed in the supplemental material (supplemental material). The study was conducted in accordance with the declaration of Helsinki and all subjects gave written informed consent to participate. The Ethics Committee of the Canton of Zurich approved the study (BASEC-Nr 2019-01604) and the study was registered at www.ClinicalTrials.gov, NCT04156789 on 11 August 2019.

2.2. Measurements

2.2.1. Pulse Wave Analysis

Subjects had to rest for 10 min in a supine position before the pulse wave analysis maneuver was performed. Afterwards, radial artery pulse waveforms were recorded using the SphygmoCor System (AtCor Medical, Sydney, NSW, Australia). Approximately 10 radial pulse waves were measured to generate a corresponding central aortic pressure waveform by using a validated mathematical transfer function [21]. The inflection point of the aortic pressure waveform was determined using an algorithm that divides the aortic pressure wave into an early and late systolic peak and corresponds to the onset of the reflected wave returning from the peripheral arteries (Figure 1).

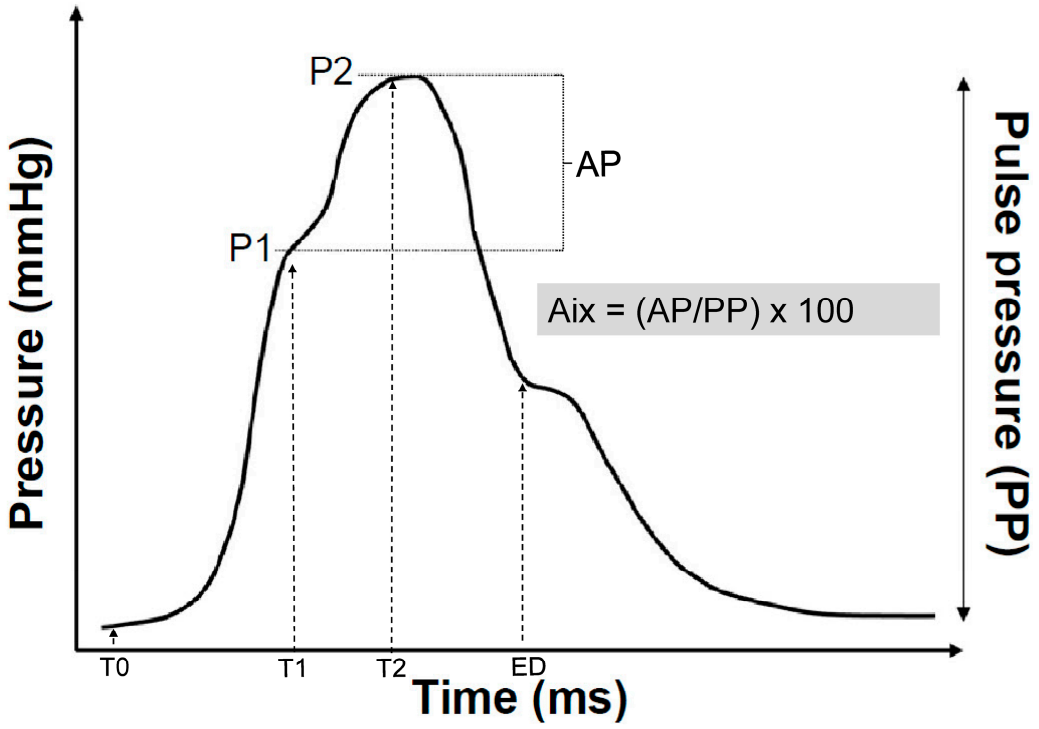

Figure 1. Schematic presentation of the pulse wave curve measured at the A. radialis. After the foot of the pulse (T0), indicating the onset of ejection, the pressure wave rises to an initial peak where it forms a shoulder (P1). This is the peak of the primary left ventricular ejection pressure. The second shoulder (P2) represents the peak of the arterial reflection wave. The difference between P2 and P1 is called augmentation pressure (AP). The end of ejection (ED) is the point of closure of the aortic valve and time of the end of systole. The augmentation index (AIx) is calculated as the difference between the second (P2) and first (P1) systolic peak pressure and is expressed as percentage of the central PP: AIx (%) = [(P2 − P1)/PP] × 100.

