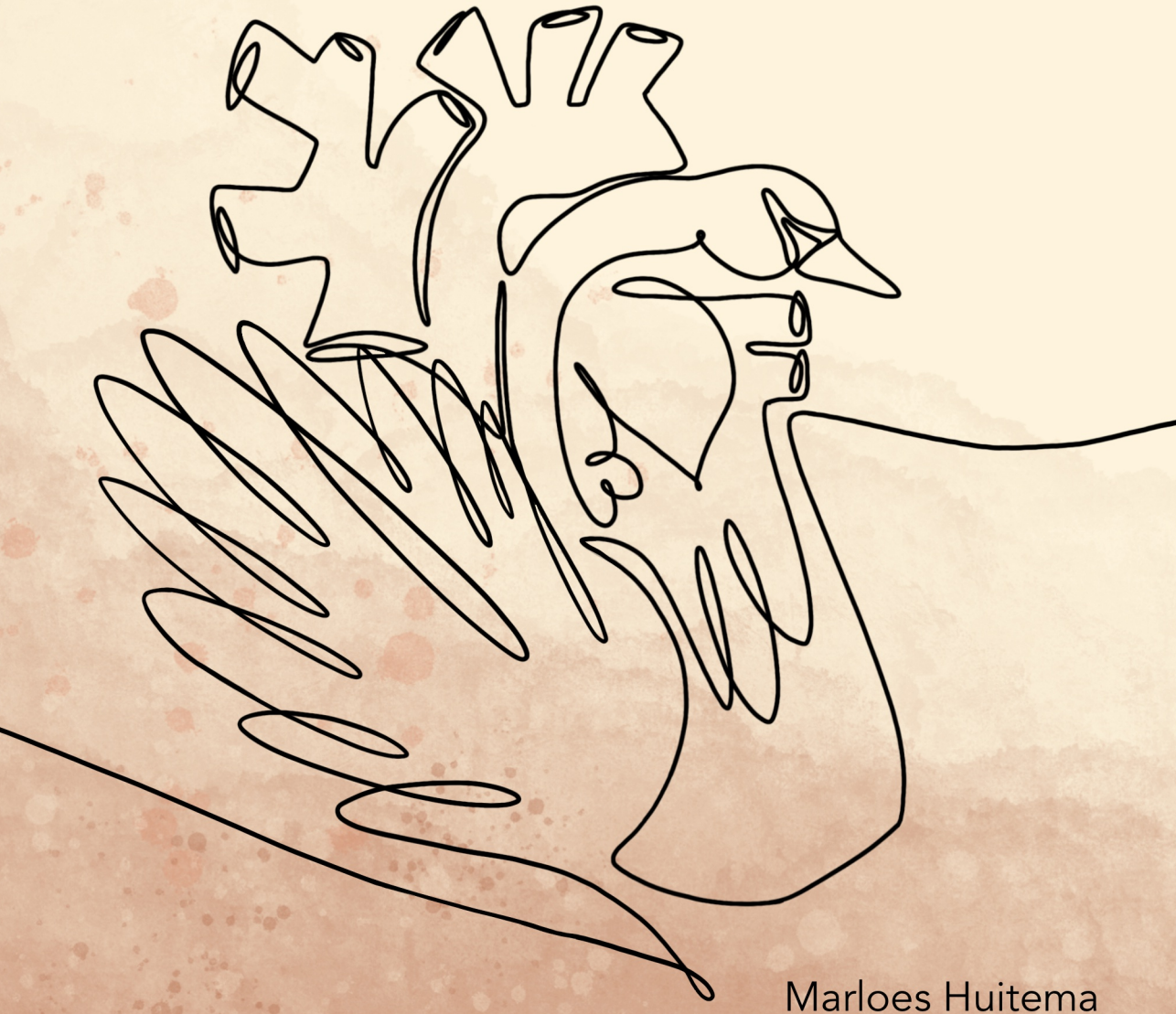
SARCOIDOSIS ASSOCIATED PULMONARY HYPERTENSION

an exploratory journey



Marloes Huitema

Sarcoidosis Associated Pulmonary Hypertension

An exploratory journey

Marloes Petra Huitema

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An exploratory journey

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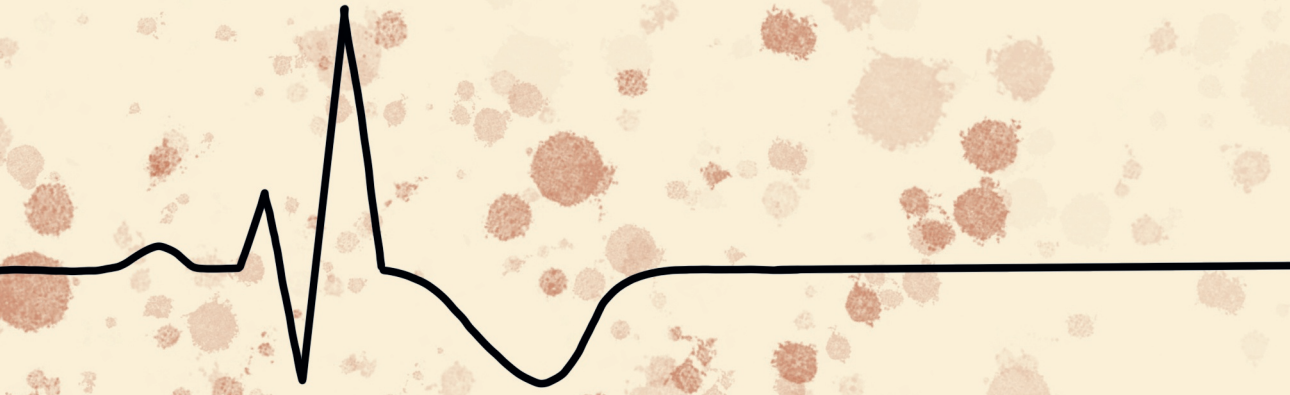

CHAPTER 1

Introduction

Marloes P. Huitema

Based on: 'Pulmonary hypertension complicating pulmonary sarcoidosis', Netherlands Heart Journal. 2016;24:390–399.

Background

Sarcoidosis

Sarcoidosis, also known as Besnier-Boeck disease, is a multisystemic disorder of unknown aetiology. It is an orphan disease, with an estimated prevalence of 5–160 per 100,000 inhabitants depending on the world region.[1] It is characterised by non-necrotising granulomas which may present in multiple organs, particularly in the lung and lymphatic system, skin and eyes. It was the late 1800s when sarcoidosis was recognised in a patient with unusual skin lesions, and around 1915 dr. Schaumann was the first to describe it as a rather multisystemic condition.[2] Despite the long recognition and decades of research, the exact cause and epidemiology of sarcoidosis remains unclear. The current theory describes a dysregulated immune response against certain environmental antigens, in which the triggering antigen varies between ethnic groups, geographic location and individual genetic backgrounds.[3] Diagnosis is challenging and should include compatible clinical findings combined with histologic evidence of non-necrotising granuloma's in biopsy samples or compatible cytology obtained during broncho-alveolar lavage, with exclusion of alternative causes of granuloma's.[4] The clinical course in sarcoidosis is highly variable and may range from spontaneous resolution to severe and chronic disease. Historically, pulmonary sarcoidosis was divided into Scadding stages based on chest X-ray, as described in Table 1.1.[5] Nowadays more accurate imaging technologies such as high resolution chest-CT are available.[6] The decision to initiate treatment for sarcoidosis, depends on the risk of organ failure or death and the patients quality of life.[3] First line treatment for sarcoidosis are glucocorticoid agents. Second line treatment (methotrexate, azathioprine, leflunomide and myocophenolate) or third line treatment (infliximab) can be considered if corticosteroids are risky, or if more aggressive or steroid-sparing treatment is warranted.[7]

Table 1.1: Scadding stages on chest X-ray[5]

Scadding stage 0	Absence of abnormalities
Scadding stage I	Bilateral hilar lymphadenopathy
Scadding stage II	Bilateral hilar lymphadenopathy and parenchymal infiltration
Scadding stage III	Parenchymal infiltration without hilar lymphadenopathy
Scadding stage IV	Pulmonary fibrosis

Pulmonary hypertension

Pulmonary hypertension (PH) is defined in the 2015 ESC/ERS guideline for the diagnosis and treatment of pulmonary hypertension as a mean pulmonary artery pressure (PAP)

of ≥25mmHg at rest, measured during right heart catheterisation (RHC).[8] In healthy people, mean PAP at rest normally is 14.0±3.3mmHg.[9] PH can be distinguished into pre-capillary PH with pulmonary vascular disease, post-capillary PH due to left heart disease or combined pre-and post-capillary PH by measuring pulmonary vascular resistance (PVR) and pulmonary capillary wedge pressure (PCWP). Recently in the 2022 ESC/ERS guideline for the diagnosis and treatment of pulmonary hypertension the definition has been revised.[10] An overview of definitions is given in Table 1.2. In this thesis, we use the 2015 definitions.

Table 1.2: Definitions of pulmonary hypertension

	2015 ESC/ERS GUIDELINE	2022 ESC/ERS guideline
Pre-capillary PH	Mean PAP ≥25 mmHg PCWP ≤15 mmHg	Mean PAP >20 mmHg PCWP ≤15 mmHg PVR >2WU
Isolated post-capillary PH	Mean PAP ≥25 mmHg PCWP >15 mmHg	Mean PAP >20mmHg PCWP >15 mmHg PVR ≤2WU
Combined pre-and postcapillary PH	Mean PAP ≥25 mmHg PCWP >15 mmHg DPG ≥7mmHg and/or PVR>3WU	Mean PAP >20 mmHg PCWP >15mmHg PVR >2 WU

DPG = diastolic pressure gradient; PAP = pulmonary artery pressure PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance.

As listed in Table 1.3, PH has been categorised by the World Health Organisation (WHO) into different classification subgroups based on multiple underlying clinical conditions according to the shared clinical presentation, pathological findings, haemodynamic characteristics and treatment strategy.

Sarcoidosis associated pulmonary hypertension

Epidemiology

PH is increasingly recognised as a serious complication of pulmonary sarcoidosis. There are no clear data regarding the true prevalence of sarcoidosis associated pulmonary hypertension (SAPH). Prevalence in tertiary centres varies between 5–20%.[12–14] Notably, many studies do not incorporate the diagnostic gold standard RHC, and interpret results with echocardiographic measurements only. The prevalence of PH may increase to over 50% in sarcoidosis patients with persistent or unexplained dyspnea,[15,16] and over 70% in patients awaiting lung transplant.[17,18]

Table 1.3: Clinical classification of pulmonary hypertension (PH)

WHO group 1: Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4 PAH associated with: connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis
1.5 PAH with overt features of venous/capillary involvement
1.6 Persistent PH of the newborn syndrome
WHO group 2: Pulmonary hypertension due to left heart disease
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH
WHO group 3: Pulmonary hypertension due to lung disease and/or hypoxeamia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders
WHO group 4: Chronic thromboembolic pulmonary hypertension or other pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstruction
WHO group 5: Pulmonary hypertension with unclear multifactorial mechanism
5.1 Haematological disorders
5.2 Systemic and metabolic disorders
5.3 Others (pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension)
5.4 Complex congenital heart disease

Adapted from Simmoneau et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. ERJ 2019.[11] LVEF = left ventricular ejection fraction; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

Aetiology

In patients with WHO group 3 PH the mean PAP rarely exceeds 35mmHg. In sarcoidosis, higher values are frequently found[19] and sarcoidosis is therefore not always comparable to other interstitial lung diseases (ILD). PH in sarcoidosis is officially classified as WHO group 5 PH (Table 1.3): PH with an unknown and/or multifactorial mechanism.[8] However, SAPH may show characteristics of WHO group 2, 3, 4 and possibly group 1. The majority of patients with SAPH fit into WHO group 3, suffering a more advanced stage of sarcoidosis often including fibrosis.[12,13,16,20] In this group PH is most likely caused by *destruction of the distal capillary bed and resultant hypoxaemia*. However, data to support this mechanism are scarce.[15,21] Approximately 32–50% of the patients with SAPH have no significant fibrosis or parenchymal disease,[12,13,20] suggesting other contributing mechanisms. As for WHO group 4 PH, it is known that patients with

sarcoidosis have an increased risk of venous thrombo-emboli[22,23] which should raise awareness for *chronic thrombo-embolisms* as cause of PH. *Post-capillary PH (WHO group 2)* can present in sarcoidosis as an expression of systolic, diastolic and subclinical left ventricular dysfunction.[24,25] In a retrospective study consisting of 130 sarcoidosis patients of all stages with a PH prevalence of 54%, an elevated PCWP >15mmHg was measured in 29%.[16] In these patients screening for cardiac sarcoidosis by cardiac magnetic resonance imaging and/or 18-F-fluorodeoxyglucose positron emission tomography should be considered.[24] Pulmonary vascular disease such as in WHO group 1 PH is suggested by *granulomatous vasculopathy* and *local increased vasoreactivity*. An autopsy study in 40 sarcoidosis patients showed granulomatous pulmonary vascular involvement in all patients.[26,27] It frequently causes occlusion of arterioles or venules[26] what might resemble the presentation of pulmonary veno-oclusive disease.[20,26] As for local increased vasoreactivity, acute vasoresponsiveness (defined as a decrease in mean PAP of ≥10mmHg to an absolute value of mean PAP ≤40mmHg, with an increased or unchanged cardiac output[8]) was shown in several patients with SAPH during acute vasodilator challenge with inhaled nitrogen oxide or prostacyclin. In clinical studies increased vasoreactivity was not a predictor for response to PH-targeted therapy.[28,29] There are several other causes of PH in sarcoidosis. For example *extrinsic compression of pulmonary vessels* by enlarged lymph nodes or fibrosing mediastinitis.[20,26,30] It occurs more frequently in chronic sarcoidosis, and presented in 21% of the PH patients with radiographic stage IV sarcoidosis.[20] Furthermore, hepatic sarcoidosis is present in up to 70% of sarcoidosis patients[31] which may cause *portal hypertension*. Approximately 1–5% of patients with portal hypertension develop PH,[8] mostly due to liver cirrhosis. Lastly, *obstructive sleep apnea*, a known cause for group 3 PH, is present in 17–64% of sarcoidosis patients compared to 9–24% in the general population,[32,33] possibly due to weight gain in corticosteroid therapy, reduced lung volumes in pulmonary fibrosis and sarcoidosis in the upper respiratory tract.