The AIx quantifies the augmentation of the central aortic pressure, thereby representing a measure of the peripheral arterial wave reflection. AIx can be calculated as the difference between the second (P2) and the first systolic peak pressure (P1) and is expressed as a percentage of the central pulse pressure (PP):

$$\text{AIx (\%)} = [(\text{P2} - \text{P1})/\text{PP}] \times 100$$

As AIx is influenced by heart rate [22,23], the index is reported after being adjusted to a heart rate of 75 bpm, unless otherwise stated. SphygmoCor Px software adjusts the AIx at an inverse rate of 4.8% for each 10bpm increment. Only measurements with an operator index of 75 and above were accepted so as to ensure a high measurement quality.

2.2.2. Home-Based Sleep Study

Home sleep apnea testing (HSAT) was performed using the ApneaLinkTM Plus device (ResMed Corporation, Poway, Calif). This overnight respiratory polygraphy is a non-invasive medical examination technique, routinely applied to detect sleep-related breathing disorders. The study subjects were instructed in the usage of the device to install it on their own for the study night. The ApneaLinkTM Plus device records the nasal respiratory pressure signal as a surrogate of the nasal flow, respiratory movements by a thoracic impedance belt, and finger pulse oximetry. A blinded scorer, who was not involved in the organization and conduction of this study, scored the results of the sleep studies according to the current American Academy of Sleep Medicine (AASM) guidelines [24]. Apneas are defined as a cessation of airflow by ≥90% lasting >10 s, and hypopneas as a reduction in airflow of at least 30% lasting >10 s, associated with a drop in oxygen

saturation of ≥3%. OSA severity was quantified as the number of apneas/hypopneas per hour (AHI) and oxygen desaturations ≥ 3% per hour (ODI) of sleep study. AHI thresholds according to the AASM Task Force of AHI ≥5, ≥15, and ≥30 were used to define mild, moderate, and severe OSA, respectively [25].

2.3. Data Analysis and Statistics

All data are presented as mean ± standard deviation (SD) or median (quartiles), unless otherwise stated. Multivariable regression analysis was used to investigate the association between AIx and AHI, adjusted for prespecified predictors for Aix, such as height, sex, current smoker, systolic blood pressure, antihypertensive drug, and corticosteroids. A residual analysis of the final model was performed to check the regression assumption. A two-sided *p*-value of <0.05 was considered to be statistically significant.

3. Results

3.1. Study Participants and Baseline Characteristics

A total of 65 sarcoidosis patients underwent pulse wave analysis measurements. Because of an insufficient measurement quality, three sarcoidosis patients had to be excluded. Five sarcoidosis patients were excluded due to missing sleep studies. A total of 57 subjects entered the final analysis (Figure 2).

The mean (SD) age was 51 (11.9) years and 26 (46%) participants were female. Here, 11% of the sarcoidosis patients were current smokers. The detailed patients' characteristics are shown in Table 1.

Table 1. Baseline characteristics.

	Total N = 57
Age, years	51 (11.9)
Female/Male	26/31
Height, cm	171.6 (9.2)
Weight, cm	75.9 (14.1)
BMI, kg/m^2	25.6 (3.6)
Pulmonary sarcoidosis, N (%)	56 (98.2)
Scadding I, N (%)	11 (19.3)
Scadding II, N (%)	41 (71.9)
Scadding III, N (%)	3 (5.3)
Scadding IV, N (%)	1 (1.8)
Extrapulmonary sarcoidosis, N (%)	37 (64.9)
Cardiac sarcoidosis, N (%)	17 (29.8)
Ocular sarcoidosis, N (%)	5 (8.8)
Cutaneous sarcoidosis, N (%)	9 (15.8)
Current smoker, N (%)	6 (11)
Pack years, N	0 (0/9)
Blood pressure systolic (office), mmHg	124 (17.6)
Blood pressure diastolic (office), mmHg	82 (9.7)
Pulse, min^{-1}	74 (11.7)
Arterial hypertension, N (%)	7 (12)
Dyslipidemia, N (%)	3 (5.3)
Diabetes, N (%)	0 (0)
Coronary artery disease, N (%)	3 (5.3)
Antihypertensive drugs, N (%)	15 (26)
Corticosteroids, N (%)	17 (29.8)
CRP, mg/L	1.2 (0.6/2.3)
ACE, U/L	41.1 (24.6/53.8)
Neopterin, ng/mL	2.1 (1.6/2.9)
sIL-2R, pg/ml	281.3 (211.9/382.1)
AHI, events/h	3.8 (1.2/7.5)