Suspicion of PH

Establishing the diagnosis of PH in sarcoidosis is challenging. Suggestive symptoms for PH are non-specific, and include out of proportional dyspnea, dizziness, cough and chest pain, or signs such as elevated jugular venous pressure, S3 or S4 heart sounds, lower extremity edema or right ventricular heave. These signs are usually associated with more advanced PH.[15] During follow-up of sarcoidosis, several routine tests may raise suspicion of PH, such as pulmonary function and exercise testing, biomarkers or electrocardiogram and imaging modalities. Associated parameters of pulmonary function testing include a decreased forced vital capacity, total lung capacity[13] and

decreased diffusion capacity of carbon monoxide.[12] However, PH also occurs in sarcoidosis patients with near-normal lung function tests.[34] Furthermore, the 6-minute walk test (6MWT) can also raise suspicion of PH in case of a distance of less than 450 meters and oxygen desaturation,[12,35,36] although this may also be influenced by other factors such as airway disease, cardiac disease, fatigue and muscle involvement. Cardiopulmonary exercise testing for detecting PH has not been studied systematically in sarcoidosis. In pulmonary arterial hypertension, reduced maximum oxygen uptake (VO2max), increased ventilator inefficiency, early lactate acidosis, decreased end-expiratory CO2 and reduced O2 pulse are suspicious for PH, although non-specific.[37] In ILD, peak exercise capacity and CO2 production are significantly lower in patients with PH.[38] Furthermore, brain natriuretic peptide (BNP) is a biomarker for heart failure in general, including right ventricular failure in PH. It is significantly increased in ILD patients with an invasive systolic PAP >40mmHg, but significantly higher in patients with increased PCWP.[39] An ECG can show abnormalities suggesting right ventricular overload including P-pulmonale, right axis deviation, signs for right ventricular hypertrophy or strain, right bundle branch block and QTc prolongation,[8] often present in more severe PH. As for imaging, chest computed CT is performed in the diagnostic process of sarcoidosis and follow up for suspected disease progression. A dilated pulmonary artery on chest computed tomography (CT) may raise suspicion of PH,[8] with a cut-off value of ≥29mm for the pulmonary artery, or a ratio of the pulmonary artery diameter to the ascending aorta diameter of ≥1. However, two studies[40,41] found no correlation between the pulmonary artery diameter and the mean PAP in patients with fibrotic lung disease. Other chest CT parameters suggestive for PH are right ventricular enlargement or a segmental artery : bronchus ratio > 1 : 1, but these measurements seem to have less value in clinical practice. Cardiac magnetic resonance imaging is used in the workup for diagnosing cardiac sarcoidosis, and is a valuable tool to accurately and reproducibly assess the right ventricular dimension, morphology and function, stroke volume, cardiac output, pulmonary artery distensibility and right ventricular mass.[42]

Screening by echocardiography

Echocardiography has a leading role in PH screening.[8] Right ventricular systolic pressure (RVSP) is one of the main echocardiographic parameters, and obtained by measuring the peak tricuspid regurgitation velocity (TRVmax) and apply the simplified Bernoulli equation (RVSP=4*[TRVmax]^2), and add the right atrial pressure.[43] The 2015 ESC/ERS PH guideline recommends the additional use of secondary signs for PH, which are shown in Figure 1.1. Following this guideline patients can be classified into low, intermediate or high PH probability (Table 1.4).[8] Literature on echocardiographic findings specifi-

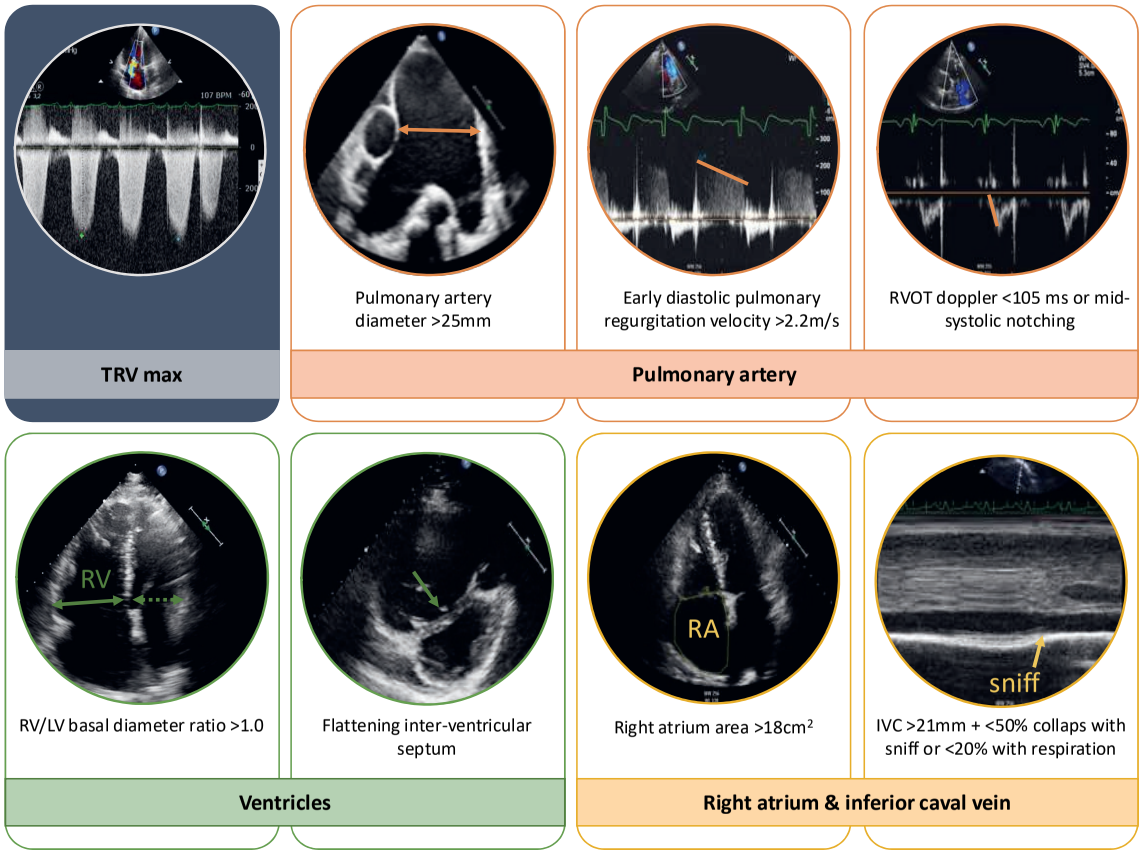

Figure 1.1: Echocardiographic signs of pulmonary hypertension.
IVC = inferior caval vein; LV = left ventricle; RV = right ventricle; RVOT = right ventricular outflow tract; TRV max = maximum tricuspid regurgitation volume.

cally in sarcoidosis patients is scarce. A meta-analysis of 29 studies investigating the echocardiographic diagnostic accuracy for PH showed a modest diagnostic accuracy and modest correlation with invasively measured pulmonary artery pressures.[44] In patients with interstitial lung diseases it was shown that the RVSP was measurable in only half of the patients, with a weak or no correlation with the invasively measured systolic PAP.[45,46] Although echocardiography has insufficient accuracy to predict the exact PAP, it is suitable to use as a screening tool, also with the advantage to detect other cardiac abnormalities that may cause dyspnea.

Table 1.4: Classification of echocardiographic PH probability in accordance to the ESC/ERS guideline[8]

Echocardiographic pulmonary hypertension probability	Peak tricuspid regurgitation velocity (m/s)	At least two secondary signs of different categories (Figure 1.1)
Low	≤2.8 or not measurable	No
Intermediate	≤2.8 or not measurable	Yes
	2.9–3.4	No
High	2.9–3.4	Yes
	>3.4	Not required

Diagnosis by right heart catheterisation

RHC remains the gold standard for diagnosing PH.[8] During this procedure, a Swan-Ganz catheter is advanced into the pulmonary artery for pressure measurement at end-expiration during a normal breathing cycle. Measurements are taken in the pulmonary artery, wedge position, right ventricle and right atrium (Figure 1.2). Even though complication rates are low,[47] the invasive nature of this diagnostic modality makes it unsuitable for routine use. RHC is considered in patients with an intermediate or high PH probability on echocardiography or during screening for lung transplant.[8]

Management

For optimal treatment of SAPH, a multidisciplinary approach involving cardiologists, pulmonologists and radiologists, all specialised in PH and interstitial lung disease, is mandatory. In all patients with SAPH, supportive therapy including oxygen therapy, diuretics and other treatment for heart failure should be initiated when necessary. For selected patients with end-stage pulmonary parenchymal sarcoidosis or SAPH who failed therapy, single or bilateral lung transplant can be a feasible option. Treatment of SAPH has only been studied in small groups, and there is no solid proof for any form of therapy. The treatment goal is to improve the vascular, haemodynamic and functional outcomes. Pharmacological treatment strategies for SAPH can be divided

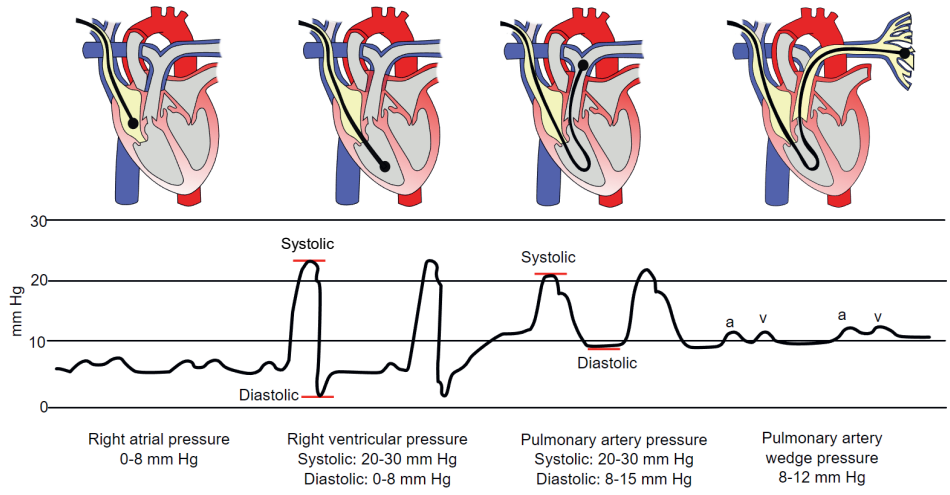

Figure 1.2: Haemodynamic measurements during right heart catheterisation.
Adapted from PCI pedia. Figure by April, 2014. CC BY-NC-SA 3.0. https://www.pcipedia.org/images/6/64/RightHeart_Waveforms_Fig1.svg.

into sarcoidosis-targeted and PH-targeted treatment, and should be directed to the underlying mechanisms of PH in sarcoidosis. Sarcoidosis-targeted therapy can be considered in patients with active granulomatous inflammation as likely cause of PH, following a step-wise approach for the management of first-line, second-line or third-line treatment with immunosuppressive therapy.[48] A small study showed improvement after treatment with high doses of glucocorticosteroids in three out of ten patients with SAPH, but all five patients with stage IV PH did not respond to this treatment. Patients with compression of the pulmonary artery due to enlarged lymph nodes might also benefit from immunosuppressive treatment.[20] As for PH targeted therapy, this is reserved for patients with pulmonary arterial hypertension or CTEPH.[49] The use in sarcoidosis patients with PH is off-label and may be initiated in specific patients after multidisciplinary consensus, with close monitoring. The literature on this topic is scarce and mostly based on case series. Sarcoidosis patients with extensive fibrotic remodeling are less likely to respond to vasodilators, and treatment might worsen oxygenation since the physiological hypoxemic vasoconstriction is inhibited. As a result, there is an increased blood flow to areas with poor ventilation that might lead to a shunt or ventilation/perfusion discrepancy, as described in patients with idiopathic pulmonary fibrosis.[50] Other possible complications include acute pulmonary edema and hypoxemia.[29] Prostacyclin analogues (epoprostenol, iloprost) induce relaxation of the vascular smooth muscle by stimulating the production of cyclic AMP and growth inhibition of smooth muscle cells.[51] In case series of patients with SAPH treated with single agents

or combined PH targeted therapy, improvement in haemodynamics, quality of life and 6MWT distance has been observed.[29,52] The only double-blind placebo-controlled trial of PH targeted therapy in SAPH was performed with bosentan, an endothelin receptor antagonists (ERA).[53] ERA's antagonise the activation of the endothelin receptor that causes vasoconstriction and proliferation of vascular smooth muscle cells.[54] After a 16 week period of treatment, bosentan did decrease the mean PAP and PVR, but no improvement in 6MWT or quality of life was observed. A prospective case series of 21 patients sarcoidosis patients with PH receiving treatment with ambrisentan was terminated prematurely in >50% of the patients, due to edema and/or progressive dyspnea.[55] For macitentan there were no published data at the start of this thesis. Phosphodiesterase 5 inhibitors (sildenafil, tadalafil) cause pulmonary vasodilatation by inhibit the breakdown of cyclic GMP by phosphodiesterase type 5.[56] Improvement in haemodynamics were reported in a subgroup of patients awaiting lung transplant.[18] Some cases suggest successful treatment in sarcoidosis patients with less severe PH.[57,58] Riociguat, a guanylate cyclase stimulator and selexipag had not been studied before the start of this thesis.

Prognosis

Mortality in sarcoidosis patients is significantly increased if PH is present, independent of pulmonary function.[17,20] For 22 patients with haemodynamically confirmed SAPH, the 1-, 2-, and 5-year survival was found to be 84, 74 and 59%, compared with 100, 96 and 96% in matched sarcoidosis patients without PH (p=0.003).[20] However, data are scarce and mainly based on small and specific patient populations. Post-transplant 1, 3 and 5 year survival rates in sarcoidosis were 86%, 76% and 69% respectively.[59]

Aims and outline of this thesis

This thesis aims to explore the prevalence, diagnosis and phenotype of PH in sarcoidosis. Literature regarding SAPH is scarce, therefore in 2015 we launched a prospective cohort study called the PULSAR (PULmonary hypertension in pulmonary SARcoidosis) in order to answer these questions. This cohort consists of 399 mainly Caucasian patients with (a history of) pulmonary sarcoidosis who were newly referred to our tertiary sarcoidosis centre, and underwent PH screening by echocardiography, laboratory and ECG, and were referred for RHC if indicated. This study forms a cornerstone for this thesis.

The first part of this thesis investigates the prevalence and aetiology of SAPH. *Chapter 2* investigates the prevalence of PH in the PULSAR cohort. In *chapter 3* we aimed

to describe phenotypes of SAPH to clarify different aetiologies. *Chapter 4* explores pulmonary vascular changes in sarcoidosis patients with and without PH by using intravascular ultrasound.

The second part elaborates on the question how to diagnose PH in sarcoidosis. *Chapter 5* describes the value of transthoracic echocardiography and classification systems as recommended by the 2015 ESC/ERS guideline for PH, whereas in *chapter 6* the focus is on right ventricular systolic pressure in relationship to invasive PAP. Research regarding the value of knowledge based reconstruction, a method to determine 3D volumes of the right ventricle is described in *chapter 7*. Last, *chapter 8* presents a retrospective study on pulmonary artery measurements on chest-CT as a predictor for PH.

In the third part, *chapter 9* investigates treatment effects of Macitentan in sarcoidosis patients, and *chapter 10* provides us with data on survival of the PULSAR cohort in order to establish prognosis of SAPH.

The fourth and final part formed by *chapter 11*, aims to provide the clinician with recommendations on the diagnosis and treatment of SAPH.

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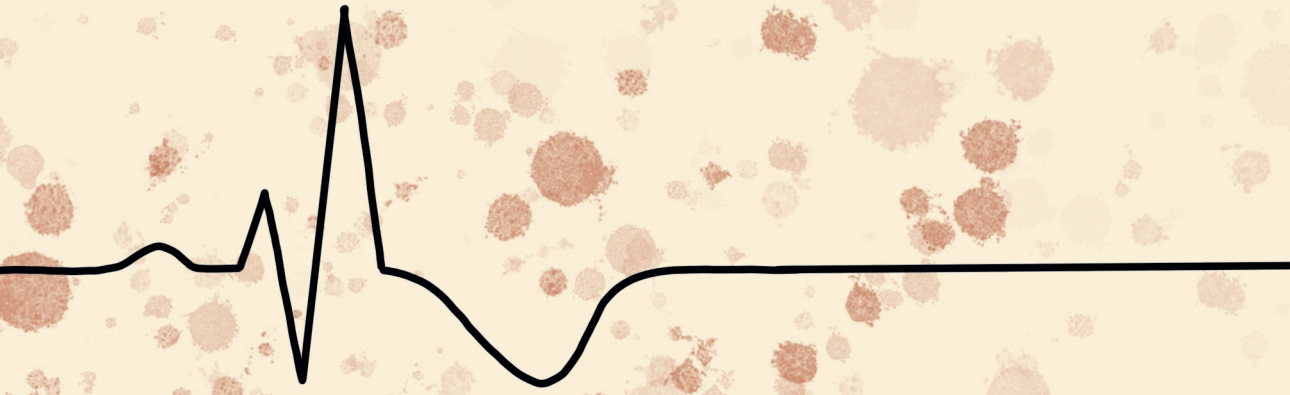
PART I

EPIDEMIOLOGY AND AETIOLOGY



CHAPTER 2

Prevalence of pulmonary hypertension in pulmonary sarcoidosis: the first large European prospective study

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To the Editor:

Sarcoidosis is a systemic disease of an unknown aetiology, in which non-caseating granulomas are formed in one or multiple organs, with pulmonary involvement in >90% of the sarcoidosis patients.[1] Pulmonary hypertension (PH), defined as a mean pulmonary artery pressure of ≥25mmHg by right heart catheterisation (RHC),[2] is a well recognised complication of sarcoidosis, associated with significant increase in mortality.[3,4] Although the first case of PH in sarcoidosis was described in 1949,[5] the exact prevalence remains unclear. Only three studies have previously investigated the PH prevalence independently of suggestive symptoms and signs for PH, resulting in prevalence rates of 5.7%, 14% and 20.8%.[6–8] In patients with complaints suggestive of PH or those awaiting lung transplant, rates of PH up to 79% have been reported.[9–11] Unfortunately, most studies are retrospective and have used an echocardiographic definition for PH (increased right ventricular systolic pressure (RVSP) of ≥40mmHg), lacking RHC as gold standard. A European Caucasian cohort has never been studied. The PULmonary hypertension in pulmonary SARcoidosis (PULSAR) study prospectively investigates the PH prevalence in patients with pulmonary sarcoidosis referred to a Dutch tertiary sarcoidosis centre (www.trialregister.nl; registration number NTR5295). This study was funded by ZonMw (The Netherlands Organisation for Health Research and Development).

Between August 2015 and October 2017, this cross-sectional study prospectively investigated the prevalence of PH in patients with histologically confirmed or confident clinical diagnosis of sarcoidosis. Patients with an age of ≥18 years who were newly referred to the pulmonology department of the St Antonius Hospital Nieuwegein (the Netherlands), a tertiary centre for sarcoidosis and PH, were asked for informed consent and underwent PH screening. Baseline data were recorded on ethnicity, Scadding stage on chest radiography,[12] pulmonary function test and chest computed tomography. PH screening consisted of thorough history taking, physical examination and echocardiography by the same experienced physician. Based on the European Society of Cardiology/European Respiratory Society guideline for PH,[2] patients were divided into three groups: 1) low PH probability, with maximal tricuspid regurgitation velocity (TRVmax) absent or ≤2.8m·s^{-1} without secondary PH signs; 2) intermediate PH probability, with TRVmax absent or ≤2.8m·s^{-1} with secondary PH signs, or 2.9–3.4m·s^{-1} without secondary PH signs; and 3) high PH probability, with TRVmax 2.9–3.4m·s^{-1} with secondary PH signs, or TRVmax >3.4m·s^{-1}.

Secondary PH signs were divided into three groups in accordance to the guideline: ventricles, pulmonary artery, and right atrium. Secondary signs were counted as present if one or more secondary PH signs of at least two different secondary sign groups were present. All patients with intermediate or high probability were referred for RHC. Presence of PH was defined as a mean pulmonary artery pressure of ≥25mmHg. Patients with PH were discussed in a multidisciplinary PH team for the final diagnosis. Patients with a low PH probability with minor secondary signs for PH (defined as only one secondary sign or two secondary signs from the same group) were re-evaluated after 1 year. In case of progression, patients were still referred for RHC.

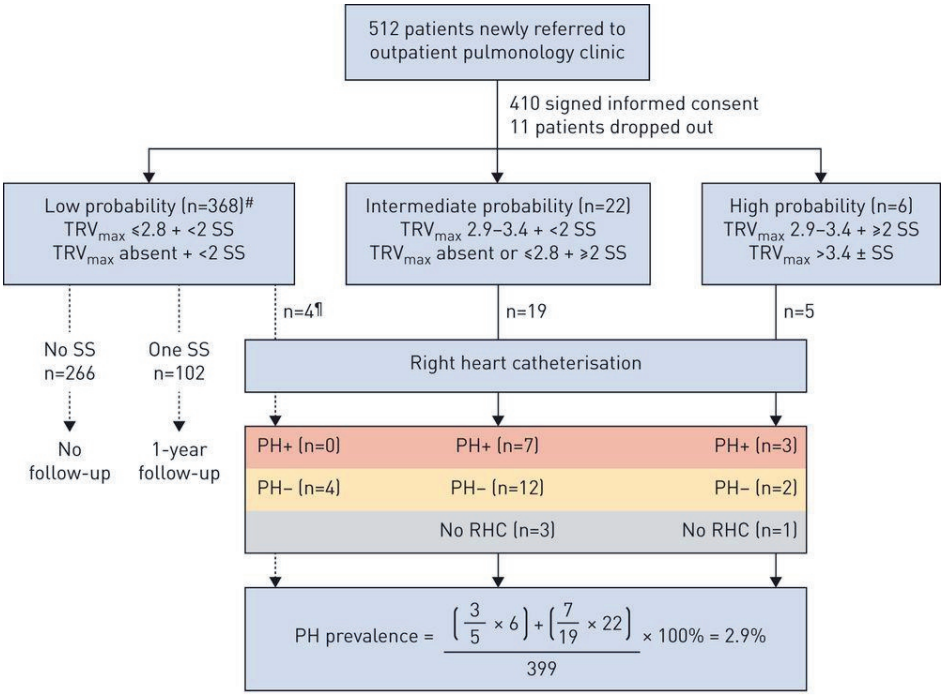
As shown in Figure 2.1, 512 patients were eligible for inclusion, of whom 399 patients signed informed consent and underwent PH screening (57.9% male, mean±SD age 49.4±11.6 years). The main ethnicity was Caucasian (90.5%). Patients had a mean±SD history of sarcoidosis for 6.0±8.2 years, and 20% had Scadding stage IV sarcoidosis. Low, intermediate and high PH probability was present in 92.2%, 5.5% and 1.5%, respectively. High or intermediate PH probability was present in 28 patients, of whom four refused RHC. Of the low PH probability group and inconclusive echocardiograms, four patients underwent RHC based on clinical judgement, of whom none had PH. In total, 28 patients underwent RHC. In 10 out of these 28 patients, PH was present. One patient had a post-capillary component.

As shown in Figure 2.1, patients with PH had a longer history of sarcoidosis and presented with Scadding stage IV more often. Three out of the 10 patients developed PH in the absence of significant fibrosis.

Based on the results of echocardiography and RHC, the PH prevalence was calculated. Because a few patients with high and intermediate PH probability did not undergo RHC, the fraction with PH of the patients who underwent RHC within either one of the PH probability groups was multiplied by the total number of patients of the same PH probability group. The estimated PH prevalence in this cohort of sarcoidosis patients is 2.9%. This number could range from 2.5% (if all of the missing RHCs in the high and intermediate probability groups ruled out PH) up to 3.5% (if all confirmed PH).

Of the low PH probability group, 102 patients had minor secondary signs. 98 underwent re-evaluation after 1 year. Only two patients showed progression of the secondary signs, in one of whom PH was ruled out by RHC. The other patient had developed a severe cardiomyopathy due to cardiac sarcoidosis with a subsequent post-capillary PH.

The PULSAR study is the first large study investigating the PH prevalence in a predominantly Caucasian cohort of almost 400 consecutive sarcoidosis patients referred to a



	PH present	PH absent
Subjects n	10	18
Male %	70.0	55.6
Age years	56.3±12.9	54.2±12.1
Caucasian %	90.0	100.0
Duration of disease years	13.2±7.4	5.3±10.3
Scadding stage %		
0	0	13.3
I	10.0	13.0
II	20.0	3.0
III	0	33.3
IV	70.0	56.7
FVC % pred	77.7±19.2	95.6±19.0
FEV_1 % pred	60.5±15.2	88.1±17.5
Single-breath D_{LCO} % pred	53.2±18.5	69.5±18.3
Mean PAP mmHg	33.1±12.0	16.5±3.1
PVR Wood units	3.8±2.6	0.8±0.4
Cardiac output L·min^{-1}	6.0±1.6	6.5±1.7
PCWP mmHg	10.2±5.0	9.9±3.6

Figure 2.1: Flow chart for pulmonary hypertension (PH) screening, including outcomes for patients with PH present compared to PH absent.