Table 1. *Cont.*

	Total N = 57
ODI, events/h	5.3 (1.7/13.4)
Mild OSA, N (%)	16 (28.1)
Moderate OSA, N (%)	5 (8.8)
Severe OSA, N (%)	2 (3.5)

BMI: body mass index; CRP: c-reactive protein; ACE: angiotensin converting enzyme; sIL-2R: soluble interleukin-2 receptor; AHI: apnea–hypopnea index; ODI: oxygen desaturation index; OSA: obstructive sleep apnea.

Serum inflammation markers (CRP, Soluble interleukin 2 receptor (sIL-2R) and neopterin) and angiotensin converting enzyme (ACE) were not elevated. The median (quartiles) AHI and ODI were 3.8 (1.2/7.5) events/h and 5.3 (1.7/13.4) events/h, respectively. Here, 23 (40%) sarcoidosis patients had at least mild OSA (AHI $\geq$ 5), while 7 (12%) patients showed an AHI $\geq$ 15/h.

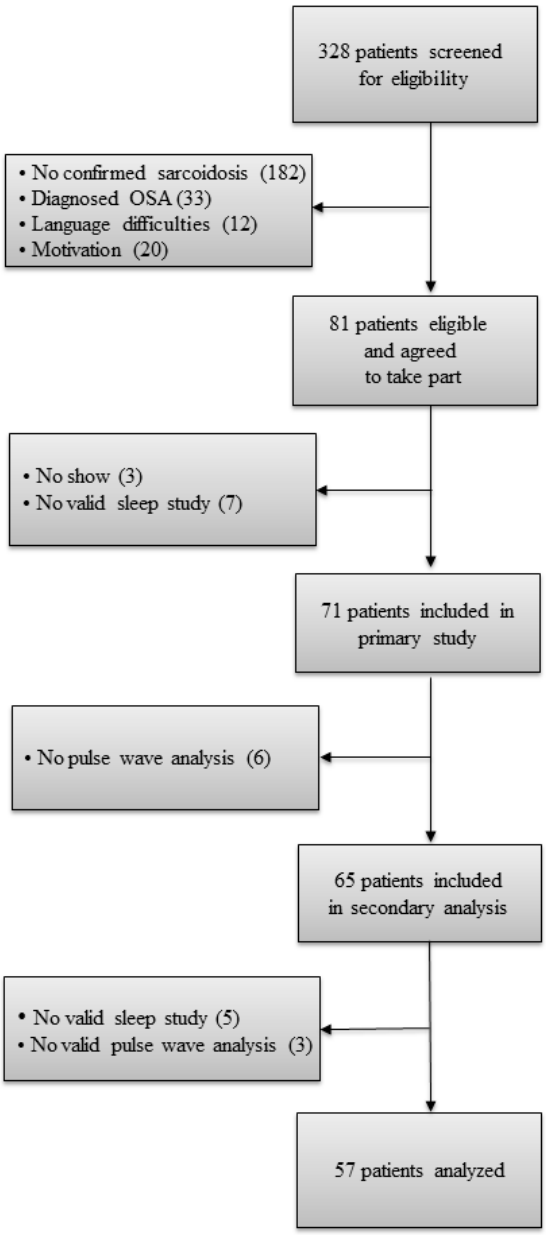

Figure 2. Study flow chart.

3.2. Pulse Wave Analysis of Sarcoidosis Patients

The mean (SD) Aortic AIx was 20.5 (8.6)%. Further parameters for the pulse wave are shown in Table 2.

Table 2. Pulse wave analysis parameters.

Aortic AIx (AP/PP) @HR 75, %.	**20.5 (8.6)**
P1 height, mmHg	23 (20/27)
Aortic T1, ms	113.1 (7.6)
Aortic T2, ms	212.2 (22.8)
Peripheral AIx, %	82.6 (13.8)
End systolic pressure, mmHg	106.4 (12.4)
Ejection duration, ms	293.9 (22.3)
Heart rate, min^{-1}	71.9 (11.1)
Radial systolic pressure, mmHg	123.3 (15.1)
Radial diastolic pressure, mmHg	80.5 (9.1)

Values are mean (SD) or median (quartiles). AIx: augmentation index; AP: augmented pressure; PP: pulse pressure; HR: heart rate; P1: first systolic peak pressure; T1: time to first peak; T2: time to second peak.