TRVmax = maximal tricuspid regurgitation velocity; SS = secondary signs; RHC = right heart catheterisation; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 s; DLCO = diffusing capacity of the lung for carbon monoxide; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; PCWP = pulmonary capillary wedge pressure. # three patients had an inconclusive echocardiogram; ¶ none of the four patients with low PH probability undergoing RHC had PH. Data are presented as mean±SD, unless otherwise stated.

tertiary sarcoidosis centre using echocardiography and, if indicated, RHC. As a result, the PH prevalence is estimated to be around 3%. Three studies previously investigated the PH prevalence in sarcoidosis independently of symptoms or signs for PH. Handa et al.[6] were the first, investigating 246 consecutive Japanese sarcoidosis patients visiting the outpatient clinic for follow-up, defining PH as an RVSP of ≥40mmHg on echocardiography. They found an echocardiographic PH prevalence of 5.7%. Bourbonnais et al. and Samavati et al.[7] prospectively evaluated 141 sarcoidosis patients with echocardiography, followed by RHC in 35 patients. PH was defined as an RVSP of ≥40mmHg in the absence of significant left heart dysfunction. RHC was performed in these patients, and also in patients with inconclusive echocardiography with repeatedly abnormal 6-min walk test outcomes despite optimisation of therapy. They found a PH prevalence of 14%. 88% were African American descendants, who are more likely to have sarcoidosis-associated PH compared to Caucasians.[13] In a third study, Alhamad et al.[8] investigated 96 Arab sarcoidosis patients, defining PH as an RVSP of ≥40mmHg as measured by echocardiography. A prevalence of 20.8% was reported, with a predominance of female PH patients. The prevalence of 3% in our population is significantly lower. This might be due to a less biased and well defined study population. Furthermore, prevalence of PH might differ between ethnicities.

Although this study presents the largest cohort of sarcoidosis patients prospectively investigated for PH, there are several limitations. First, not all patients underwent the gold standard RHC due to ethical considerations. We acknowledge that echocardiography might not always rule out PH correctly in patients with low PH probability. In clinical practice, the decision to perform RHC should outweigh the potential risks. Secondly, we aimed to minimise selection bias; however, some bias could not be avoided, since patients with worse disease severity are more likely to be referred to a tertiary centre. Finally, 62% of all patients were on immunosuppressive therapy at baseline, which might influence the haemodynamic profile at the moment of screening.

In conclusion, the PH prevalence is estimated to be around 3% in a cohort of predominantly Caucasian sarcoidosis patients referred to a Dutch tertiary centre. It can be suggested that there are ethnic differences in the prevalence of PH.

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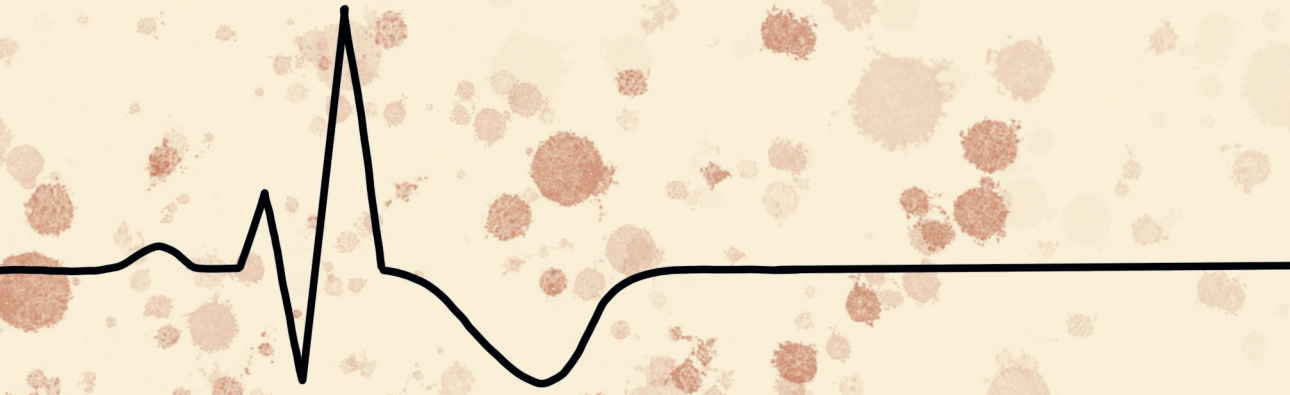

CHAPTER 3

Clinical phenotypes of sarcoidosis-associated pulmonary hypertension

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Abstract

Background: Pulmonary hypertension (PH) is a known complication of pulmonary sarcoidosis and its aetiology is unclear. Different pathophysiological mechanisms in sarcoidosis-associated pulmonary hypertension (SAPH) are known. Clinical phenotyping can aid clinicians in choosing the optimal treatment strategy. This study aimed to describe clinical phenotypes of SAPH and their characteristics.

Methods: A retrospective cohort study was performed on all SAPH patients at a tertiary referral centre. All patients were extensively analysed and discussed case by case in a multidisciplinary expert team to determine the most likely pathophysiological mechanism of PH. Patients were then classified into conceptual clinical phenotypes.

Results: Forty (40) patients with SAPH were identified between 2010 and 2019. Three patients were classified as the postcapillary phenotype. Of the remaining 37 patients with precapillary PH, six were classified as 'compression of pulmonary vasculature', 29 as 'parenchymal', one as 'suspected vasculopathy' and one as 'chronic pulmonary emboli' phenotypes. Of the patients with compression of pulmonary vasculature, four showed compression by fibrotic disease and two by active sarcoidosis-based disease. Within the parenchymal phenotype, 20 patients (69%) showed pulmonary vascular resistance >3.0WU and had significantly lower diffusing capacity of the lung for carbon monoxide compared with the nine patients (31%) with pulmonary vascular resistance ≤3.0WU.

Conclusion: SAPH has multiple pathophysiological mechanisms and clinical phenotypes in this retrospective study. Future studies are necessary to examine how these phenotypes can affect appropriate treatment and prognosis.

Introduction

Sarcoidosis is a rare systemic inflammatory disease of unknown aetiology. It is characterised by formation of non-caseating granulomas in the affected tissues. Pulmonary hypertension (PH) is a serious complication of sarcoidosis, with a suggested prevalence of 3–20%, and is associated with increased morbidity and mortality.[1–4] Based on the European PH guidelines, PH is classified into five different groups and within each group there is similar pathology, haemodynamics and therapeutic approaches.[5] Sarcoidosis-associated PH (SAPH) is classified into group V; this is based on the diverse underlying pathophysiological mechanism of SAPH. SAPH is most commonly due to destruction of pulmonary vasculature by fibrosis and subsequent hypoxaemia. However, SAPH can also occur in the absence of significant pulmonary fibrosis. Furthermore, there is a poor correlation between pulmonary function test results, blood gas tensions and pulmonary haemodynamics, which indicates that fibrosis and hypoxaemia alone cannot account for all.[3,6–8] Other mechanisms have been described, such as specific vasculopathy, left heart disease and extrinsic compression of the pulmonary vasculature.[3,9–11] Patients with sarcoidosis also have a higher prevalence of pulmonary emboli and sleep apnoea.[12–15] These different mechanisms might have implications for the disease, including therapy and prognosis.[9] Differentiating between clinical phenotypes of SAPH may guide clinicians, but this has only been described in review articles.[16,17] This study aimed to describe clinical phenotypes of SAPH based on the analysis of a single-centre cohort study. We report the analysis of demographics, pulmonary haemodynamics, aetiology, and functional parameters between clinical phenotypes of SAPH.

Methods

Patient selection

All patients with sarcoidosis who were diagnosed with PH between 2010–2019 at the St. Antonius Hospital (The Netherlands), which is a tertiary referral centre for both sarcoidosis and PH, were identified and retrospectively studied by chart review. Sarcoidosis diagnosis was based on current guidelines.[18] The diagnosis of PH was based on the results of right heart catheterisation (RHC).[5] Local institutional review board approval was obtained.

Clinical and functional assessment

Echocardiography, laboratory testing, pulmonary function tests, chest X-rays and high-resolution chest computed tomography (HRCT) were performed for all patients within 6 months of RHC. If available, data regarding arterial blood gas analysis, ventilation perfusion scintigraphy (V/Q scan), contrast-enhanced chest CT, pulmonary angiography, polysomnography (PSG), cardiac magnetic resonance imaging (CMR), and fluorodeoxyglucose positron emission tomography (FDG PET/CT) were obtained. Predicted values of the pulmonary function test were calculated according to the European Respiratory Society guidelines.[19] An experienced independent radiologist reviewed all chest X-rays and HRCTs. Scadding classification on chest X-ray was used to classify patients into Scadding stages 0–IV.[20] HRCT was evaluated for lung parenchymal abnormalities including ground-glass opacities, honeycombing, consolidations, emphysema, traction bronchiectasis, and fibrosis. The total disease extent was classified as not significant (<5% in the total lung area), intermediate (5–20%) or severe (>20%).[21] A V/Q scan was performed if chronic pulmonary emboli were suspected. A pulmonary angiography was performed when V/Q was abnormal. PSG was performed when obstructive sleep apnoea (OSA) was suspected. Diagnosis of OSA was based on an apnoea/hypopnoea index (AHI) >5 events/hour. Severity of OSA was classified as mild (AHI 5–15), moderate (AHI 15–30) or severe (AHI >30).[22] FDG PET/CT was used to determine sarcoidosis activity and location of disease. An experienced independent nuclear physician reviewed all FDG PET/CT-scans.

PH diagnosis

A diagnosis of PH was based on discussion by the multidisciplinary team (MDT) consisting of a cardiologist, pulmonologist, rheumatologist, radiologist, and nurse practitioner. PH was defined as a resting mean pulmonary artery pressure (mPAP) of ≥25mmHg at RHC. Precapillary PH was defined as a pulmonary arterial wedge pressure (PAWP) ≤15mmHg, and PH was diagnosed as postcapillary if the PAWP was >15mmHg. In accordance with international guidelines, if the PAWP was elevated, a diastolic pressure gradient ≥7mmHg and/or a pulmonary vascular resistance (PVR) >3.0 Wood Units (WU) were used to establish a diagnosis of combined postcapillary and precapillary PH.[5]

After discussion in the MDT, treatment was suggested according to the hypothesised pathophysiological mechanism. For study purposes, all patients were retrospectively classified in an unblinded manner into phenotype subgroups according to clinical characteristics and the most likely pathophysiological mechanism mentioned in the MDT report. The following clinical phenotypes classification were designed for this study:

- Postcapillary phenotype: patients with postcapillary PH, using a PAWP >15mmHg as threshold.
- Compression phenotype: patients with precapillary PH and compression of pulmonary vasculature (central or segmental pulmonary arteries) by active sarcoidosis-based inflammation, calcified lymph nodes, fibrosis or fibrosing mediastinitis. The presence of compression was assessed by contrast-enhanced chest CT or HRCT, and pulmonary angiography if necessary.
- Parenchymal phenotype: patients with precapillary PH with moderate-severe pulmonary parenchymal disease due to sarcoidosis. Patients had to fulfil one of the following criteria for moderate-severe pulmonary disease: Scadding type III or IV disease, severe obstructive (FEV1 ≤60%) or restrictive disease (FVC ≤70%). Patients of this phenotype were further stratified using PVR 3.0 WU as threshold.
- Suspected vasculopathy phenotype: patients with precapillary PH, PVR >3.0WU and a vasculopathy as the hypothesised mechanism of SAPH. Patients had no or mild pulmonary disease, defined as no obstructive (FEV1 >60%) or restrictive (FVC >70%) lung disease and minimal parenchymal changes on HRCT. Other causes of PH had to be excluded, such as severe OSA, chronic thromboembolic pulmonary hypertension (CTEPH), and compression of pulmonary vasculature.
- Chronic pulmonary emboli phenotype: presence of chronic pulmonary emboli detected by V/Q scan and confirmed by pulmonary angiography despite anticoagulation therapy for at least 3 months. This phenotype included sarcoidosis patients diagnosed with CTEPH.

Statistical analysis

Data were stored in the web-based datamanager REDCap. All statistical analyses were performed using SPSS Statistics for Windows, version 26 (Armonk, NY: IBM Corp). Descriptive statistics were used for both continuous and categorical variables. The chi-squared test or Fisher's Exact Test was used to compare categorical variables. The Student's t-test or Mann-Whitney U test was used to compare mean or median values of continuous variables. A two-tailed p-value <0.05 was considered significant.

Table 3.1: Characteristics of all patients

Variable	Value (n=40)
Male	60.0%
Age (years)	59.0±12.2
Caucasian ethnicity	72.5%
Body mass index (kg/m^2)	27.3±5.1
Biopsy-proven sarcoidosis	85.0%
Time between sarcoidosis diagnosis and PH diagnosis (years)	12.1 [7.0–21.0]
Scadding stage IV	80.0%
FDG PET/CT activity (n=35)	88.6%
Current immunosuppressive treatment	75.0%
Corticosteroids	52.5%
Non-steroid agents	45.0%
NYHA functional class	
II	22.5%
III	70.0%
IV	7.5%
Comorbidities	
Obstructive sleep apnoea	32.5%
Active or past smoker	45.0%
COPD	7.5%
Hypoxaemia requiring oxygen usage	42.5%
History of pulmonary embolism	12.5%
Cardiac sarcoidosis	10.0%
Pulmonary function tests	
FEV1 %pred	49.9±17.2
FVC %pred	63.3±22.5
FEV1/FVC	68.6±18.0
$DLCO_{SB}$ %pred (n=33)	46.5±20.7
Chest HRCT	
Total disease extend	
<5%	5.0%
5–20%	12.5%
>20%	82.5%
Pulmonary haemodynamics	
Mean PAP (mmHg)	37.0±10.7
PAWP (mmHg)	10.1±4.0
Cardiac output (L/min)	5.8±1.9
Pulmonary vascular resistance (Wood Units)	5.5±3.3

COPD = chronic obstructive pulmonary disease; DLCOSB = diffusing capacity for carbon monoxide single breath; FDG PET/CT = fluorodeoxyglucose positron emission tomography with computed tomography; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high-resolution computed tomography; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension.

Results

Table 3.1 shows the baseline characteristics of the study population. Forty patients with both sarcoidosis and PH were identified. The cohort mainly consisted of male patients (60.0%), with a mean age of 59.0 ±12.2 years. Sarcoidosis was biopsy-proven in 85.0% of patients; the diagnosis in the other patients was based on consensus by an expert team. Functional capacity was impaired in 31 patients (77.5%), with a New York Heart Association functional class of III or IV. A PSG was performed in 19 patients, of whom 13 were diagnosed with OSA (median AHI 10.5/h). A V/Q scan to exclude chronic pulmonary emboli was performed in 22 patients.

As shown in Figure 3.1, all patients except for one could be classified into different clinical phenotypes. This patient (Scadding II) had only mild parenchymal lung disease with a preserved FVC and FEV1. However, this patient showed a mildly elevated mPAP of 26mmHg and low PVR of 2.6WU. Other causes such as compression of pulmonary vasculature, OSA and chronic pulmonary emboli were ruled out. Therefore, this patient was classified as the parenchymal phenotype. Pulmonary haemodynamics of all phenotypes are shown in Table 3.2. Supplementary Table S3.1 shows baseline characteristics of all phenotypes.

Table 3.2: Pulmonary haemodynamics of all phenotypes

	Postcapillary phenotype (n=3)	Compression phenotype (n=6)	Parenchymal phenotype (n=29)	Suspected vasculopathy phenotype (n=1)	Pulmonary emboli phenotype (n=1)
Right atrial pressure (mmHg)	9.0 [8.0–10.0]	6.0 [4.0–10.8]	6.0 [3.5–7.5]	8.0	4.0
Systolic PAP (mmHg)	65.0 [52.0–85.0]	72.5 [42.5–106.3]	50.0 [44.0–66.0]	40.0	55.0
Diastolic PAP (mmHg)	25.0 [18.0–28.0]	29.5 [20.0–40.0]	25.0 [19.5–30.0]	28.0	33.0
Mean PAP (mmHg)	38.3 [36.0–40.3]	42.5 [29.5–62.1]	34.7 [26.8–42.0]	32.0	40.3
PAWP (mmHg)	18.0 [16.0–22.0]	8.0 [4.8–10.0]	10.0 [7.5–12.0]	10.0	6.0
Cardiac output (L/min)	8.5 [6.0–8.5]	5.7 [3.8–7.5]	5.1 [4.5–6.4]	7.0	7.2
PVR (Wood Units)	2.4 [1.9–3.7]	7.3 [2.6–10.9]	4.6 [2.7–8.1]	3.1	4.8

PAP = pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance.

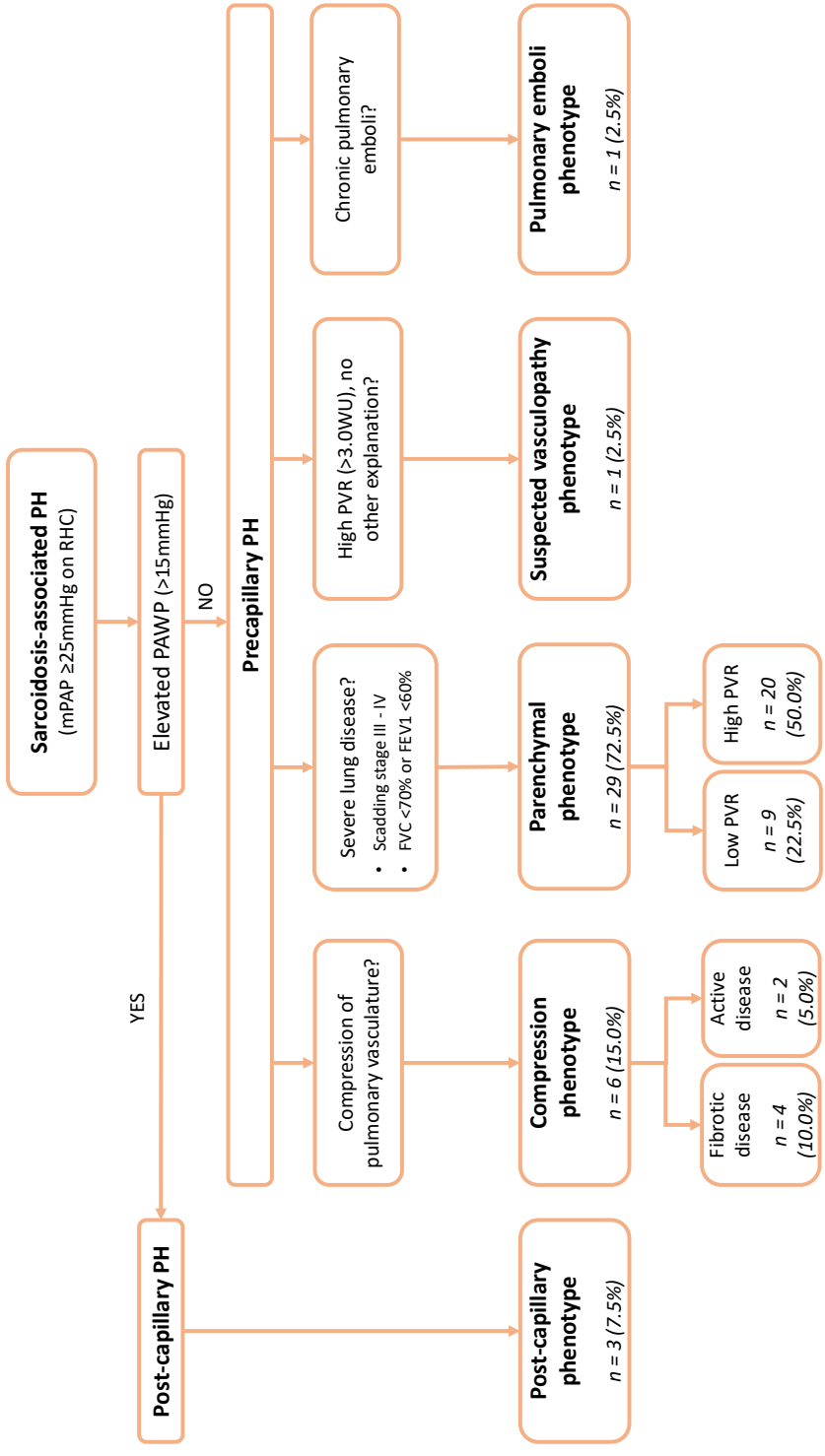

Figure 3.1: Flowchart of SAPH phenotype classification.

Postcapillary phenotype

Of the three patients (7.5%) classified as postcapillary phenotype, one was diagnosed with isolated postcapillary PH and two with combined postcapillary and precapillary PH. The patient with isolated postcapillary PH presented with a mPAP of 38mmHg, a PAWP of 22mmHg and a diastolic pressure gradient of 3mmHg, with a normal systolic but impaired diastolic left ventricular (LV) function. There was no significant valve disease and there were no signs of cardiac sarcoidosis on CMR and FDG PET/CT. The two patients with combined precapillary and postcapillary PH (mPAP 36mmHg and 40mmHg, PAWP 15mmHg and 18mmHg, PVR 2.4WU and 3.7WU) were both in Scadding stage IV and showed diastolic dysfunction with preserved systolic function on echocardiography. CMR was not performed; however, there were no suggestive symptoms of cardiac sarcoidosis and FDG PET/CT was negative in one patient.

Compression phenotype

Six patients (15.0%) showed compression of pulmonary vasculature. The baseline characteristics are shown in Supplementary Table S3.2. In four patients, compression of pulmonary vasculature was due to fibrosis or calcified lymph nodes, as seen on HRCT. One of these patients was diagnosed with fibrosing mediastinitis. All four patients had severe parenchymal lung disease (Scadding stage IV). The remaining two patients showed compression by an active inflammatory process confirmed by FDG PET/CT (Figure 3.2). Both patients (Scadding stages I and IV) responded well to immunosuppressive treatment. After 6 months, they showed improvement in functional capacity and normalisation of PAP on echocardiography.

Parenchymal phenotype

Twenty-nine patients (72.5%) were classified as the parenchymal phenotype, including the patient mentioned earlier with moderate parenchymal disease. Scadding stage IV was seen in 24 patients, stage III in one patient and stage II was seen in three patients. These three patients showed parenchymal disease on HRCT, with reduced FEV1 and FVC values. All patients within the parenchymal phenotype were further categorised into two groups according to pulmonary haemodynamics, using PVR >3.0WU as threshold. In total, 20 patients showed a PVR >3.0WU. Characteristics of both groups are shown in Supplementary Table S3.3. Comparing baseline characteristics, patients with PVR >3.0WU showed a significantly lower DLCO %pred (35.7 vs 67.0, p=0.016) and more groundglass opacities on HRCT (55% vs 0%, p=0.005). There was a trend towards worse New York Heart Association functional class (p=0.056) and lower FVC (p=0.095).

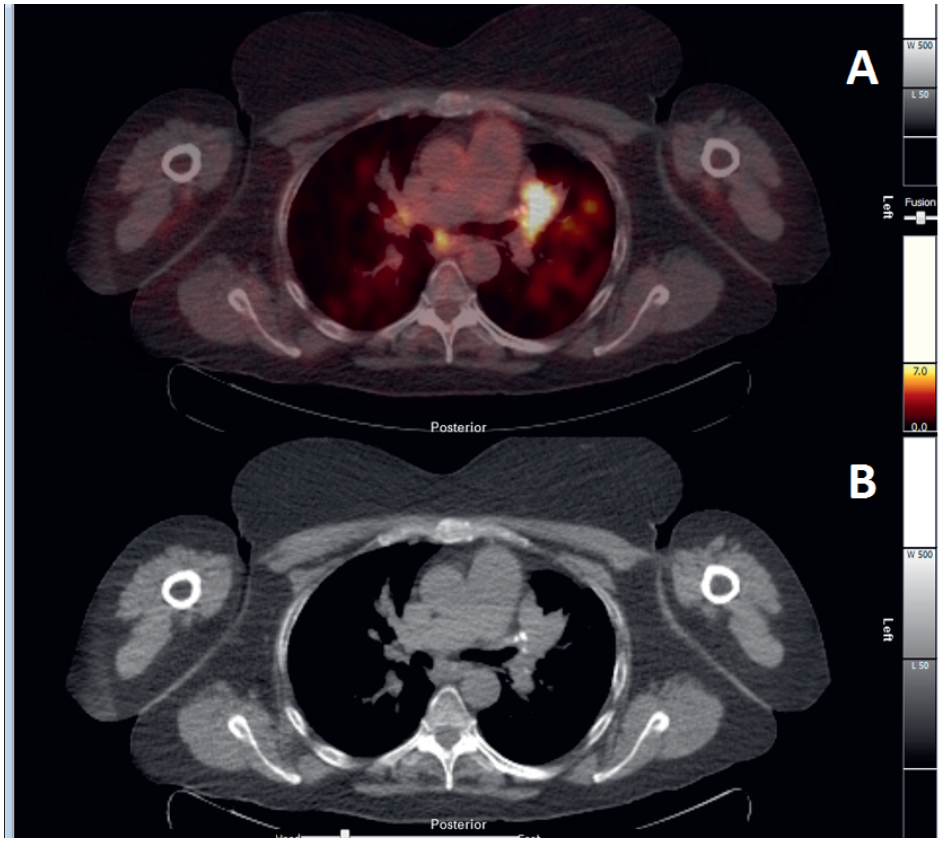

Figure 3.2: Example of compression by active disease on FDG PET/CT (A) and chest CT (B).

Suspected vasculopathy phenotype

One patient was classified as suspected vasculopathy phenotype. This patient showed Scadding stage I disease with <20% disease extent on HRCT. He had been diagnosed with OSA several years ago and had been successfully treated, showing an AHI 1.6/h on his latest PSG. RHC showed precapillary PH with mPAP 32mmHg and PVR 3.1WU. Chronic pulmonary emboli and compression of pulmonary vasculature were ruled out and FDG PET/CT showed no uptake. He was classified as suspected vasculopathy phenotype and treated with PH-targeted therapies.

Chronic pulmonary emboli phenotype

One patient (2.5%) was diagnosed with CTEPH. RHC showed mPAP 40mmHg and PVR 4.8WU. The V/Q scan was suggestive of chronic pulmonary emboli, which was confirmed by pulmonary angiography with no signs of extrinsic compression. This patient had been

diagnosed with sarcoidosis 22 years previously and showed Scadding stage IV disease with severe parenchymal disease on HRCT. PH-targeted therapies were started after diagnosis. After 6 months of treatment, the 6-minute walking distance and estimated right ventricular systolic pressure on echocardiography showed improvement; however, there was no improvement in functional class.