AHI was positively associated with a higher aortic AIx (coef. (95%CI) of 0.31 (0.09/0.52), $p = 0.006$) after adjusting for known modifying factors (age, sex, height, systolic blood pressure, current smoker, antihypertensive drugs, and steroids) (Figure 3 and Table 3).

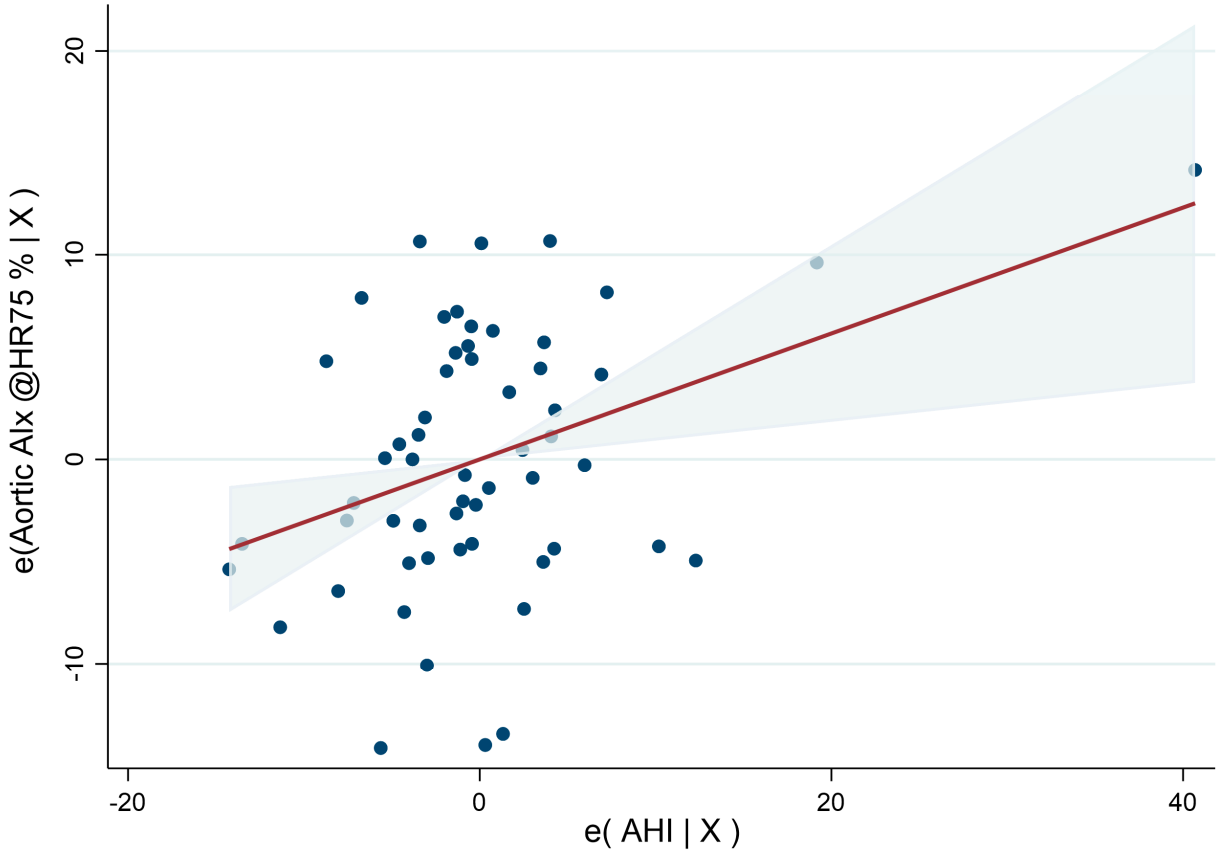

Figure 3. Added-variable plot with a 95% confidence interval between the aortic augmentation index (AIx) and apnea–hypopnea index (AHI) to display the relationship between AIx and AHI in the multivariable regression model. A higher AHI is associated with a higher Aix, while the adjusted variables (age, sex, height, systolic blood pressure, smoker, antihypertensive drug, and steroids) remained constant (Coef. 0.31, $p = 0.006$).