Discussion

This is the first study to classify a cohort of SAPH patients into clinical phenotypes according to the underlying pathophysiological mechanisms and pulmonary haemodynamics. In this cohort, postcapillary PH was found in 7.5% and precapillary in 92.5% of patients. The majority of patients with precapillary PH had severe pulmonary disease. Nevertheless, the presence of fibrosis is not essential for the development of SAPH, as 20.0% showed no fibrosis. This single-centre population showed many similarities in terms of severity of pulmonary disease and haemodynamics with the ReSAPH registry.[23] Populations differed, as the majority of the ReSAPH population consisted of African-Americans and females. Besides haemodynamics and pulmonary disease severity, the ReSAPH registry describes no other pathophysiological mechanisms. Different reviews have addressed this subject, although only two published reviews have proposed different phenotypes.[16,17] The current clinical phenotype classification system is based on the underlying pathophysiological mechanisms, as described in previous studies.[24,25] Most phenotypes were based on clear-cut diagnostic criteria; however, the suspected vasculopathy phenotype was more difficult to define. Nathan et al. described several criteria to discriminate between Group 1 (pulmonary arterial hypertension) and group 3 (severe lung disease) as a cause of PH in patients with chronic lung disease and PH. These criteria use pulmonary haemodynamics, extent of parenchymal disease and pulmonary function variables to stratify patients. This led to the criteria of PVR >3.0WU in the absence of other explanations, including severe lung disease, to classify one patient as the suspected vasculopathy phenotype. Furthermore, the distinction between PH due to chronic lung disease and pulmonary arterial hypertension is difficult, as the spectrum of severity of both the pulmonary vascular and parenchymal lung disease is most likely a continuum. This is shown in patients classified as the parenchymal phenotype, where large differences in pulmonary haemodynamics were seen. Patients with high PVR had a significantly lower DLCO as %pred and a trend towards lower functional class and lower FVC %pred. Interestingly, most patients in both groups presented with Scadding stage IV sarcoidosis and similar radiological features, which indicates that the difference in pulmonary haemodynamics is most likely driven by worsening vasculopathy. Whether

this has consequences for prognosis or therapy needs to be investigated. The ReSAPH registry showed that the severity of pulmonary haemodynamics is not associated with worse outcomes.[26] However, lower DLCO is associated with worse outcome.[10,26]

In this population, 7.5% of patients were classified as postcapillary phenotype, compared with 16–29% reported in literature.[9,23] Baughman et al. reported impaired LV systolic function in 35% of patients in the postcapillary PH group, whereas LV diastolic dysfunction was observed in all postcapillary PH patients in the current study. This could be clinically important, since LV diastolic dysfunction in patients with sarcoidosis can be a first sign of cardiac sarcoidosis.[27] Compression of the pulmonary vasculature was found in 15% of patients. Remarkably, patients with compression by fibrotic disease or calcified lymph nodes showed higher mPAP and PVR compared to patients with compression by active disease, although statistical significance was not reached due to the low number of patients. Patients with compression by active disease showed a very good clinical and haemodynamic response to immunosuppressive therapy. This has previously been reported[3,10] and suggests that PH secondary to extrinsic compression due to an inflammatory process may be (partially) reversible. One patient showed chronic pulmonary emboli. An important limitation is that a V/Q scan was only performed for 22 patients. The risk of pulmonary emboli is higher in the sarcoidosis population compared with controls.[14,15,28] However, the association between CTEPH and sarcoidosis leading to PH has only been described in one case series.[29] According to current PH guidelines a V/Q scan should be performed in patients with precapillary PH to exclude chronic pulmonary emboli, since this might have major clinical consequences.[5]

Limitations

There were several limitations to this study. The classification into phenotypes was based on clinical features and not on histopathological findings. Therefore, other pathophysiological mechanisms such as pulmonary veno-occlusive disease were not taken into account for phenotype classification. Second, the used classification system could imply that patients with multiple pathophysiological mechanisms cannot be classified. Each individual SAPH patient has to be fully assessed and multiple phenotypes are possible, as SAPH is based on a multifactorial mechanism. In addition, patients can switch between phenotypes during the course of their disease. Another limitation was the retrospective character of the study. All data were obtained by chart review and not all patients had a complete diagnostic workup. Also, patients were classified in an unblinded manner, which could impact our results. Blinding could have been useful to prevent possible bias. Furthermore, the time interval between different assessments and RHC could be up to 6 months. During this interval, other events such as new

sarcoidosis-based inflammation could have impacted RHC results. Finally, the clinical setting was a tertiary-care hospital where selection bias towards patients with more advanced disease is inevitable, which could influence the prevalence of the found phenotypes and comorbidities. Nevertheless, SAPH is a rare entity and its diagnosis and treatment should be performed in a PH expertise centre.

Conclusion

SAPH has multiple pathophysiological mechanisms and clinical phenotyping can be helpful to differentiate between these mechanisms. The majority of patients present with precapillary PH and the parenchymal phenotype is most common. Clinical phenotyping can be a first step towards personalised therapeutic decision-making in SAPH patients. However, the prognostic implications of the proposed phenotypes need to be examined in future studies.

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Appendix

Supplementary Table S3.1: Baseline characteristics of different phenotypes

	Postcapillary phenotype (n=3)	Compression phenotype (n=6)	Parenchymal phenotype (n=29)	Suspected vasculopathy phenotype (n=1)	Pulmonary emboli phenotype (n=1)
Male sex	66.7%	50.0%	58.6%	100%	100%
Age (years)	63.6 [70.0–84.0]	64.5 [58.1–71.4]	59.1 [46.7–65.6]	71.7	67.1
Duration of disease (years)	20.2 [6.9–23.1]	15.9 [6.9–28.8]	10.6 [6.5–18.0]	8.0	22.8
Scadding stage IV	66.7%	83.3%	82.8%	0%	100%
Immunosuppressive treatment	0%	33.3%	89.7%	100%	100%
NYHA functional class I–II NYHA functional class III–IV	0% 100%	50% 50%	20.7% 79,3%	0% 100%	0% 100%
Comorbidities					
Obstructive sleep apnoea	100%	33.3%	24.1%	100%	0%
Hypoxaemia requiring oxygen usage	33.3%	33.3%	48.3%	0%	100%
Pulmonary function					
FVC %pred	70.3 [68.7–71.0]	53.3 [50.1–103.3]	66.6 [44.1–77.5]	54.0	63.0
$DLCO_{SB}$ %pred	53.0 [22.8–74.5]	36.1 [30.5–69.3]	40.2 [29.3–63.4]	62.0	25.0
Total disease extend on HRCT <20% >20%	 33.3% 66.7%	 16.7% 83.3%	 13.8% 86.2%	 100% 0%	 0% 100%

$DLCO_{SB}$ = diffusing capacity for carbon monoxide single breath; FVC = forced vital capacity; HRCT = high-resolution computed tomography; NYHA = New York Heart Association.

Supplementary Table S3.2: Characteristics of patients with compression of pulmonary vasculature

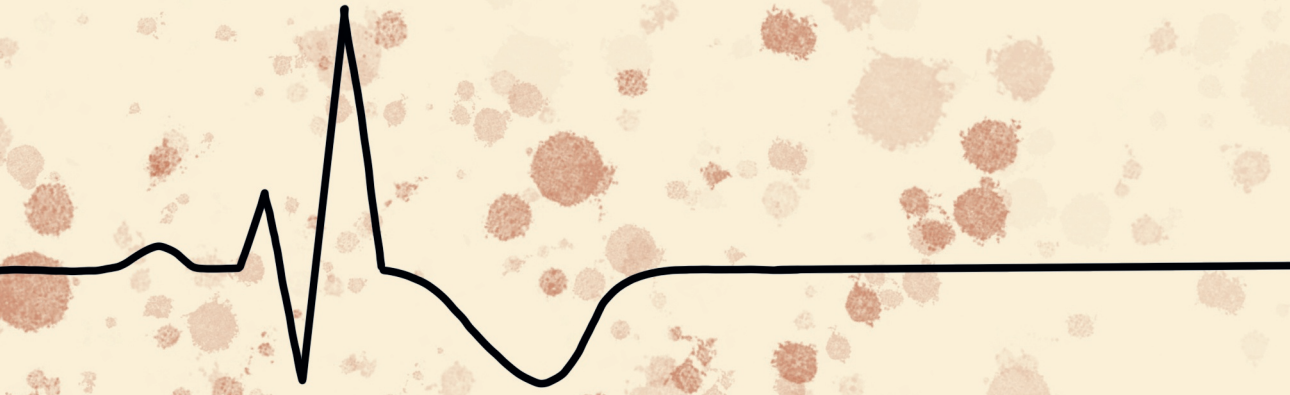
	Compression by fibrotic disease (n=4)	Compression by active inflammation (n=2)
Male	1	2
Age (years)	64.5 [59.6–70.0]	54.7–78.5
Duration of disease (years)	19.4 [10.3–41.2]	2.8–15.4
Scadding stage IV	4	1
Immunosuppressive treatment	2	0
NYHA functional class I–II NYHA functional class III–IV	1 3	2 0
Pulmonary function		
FVC %pred	50.7 [49.5–89.3]	55.6–107.0
$DLCO_{SB}$ %pred	36.1 [19.4–66.0]	36.0–67.0
Total disease extend on HRCT <20% >20%	 0 4	 1 1
Pulmonary haemodynamics		
Mean PAP (mmHg)	56.7 [37.9–62.9]	25.0–31.0
PAWP (mmHg)	5.5 [4.3–9.0]	10.0–10.0
Cardiac output (L/min)	4.8 [3.7–6.8]	5.8–8.3
PVR (Wood Units)	8.9 [7.3–12.3]	2.5–2.6

$DLCO_{SB}$ = diffusing capacity for carbon monoxide single breath; FVC = forced vital capacity; HRCT = high-resolution computed tomography; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance.

Supplementary Table S3.3: Characteristics of parenchymal phenotype

	PVR ≤3.0WU (n=9)	PVR >3.0WU (n=20)	p-value
Male	55.6%	60%	NS
Age (years)	58.8 [43.8–61.3]	59.1 [46.2–66.0]	NS
Caucasian ethnicity Non-Caucasian ethnicity	55.6% 44.4%	70% 30%	NS
Duration of disease (years)	9.1 [3.1–13.3]	12.4 [7.0–21.0]	NS
Scadding stage IV	77.8%	85%	NS
FDG PET/CT activity	100% (n=6)	80% (n=19)	NS
Immunosuppressive treatment	77.8%	95%	NS
NYHA functional class I–II NYHA functional class III–IV	44.4% 55.6%	10% 90%	0.056
Hypoxaemia requiring O2 usage	22.2%	60%	NS
Pulmonary function tests			
FEV1 %pred	49.0 [39.6–71.5]	46.1 [31.9–52.0]	NS
FVC %pred	79.0 [46.1–94.0]	63.6 [43.9–71.9]	0.095
$DLCO_{SB}$ %pred	67.0 [55.0–76.0]	35.7 [28.1–47.3]	0.016
Chest HRCT			
Groundglass	0%	55%	0.005
Honeycombing	22.2%	30%	NS
Consolidations	55.6%	40%	NS
Traction bronchiectasis	77.8%	80%	NS
Emphysema	11.1%	25%	NS
Total disease extend <20% >20%	 22.2% 77.8%	 15% 85%	NS
Pulmonary haemodynamics			
Mean PAP (mmHg)	26.3 [25.7–28.3]	38.7 [32.4–43.7]	
PAWP (mmHg)	12.0 [10.0–13.5]	9.5 [6.0–11.8]	
Cardiac output (L/min)	7.4 [5.5–8.3]	4.9 [3.7–5.5]	
PVR (Wood Units)	2.3 [1.7–2.7]	6.6 [4.5–9.5]	

$DLCO_{SB}$ = diffusing capacity for carbon monoxide single breath; FDG PET/CT = fluorodeoxyglucose positron emission tomography with computed tomography; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high-resolution computed tomography; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance.



CHAPTER 4

Intravascular ultrasound of the pulmonary arterial vasculature in patients suspected for sarcoidosis associated pulmonary hypertension

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Submitted

Abstract

Background: Pulmonary hypertension (PH) is a complication of sarcoidosis with largely unknown aetiology. Pulmonary vascular changes in sarcoidosis may contribute to the development of PH.

Research Question: Intra-vascular ultrasound (IVUS) is used to investigate pulmonary vascular disease in the distal pulmonary arteries in sarcoidosis patients suspected for PH, in correlation with haemodynamic measurements.

Study design and Methods: Consecutive pulmonary sarcoidosis patients visiting the outpatient clinic were screened for PH by echocardiography, and referred for right heart catheterisation and IVUS to assess percentage wall thickness and pulmonary vascular properties (distensibility, compliance, pulsatility). PH was defined as a mean pulmonary artery pressure of ≥25mmHg.