Table 3. Multivariable linear regression analysis of aortic AIx (AP/PP) normalized for a heart rate of 75/min and AHI, adjusted for known risk factors.

Variable	Coefficient	95% Confidence Interval	*p*-Value
AHI, events/h	0.31	0.09/0.52	0.006
Age, y	0.10	−0.09/0.29	0.314
Male sex	−4.77	−9.77/0.23	0.061
Height, m	−0.42	−0.67/−0.18	0.001
Current smoker	5.85	−0.58/12.29	0.074
Mean systolic blood pressure, mmHg	0.16	0.03/0.28	0.014
Antihypertensive drugs	4.60	−0.41/9.60	0.071
Corticosteroids	−4.38	−8.97/0.21	0.061

AIx: Augmentation index; AP: augmented pressure; PP: pulse pressure; AHI: apnea-hypopneaindex.

Addressing the influence of OSA severity on AIx, severe OSA was independently associated with increased AIx (coef. (95%CI) of 16.04 (5.41/26.68), $p = 0.004$), while mild and moderate OSA showed no association with AIx (coef. (95%CI) of 0.21 (−4.22/4.36), $p = 0.925$, coef. (95%CI) of 3.83 (−3.38/11.05), $p = 0.291$) (Table 4). Sub-analyzing the influence of AHI $\geq$ 15 (n = 7) also revealed an independent influence on AIx (coef. (95%CI) of 7.31 (0.89/13.73), $p = 0.026$).

Table 4. Multivariable linear regression analysis of the aortic AIx (AP/PP) normalized for a heart rate of 75/min and OSA severity groups, adjusted for known risk factors.

Variable	Coefficient	95% Confidence Interval	*p*-Value
OSA severity group (AHI < 5 as reference)			
Mild (AHI ≥5–<15)	0.21	−4.22/4.63	0.925
Moderate (AHI ≥15–<30)	3.83	−3.38/11.05	0.291
Severe (AHI ≥ 30)	16.04	5.41/26.68	0.004
Age, y	0.09	−0.11/0.28	0.365
Male sex	−4.24	−9.48/0.99	0.110
Height, m	−0.43	−0.68/−0.18	0.001
Current smoker	4.87	−1.83/11.57	0.150
Mean systolic blood pressure, mmHg	0.15	0.03/0.28	0.020
Antihypertensive drugs	5.00	−0.10/10.04	0.055
Corticosteroids	−4.94	−10.09/0.21	0.060

OSA: obstructive sleep apnea; AIx: augmentation index; AP: augmented pressure; PP: pulse pressure; AHI: apnea-hypopnea index.

4. Discussion

This cross-sectional study investigated arterial stiffness in a well-characterized cohort of sarcoidosis patients with and without obstructive sleep apnea (OSA). We found that an increase in AHI was independently associated with increased arterial stiffness in sarcoidosis patients.

There is growing evidence that patients with sarcoidosis have a higher risk of cardiovascular disease (CVD). A population-based cohort study retrospectively assessed the medical records of 345 sarcoidosis patients and 1:1 sex- and age-matched controls without sarcoidosis between 1976 and 2013. They found significantly increased risk for cardiovascular endpoints including stroke, coronary artery disease congestive heart failure, atrial fibrillation, and cerebrovascular incidents, even after controlling for traditional cardiovascular risk factors [4]. Arterial stiffness and endothelial dysfunction play a central role in the initiation of atherosclerosis. The aortic AIx measured by the arterial tonometry is used as an indirect index of arterial stiffness derived from aortic pressure waveform analysis [26,27]. It represents the ratio of the ejection pressure from the heart and the reflection pressure from the arterial system (Figure 1). The augmentation index (AIx) has been shown to be an independent predictor of mortality and cardiovascular events in patients with hypertensive,

cardiovascular, and renal disease in the general population [28]. Besides the prediction of cardiovascular risk, indirect measurement of arterial wall properties in sarcoidosis patients might even predict extra pulmonary involvement in sarcoidosis [10]. Saisos et al. described an increased augmentation index, increased pulse wave velocity (PWV), and reduced flow mediated dilation (FMD) in sarcoidosis patients with active disease. They reported even further deterioration of the endothelial function and arterial wall properties in sarcoidosis patients with ocular involvement, mainly uveitis, suggesting vascular dysfunction as a possible pathomechanism [10]. They reported FMD to be the strongest independent predictor for ocular involvement [10]. As a result, an understanding of increased arterial stiffness in sarcoidosis patients is of the utmost importance.

We found increased AIx values comparable to earlier studies investigating arterial stiffness in sarcoidosis patients [10]. There are several possible pathomechanisms discussed in the literature regarding increased arterial stiffness in sarcoidosis. Systemic inflammation might play a role, being a common feature of sarcoidosis and atherosclerosis [9,29,30]. Moreover, direct granulomatous involvement of the vessels and the infiltration of inflammation cells in the capillaries with consecutive microcirculatory disturbance have been described [11,31].

While sarcoidosis specific factors of arterial stiffness are under intensive investigation, there is little evidence regarding the effect of classical risk factors such as arterial hypertension, smoking status, or OSA in sarcoidosis patients. Our group found an increased prevalence of mild OSA in patients with sarcoidosis [12]. OSA is the most common form of sleep-related breathing disorder (SDB) and is characterized by repetitive breathing cessation due to narrowing of the upper airways. Endothelial dysfunction and increased arterial stiffness have been described in OSA, even in mildly symptomatic patients [14]. Our study suggests that increased respiratory event rates are associated with increased arterial stiffness in patients with sarcoidosis, even after adjusting for known modifying factors. While severe OSA was positively associated with increased AIx, mild and moderate OSA were not. This observation aligns with previous studies investigating the influence of OSA on arterial stiffness in the general population, showing a positive association between the severity of OSA and the magnitude of arterial stiffness [32]. Another reason for this observation might be shared pathomechanisms of both diseases leading to increased arterial stiffness. As a result, only severe forms of OSA might add an additional effect on the development of arterial stiffness. As such, increased arterial stiffness in OSA is considered to be a result of repetitive hypoxemia and reoxygenation resulting in oxidative stress and systemic inflammation [11]. Inflammation markers such as C-reactive protein, tumor necrosis factor-a, interleukin-6, and intercellular adhesion molecule-1 have been shown to be associated with arterial stiffness in sarcoidosis as well as in OSA patients [9,32]. It seems reasonable to assume that a lower number of apneas and hypopneas do not drive systemic inflammation to such an extent that it overrules sarcoidosis associated systemic inflammation. Oxidative stress not only triggers inflammation, but also reduces the activity of nitric oxide synthase and thus leads to a decreased production of nitric oxide increasing arterial stiffness [32]. Increased oxidative stress has also been described in patients with pulmonary sarcoidosis with even stable disease [33]. There might be no significant additional effect on the nitric oxide synthase in mild and moderate OSA. In addition, corticosteroids—the gold standard treatment of sarcoidosis—also reduce the function of nitric oxide synthetase, leading to reduced nitric oxide levels [34]. It seems noteworthy that one study showed decreased arterial stiffness in sarcoidosis patients receiving corticosteroids [9]. The authors emphasize the anti-inflammatory effect of corticosteroids inhibiting the release of inflammation mediators overruling negative medication associated vascular effects [9]. These findings were supported by studies showing preserved endothelial function in other inflammatory diseases such as Behçet's disease treated with corticosteroids [35]. While corticosteroids might deteriorate OSA by increasing weight and oedema, the positive effect on the inflammation status might counteract the effect of oxidative stress triggered by OSA. Nevertheless, corticosteroids were not associated with an increased prevalence of OSA (not shown) nor

with decreased arterial stiffness in our study. Furthermore, increased arterial stiffness in OSA is associated with a higher sympathetic activity, due to recurrent sleep fragmentation or intermittent hypoxia [19]. Measurements of single- and multi-unit muscle sympathetic nerve activity in OSA patients suggest a high sympathetic activity in patients with severe OSA, thereby supporting our finding of increased AIx in sarcoidosis patients with severe OSA. There is only limited evidence regarding autonomic dysfunction in sarcoidosis. A small prospective study with only 12 sarcoidosis patients and 12 healthy controls presented a reduced heart rate variability that might suggest reduced parasympathetic tone in sarcoidosis patients [36]. There are no data available connecting sympathetic activity and arterial stiffness in sarcoidosis patients so far. Both OSA and chronic inflammation are independently associated with insulin resistance [37,38]. Insulin resistance, measured by insulin resistance index based on the homeostasis model assessment method (HOMA-IR), was higher in patients with severe OSA compared with mild and moderate OSA [37].