Results: Between august 2015 and November 2018, 479 sarcoidosis patients were screened for PH. Thirty-two patients underwent right heart catheterisation and IVUS imaging. Thirty-one procedures were elegible for analysis, and 105 out of 124 lobes could be studied (71% male, median age 59 years). PH was present in 14 patients. Percentage wall thickness was significantly increased in the upper lobe of patients with PH compared to no PH (12.2% vs 4.4%, p=0.028). Distensibility was significantly decreased in upper lobes of PH patients (0.81 vs 1.42 %/mmHg, p=0.015) and lower lobes of PH patients (0.91 % vs 1.16%/mmHg, p=0.048). Compliance showed a non-significant difference in the upper lobes of PH patients. Pulsatility was not significantly different between groups. Distensibility and compliance had moderate negative correlations with mean PAP, most pronounced in the upper lobes (r=-0.56, p=0.002 and r=-0.50, p=0.007 respectively).

Interpretation: Pulmonary vascular changes in wall thickness and vascular properties as assessed by IVUS, show upper lobe predominance, correlating with typical patterns of sarcoidosis related abnormalities on chest-CT. A vascular component as one of the mechanisms of PH in sarcoidosis is suggested.

Introduction

Sarcoidosis is a systemic disease with formation of non-caseating granuloma's that may resolve spontaneously or evolve to hyalinised fibrosis overtime.[1] Over the past decades, the aetiology of sarcoidosis remains largely unknown. It is characterised by a highly variable clinical presentation and associated with a wide range of complications including pulmonary hypertension (PH).[2,3] PH is defined by a mean pulmonary artery pressure (PAP) ≥25mmHg as measured by the gold standard right heart catheterisation (RHC).[4,5] The prevalence of PH in sarcoidosis is dependent on the severity of sarcoidosis, as well as methodologies used to define PH.[6] It is associated with increased morbidity and mortality.[7,8] The aetiology of PH in sarcoidosis is poorly understood and classified as WHO group 5 PH due to a multifactorial/unknown mechanism.[4] It is frequently attributed to the underlying interstitial fibrotic lung disease, but may develop in absence of pulmonary fibrosis suggesting other contributing factors such as left ventricular heart disease due to cardiac sarcoidosis,[9] lymphadenopathy with vascular compression, chronic thromboembolic disease,[10] or pathologic changes in the pulmonary vasculature related to sarcoidosis.[1,11,12] Haemodynamic measurements by RHC vary between different PH etiologies. In pre-capillary PH, increase in pulmonary vascular resistance (PVR) enhances right ventricular afterload, ultimately leading to right heart failure and death.[4] PVR is a late marker of pulmonary vascular disease, and reflects a steady pulmonary pressure-flow relationship. It does not incorporate the pulsatile component of the pulmonary vasculature, accounting for approximately 25% of the right ventricular afterload.[13] Intravascular ultrasound (IVUS) is able to qualitatively and quantitatively investigate the more distal pulmonary vasculature and assess the pulsatile component. It is invasive, yet not as invasive as pulmonary biopsy and therefore an interesting tool to investigate the pulmonary vasculature. The present study investigates the pulmonary vasculature of sarcoidosis patients suspected for PH in vivo using IVUS imaging. Furthermore, the IVUS data will be correlated to haemodynamic measurements, in order to gain further insight in the complex pathology of PH in sarcoidosis.

Methods

Population and screening

Consecutive patients of the PULSAR study,[6] including patients of 18 years or above with a history of pulmonary sarcoidosis visiting the outpatient clinic of our tertiary sarcoidosis centre, were prospectively enrolled in the IVUS study if they were referred for RHC. Baseline characteristics on pulmonary function test, six-minute walk test, chest X-ray and

chest-CT were obtained from chart review. Upfront, all patients were screened for PH by transthoracic echocardiography (TTE), laboratory (NT pro BNP, troponin T) and ECG. The IVUS procedure was performed immediately after RHC by the same interventional cardiologist. Contra-indications were allergy for contrast agents, significant renal impairment (eGFR <30 ml/min/1.73m^2), coagulation disorders or pregnancy. Patients with a pulmonary capillary wedge pressure (PCWP)>15mmHg or insufficient image quality of IVUS were excluded from analysis. After RHC, patients were classified according to the 2015 ESC/ERS PH guideline as PH (mean PAP ≥25mmHg) or no PH (mean PAP<25mmHg).[4] Written informed consent was obtained in all enrolled patients. The study was in compliance with the Declaration of Helsinki and the study protocol was approved by the Institutional Ethics Committee (MEC-U, reference number NL49594.100.14).

Right heart catheterisation

RHC was performed using a 7 French Swan Ganz catheter inserted into the right femoral vein. Patients were heparinised with 5000IE heparin. Haemodynamic measurements were taken during end-expiration, including systolic and diastolic pulmonary artery pressure (PAP), right atrial and ventricular pressure, PCWP (or left ventricular end diastolic pressure (LVEDP) if the PCWP was inconclusive) and cardiac output (CO) measured in threefold by the thermodilution method. Calculations were made for mean PAP ([systolic PAP+2*diastolic PAP]/3), PVR ([mean PAP-PCWP]/CO), pulse pressure (systolic PAP-diastolic PAP).[5] Furthermore, pulmonary arterial compliance (PAC) was estimated by stroke volume/pulse pressure, and resistance-compliance time (RC-time) was estimated by PVR*PAC.[14]

IVUS

IVUS imaging of the pulmonary arteries was performed immediately after the haemodynamic measurements by introducing the IVUS catheter over the guidewire (Volcano 45mHz Revolution catheter). 5000IE of heparin was infused a second time. In all patients it was attempted to image the left upper lobe (LUL), left lower lobe (LLL), right upper lope (RUL) and right lower lobe (RLL), The IVUS catheter was advanced distally in the selected lobe and the position was visualised by selective pulmonary angiography. First, the catheter was hold still to record a most distal image for at least three representative cardiac cycles. Afterwards, the IVUS catheter was withdrawn with a pullback velocity of 0.5mm/s. All images were recorded and digitalised for analysis.

Images were analysed using QCU-CMS (Medis Medical Imaging Systems, the Netherlands) lab by the same observer blinded to all clinical and haemodynamic data. Good image quality was defined as complete circumferential demarcation of the lumen area.

As shown in Figure 4.1, the mean wall thickness over the entire length of the pullback record was determined by measuring the vessel area (VA) and lumen area (LA) of one image per second. Recordings with overall poor image quality or less than 20 frames (<10mm length) were excluded from analysis. Single frames with inadequate image quality during pullback were marked and interpolated by the QCU-CMS lab technology. Percentage wall thickness area (WT) was calculated for each frame by the formula ([VA-LA]/VA*100%). Mean percentage WT was calculated for the full pullback length. At the most distal point, the lumen was measured peak systolic and end diastolic and averaged over three cardiac cycles. Pulmonary vascular properties were evaluated by calculating indices of arterial stiffness including pulsatility, compliance and distensibility.[15,16] The formula's and definitions are given in Table 4.1.

Survival

Data on adverse events and serious adverse events within 30 days of the procedure were recorded. Data on mortality of all patients were obtained from the Dutch national death registration (consultation date 26-02-2021).

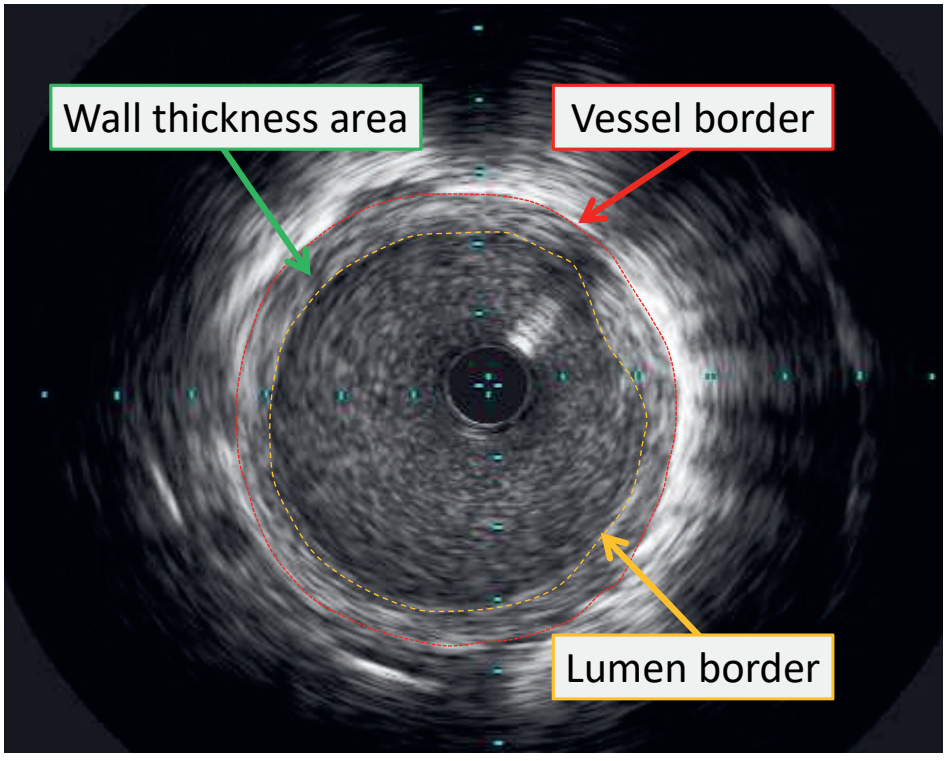

Figure 4.1: IVUS measurements on vessel area and lumen area.

Table 4.1: Definitions and formulas for arterial stiffness

Pulmonary vascular property	Definition	Formula
Pulsatility	Relative change in arterial cross sectional area	(LAs-LAd)/LAd
Compliance	Absolute cross sectional area change for a given pressure change	(LAs-LAd)/pulse pressure
Distensibility	Relative percentage in cross sectional area change for a given pressure change	((LAs-LAd)/LAd)/pulse pressure)*100%

Statistical analysis

Statistical analyses were performed using R (Version 4.1.1; www.r-project.org). Between group comparisons utilised Chi-square and Fisher's exact tests (for categorical data) and Wilcoxon signed rank tests (for continuous data). Descriptive statistics using frequencies (percentages) and median (IQR) were utilised where appropriate. Correlations were assessed using Pearson's correlation coefficient. Two-sided P values <0.05 were considered statistical significant. Event numbers on mortality were too low to perform statistical analysis.

Results

Population and screening

Between August 2015 and November 2018, 479 patients were included in the PULSAR study and screened for PH. In total, 36 patients were referred for RHC. As shown in the flowchart (Figure 4.2) 32 patients agreed to participate to the IVUS procedure. One patient underwent the IVUS procedure two times because of sudden increase of dyspnea and echocardiographic signs for PH one and a half year after the initial IVUS procedure (both procedures included in the analysis). Two patients were excluded, one due to a PCWP >15mmHg and the other due to insufficient IVUS image quality. In total 31 IVUS procedures have been analysed. Baseline characteristics are given in Table 4.2. The total cohort consisted of 71% male patients with a median age of 59 years (IQR 51, 67). PH was present in 14 patients. Patients with PH had a significantly longer history of sarcoidosis, more often in the need of supplemental oxygen therapy, lower FVC% and FEV1% predicted, and a larger main pulmonary artery diameter on chest-CT.

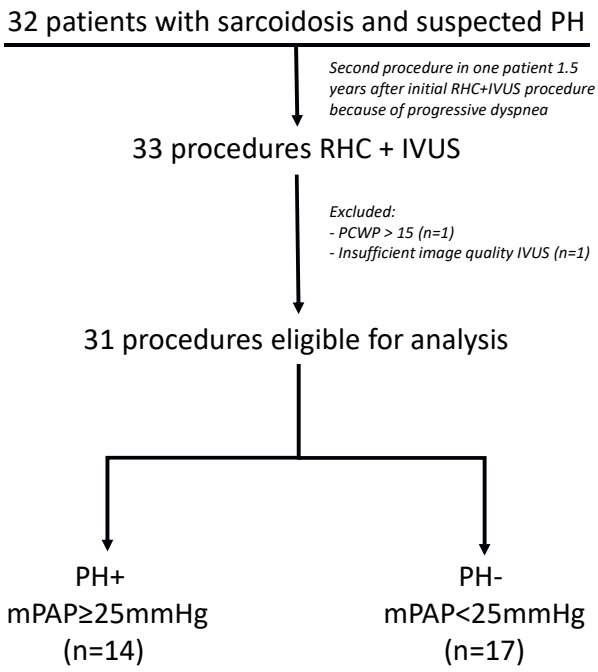

Figure 4.2: Flowchart patient selection and haemodynamic outcomes of right heart catheterisation. IVUS = intravascular ultrasound; mPAP = mean pulmonary artery pressure; PH = pulmonary hypertension; RHC = right heart catheterisation.

Haemodynamics

Data on haemodynamics during RHC and IVUS outcomes have been summarised in Table 4.3. In patients with PH compared to patients without PH, PVR and pulse pressure were significantly higher patients with PH (3.41 versus 1.31 WU, p<0.001 and 22 versus 16 mmHg respectively, p=0.003). There was no difference in CO or PCWP. PAC was significantly lower in patients with PH compared to no PH (3.37 vs 4.31 mL/mmHg, p=0.008) and correlated moderately negative with mean PAP and PVR (-0.51, p=0.005 and -0.60, p=<0.001 respectively. RC time was significantly higher in patients with PH (0.73 vs 0.45 seconds, p=0.009), and correlated moderately with mean PAP (r=0.48, p=0.082) and weak with PVR (r=0.38, p=0.04).