The finding that increased AHI might lead to an additional increase in arterial stiffness in sarcoidosis patients is clinically relevant. First, sarcoidosis patients already have an increased cardiovascular risk, and untreated OSA might put sarcoidosis patients at even higher cardiovascular risk [4].

Second, once OSA is diagnosed, therapy options are available that could reduce cardiovascular risk in sarcoidosis patients. In 2019, the American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for the Primary Prevention of cardiovascular disease named auto immune and inflammatory diseases a "risk enhancer". The guidelines suggest statin initiation or intensification in primary prevention in those patients [39]. There is evidence that CPAP therapy might reverse endothelial dysfunction and thereby reduce cardiovascular risk in OSA patients [19]. Hence, sarcoidosis patients should be screened for OSA, particularly when they suffer increased daytime sleepiness or fatigue. It seems reasonable to assume that OSA treatment might improve the cardiovascular risk profile in sarcoidosis patients.

However, a recent meta-analysis pointed out that the majority of recent RCTs have failed to demonstrate convincing evidence for the benefits of CPAP on cardiovascular risk in the general population, except in patients with hypertension [40]. If CPAP therapy reduces endothelial dysfunction in sarcoidosis, patients should be evaluated in future randomized controlled trials.

There are some limitations to this study. Most of our sarcoidosis patients with OSA had only a mild form of the disease. Hence, the positive association found in severe OSA was based only on a few observations. Further investigations of arterial stiffness in sarcoidosis patients with severe OSA are needed to underline our results. Furthermore, there are several inflammation markers noted in the literature that are associated with increased arterial stiffness in OSA and sarcoidosis. We only investigated a limited amount of these markers due to the great number of included patients and limited resources.

5. Conclusions

This study showed evidence of an independent influence of increased AHI on arterial stiffness in sarcoidosis patients. These findings have important implications, given the importance of aortic stiffness for cardiovascular risk and the potential of therapeutic interventions such as CPAP therapy. These data underline the need for intensive screening efforts for OSA in sarcoidosis. Further studies should be conducted to confirm that severe OSA is an independent predictor of increased arterial stiffness in sarcoidosis.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jvd2010011/s1, Section S1: Inclusion and Exclusion Criteria.

Author Contributions: Conceptualization, M.R., N.A.S., D.F. and M.K.; data curation, S.M. and T.G.; formal analysis, M.R., N.A.S., T.G. and M.K.; funding acquisition, M.R. and M.K.; investigation, M.R., N.A.S., S.M., T.G. and D.F.; methodology, N.A.S.; resources, M.R. and M.K.; supervision, M.R., D.F. and M.K.; writing—original draft, M.R.; writing—review and editing, N.A.S., S.M., T.G. and M.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: All procedures were reviewed and approved by the Cantonal Ethics Committee Zurich (BASEC-Nr 2019-01604) and conformed to the Declaration of Helsinki.

Informed Consent Statement: All participants provided written informed consent to participate in the study.

Data Availability Statement: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest: Malcolm Kohler reports grants and personal fees from Bayer, personal fees from Novartis, personal fees from Boehringer, personal fees from GSK, personal fees from Astra Zeneca, grants from Roche, personal fees from CSL Behring, and personal fees from Mundipharma, during the conduct of the study. The authors report no other conflicts of interest in this work. Thomas Gaisl reports personal fees from Bayer (outside the submitted work) during the conduct of this study.

Abbreviations

AHI	Apnea-hypopnea index
AIx	Augmentation index
AP	Augmentation pressure
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
Coef.	Coefficient
CPAP	Continuous positive airway pressure
CVD	Cardiovascular disease
CRP	C-reactive protein
FMD	Flow mediated dilation
HR	Heart rate
IL-6	interleukin-6
Min	Minute
NSAID	Non-steroidal anti-inflammatory drug
OSA	Obstructive sleep apnea
ODI	Oxygen-desaturation index
PP	Pulse pressure
PWV	Pulse wave velocity
SD	Standard deviation
SDB	sleep-related breathing disorder
TNF-α	tumour necrosis factor-α

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