Intravascular ultrasound

In 31 IVUS procedures, a total of 105 lobes have been studied. The maximum lumen diameter in systole at the most distal point of the vessel ranged from 1.8mm to 6.2mm. Lower lobes were more often accessible compared to upper lobes (90.3% versus 79.0%)). Wall thickening could be assessed in 76.6% of all lobes, whereas pulmonary vascular properties could be assessed in 84.7% of the patients.

Table 4.2: Baseline characteristics and comparison between patients with and without PH

Variable	Total (n=31)	PH+ (n=14)	PH- (n=17)	P-value
Age (years)	59 [51, 67]	62 [50, 71)	57 [54, 62]	0.4
Sex (male)	22 (71%)	11 (79%)	11 (65%)	0.5
Etnicity (caucasian)	29 (94%)	12 [86%)	17 (100%)	0.2
BMI (kg/m^2)	28.1 [24.1, 29.1]	28.0 [24.0, 34.9]	28.1 [26.2, 29.0]	0.8
Scadding stage (0/1/2/3/4)	2/5/6/1/16	0/2/3/0/9	2/3/3/1/7	0.7
Duration of sarcoidosis (years)	6 [2, 15]	14 [8, 19]	2 (2, 6)	0.003
Immunosuppressive therapy (yes)	24 (77%)	12 [86%)	12 (71%)	0.4
Oxygen therapy (yes)	4 (13%)	4 (29%)	0	0.032
NYHA FC (I/II/III/IV)	3/14/14/0	0/6/8/0	3/8/6/0	0.3
NT pro BNP (pg/ml)	76 [36, 252]	212 [44, 340]	60 [27, 115]	0.2
Troponin T >0.014 (yes)	12 (40%)	7 (50%)	5 [31%]	0.3
FVC (% predicted)	88 [72, 104]	72 [63, 86]	101 [87, 106]	0.005
FEV1 (% predicted)	70 [56, 89]	55 [48, 65]	84 [73, 98]	<0.001
FEV1/FVC (ratio)	0.70 [0.60, 0.79]	0.64 [0.50, 0.77]	0.73 [0.66, 0.80]	0.2
DLCO SB (% predicted)	63 [40, 78]	52 [32, 67]	69 [50, 80]	0.081
MPAD (mm)	31.5 [28.2, 35.5]	33.5 [31.2, 39.5]	29.5 [27.2, 31.8]	0.028
MPAD indexed for BSA (mm/m^2)	15.63 [13.35, 17.99]	16.21 [14.42, 18.54]	14.69 [12.30, 16.18]	0.076
CT Total disease extend (<5/5-20/>20%)	4/5/17	1/3/10	3/2/7	0.5
TTE PH classification (Low/Intermediate/High)	2/19/10	0/6/8	2/13/2	0.018
TTE RVSP (mmHg) n=23	41 [38, 46]	46 [43, 57]	40 [30, 42]	0.032
TTE TAPSE	21.0 [20.0, 25.0]	20.7 [20.0, 22.0)	22.5 [20.6, 26.5]	0.2

Data are expressed as number (%) or median [1st and 3rd IQR]. BMI = body mass index; BSA = body surface area; DLCO SB= single breath diffusion capacity for carbonmonoxide; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; NT-proBNP= N-terminal pro-Brain Natriuretic Peptide; MPAD = main pulmonary artery diameter; PAP= pulmonary artery pressure; NYHA = New York Heart Association Functional Class; PH = pulmonary hypertension (mean PAP ≥25mmHg); RVSP = right ventricular systolic pressure; TAPSE = tricuspid annular plain systolic excursion; TTE = transthoracic echocardiography.

Percentage Wall Thickness area

As shown in Table 4.3, mean percentage WT over the full pullback length was most pronounced in the upper lobes of patients with PH compared to patients without PH (12.2% vs 4.4%, p=0.028). This difference was not present in the lower lobes (7.0% vs 6.0%, p=0.3).

Table 4.3: Haemodynamic profile and IVUS data in patients with PH compared to patients without PH

Variable	Total (n=31)	PH+ (n=14)	No PH (n=17)	P value
Mean PAP (mmHg)	21 (17, 28)	28 (26, 36)	18 (15, 20)	<0.001
Cardiac output (L/min)	5.53 (5.04, 7.10)	5.70 (5.16, 7.15)	5.50 (4.97, 7.00)	>0.9
PCWP (mmHg)	8.0 (6.0, 10.5)	9.5 (6.2, 10.8)	8.0 (6.0, 10.0)	0.4
PVR (WU)	2.38 (1.21, 3.65)	3.41 (2.43, 4.73)	1.31 (0.92, 2.70)	<0.001
PA Pulse pressure (mmHg)	18 (14, 23)	22 (20, 30)	16 (14, 18)	0.003
PAC (mL/mmHg)	4.15 (3.36, 5.49)	3.37 (2.02, 5.39)	4.31 (3.80, 7.68)	0.08
RC time (sec)	0.62 (0.42, 0.83)	0.73 (0.63, 0.85)	0.45 (0.34, 0.69)	0.009
All lobes				
Percentage wall thickness (%)	7.8 (5.6, 11.9)	9.9 (7.5, 13.3)	7.0 (4.3, 11.5)	0.066
Pulsatility (%)	21 (17, 24)	21 (17, 23)	20 (18, 24)	0.9
Compliance (mm^2/mmHg)	0.09 (0.05, 0.11)	0.07 (0.05, 0.10)	0.10 (0.07, 0.13)	0.10
Distensibility (%/mmHg)	1.19 (0.89, 1.52)	0.93 (0.65, 1.16)	1.34 (0.94, 1.60)	0.015
Upper lobes				
Percentage wall thickness (%)	6.8 (4.2, 14.6)	12.2 (6.6, 15.7)	4.4 (3.4, 11.0)	0.028
Pulsatility (%)	21 (16, 25)	20 (15, 24)	22 (18, 26)	0.4
Compliance (mm^2/mmHg)	0.08 (0.06, 0.14)	0.07 (0.03, 0.09)	0.09 (0.07, 0.14)	0.066
Distensibility (%/mmHg)	1.19 (0.83, 1.64)	0.81 (0.67, 1.18)	1.42 (1.06, 1.64)	0.015
Lower lobes				
Percentage wall thickness (%)	6.0 (4, 13)	7.0 (6, 15)	6.0 (3, 12)	0.3
Pulsatility (%)	20 (16, 26)	21 (17, 28)	20 (16, 25)	0.5
Compliance (mm^2/mmHg)	0.09 (0.05, 0.11)	0.07 (0.05, 0.10)	0.10 (0.07, 0.13)	0.10
Distensibility (%/mmHg)	1.08 (0.81-1.50)	0.91 (0.65-1.17)	1.16 (1.02, 1.59)	0.048

Data are expressed as median [1st and 3rd IQR]. PH+ = mean PAP ≥25mmHg; PA = pulmonary artery; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance

Pulmonary vascular properties

In patients with PH compared to no PH, pulsatility did not show significant differences. Distensibility was significantly decreased in the upper lobes (0.81 versus 1.42%/mmHg p=0.015) and lower lobes (0.91 versus 1.16%/mmHg, p=0.048). Compliance only showed a trend towards significance in the upper lobes of PH patients (0.07 versus 0.09 mm^2/mmHg, p=0.066). For the lower lobes there was no significant difference.

As shown in Table 4.4, there was a moderate negative correlation between mean PAP and upper lobe compliance and distensibility (r=-0.50, p=0.007 and r=-0.56, p=0.002 respectively). In the lower lobes only compliance showed a significant but weak negative correlation. Mean percentage WT correlated moderately with mean PAP in the upper lobes (r=0.42, p=0.028), and showed no significant correlation in the lower lobes. Correlations with PVR were generally less robust, showing only moderate negative cor-

relations for compliance and distensibility. Again, the strongest negative correlations were present in the upper lobes (r=-0.42, p=0.027 and r=-0.44, p=0.021 respectively).

Table 4.4: Pearson correlations of IVUS measurements with mean PAP and PVR

	Percentage wall thickness		Compliance		Distensibility	
	Mean PAP	PVR	Mean PAP	PVR	Mean PAP	PVR
All lobes	r=0.40 p=0.037	r=0.37 p=0.051	r=-0.39 p=0.032	r=-0.37 p=0.043	r=-0.48 p=0.008	r=-0.41 p=0.023
Upper lobes	r=0.42 p=0.028	r=0.39 p=0.046	r=-0.50 p=0.007	r=-0.42 p=0.027	r=-0.56 p=0.002	r=-0.44 p=0.021
Lower lobes	r=0.23 p=0.231	r=0.22 p=0.256	r=-0.39 p=0.032	r=-0.37 p=0.043	r=-0.35 p=0.060	r=-0.35 p=0.057

Pearson correlations with mean PAP and PVR for percentage wall thickness and vascular properties. Cut off p-value = <0.05. PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance.

Complications

Two patients developed a pulmonary embolism within 30 days of both procedures. One developed a bilateral pulmonary embolism two days after the procedure with a clinical presentation of deep venous thrombosis. In these two days the patient had been immobile without thrombosis prophylaxis. The other patient developed a pulmonary embolism ten days after the procedure, without a clinical presentation of deep venous thrombosis. Two years later this patient developed another pulmonary embolism, unprovoked. Both patients were adequately treated with heparin during the procedure and made full recovery. No other complications occurred.

Survival

Patients were followed up for a median of 3.9 years (3.4, 4.8). During follow up, 5 patients died. Event numbers were too low to perform statistical analysis on risk factors for mortality.

Discussion

This study aimed to investigate early changes in the pulmonary vasculature of sarcoidosis patients suspected for PH by using IVUS imaging. We imaged a mean of 3.4 lobes per patient with a lumen diameter ranging from 1.8 to 6.2mm, and were able to assess wall thickness consisting of the intima and media layers of the pulmonary vessel, and pulmonary vascular properties including compliance and distensibility. Percentage wall

thickness only was significantly increased in the upper lobe of PH patients compared to no PH (12.2% vs 4.4%), in the lower lobes there was no significant difference. Distensibility was most decreased in the upper lobes of patients with PH compared to no PH (0.81 vs 1.42 %/mmHg), and less pronounced decreased in the lower lobes (0.91 %/mmHg vs 1.16%/mmHg).

Increased mean percentage WT was present in sarcoidosis patients with and without PH, but higher in patients with PH. The degree of percentage WT is variable among different study populations. Most studies measured percentage WT at a most distal single image of the selected lobe instead of a full pullback.[17–21] Shen et al. studied the lower lobes of 40 PAH patients (25 with connective tissue disease (CTD) and 15 with other causes of PH, mean PAP 46.3±10.0mmHg and 53.5±16.4mmHg respectively) and 11 CTD patients without PH.[19] It showed significantly increased percentage WT in PAH-CTD patients (13.6%) and other PAH patients (14.4%) compared to CTD patients without PH (9.6%). Lau et al. investigated eight patients with idiopathic or CTD related PAH (mean PAP 48±3mmHg) compared to eight age and sex matched controls, and found significantly increased percentage WT in PAH compared to controls (34% vs. 17% p=0.001).[20] Notably, percentage WT in both PAH patients and apparently healthy controls was much higher compared to the present and previous studies.[17–19,21] While most studies focused on PAH patients, Domingo et al. investigated 46 pre-lung transplant patients with a wedge ≤15mmHg, including 18 COPD patients (eight with PH, mean PAP 26±2mmHg) and 28 interstitial lung disease (ILD) patients (13 with PH, mean PAP 27±2mmHg) compared to ten controls.[21] Percentage WT was higher in patients with PH, but also more pronounced in COPD compared to ILD. This indicates that percentage WT is not only related to pulmonary vascular remodeling due to PH, but also other pathophysiologic mechanisms in COPD or sarcoidosis, such as inflammation or vascular granulomas.

IVUS and haemodynamic measurements by RHC are able to capture pulmonary vascular properties to evaluate vascular stiffness, which is a resultant of vascular remodeling but also an important factor in the mechanobiological feedback system of PH.[22] Arterial stiffness is associated with mortality, even in patients with normal PVR.[16,23] In this study, PAC and RC time estimated by RHC were significantly different between patients with and without PH. It was previously shown that PAC has a greater dynamic range in patients with mild pulmonary vascular disease compared to PVR, and therefore could be more accurate to detect early phases of disease.[24] In this IVUS study, distensibility assessed by IVUS was the strongest discriminator for the presence of PH. The most robust correlation with PVR was present in the upper lobes (r=-0.56, p=0.002). Compliance showed a less robust but significant correlation. Previous studies showed significantly

reduced compliance and distensibility in patients with PAH compared to controls.[16,17,19,20] Again, mild decrease in mean PAP was associated with greater loss of compliance and distensibility, while in high mean PAP changes were very small.[19,20] This emphasises the rationale for early intervention and treatment during the course of PH. The effect of PH targeted therapy on wall thickening and pulmonary vascular properties is unclear. Lau et al. found no significant differences in percentage WT or pulmonary vascular properties after six months of bosentan therapy.[20] However, these patients had high mean PAP on baseline and given the strong inverse correlation of pulmonary vascular properties with haemodynamics, treatment in earlier stages of PH might result in more significant improvement. In the study of Rodes-Cabau et al, investigating 20 patients with primary PH (mean PAP 63mmHg), epoprostenol infusion significantly increased pulsatility by 53% and decreased pulmonary/elastic strain index by 41%.[18]

The exact mechanism of PH in sarcoidosis is not yet understood and is likely to be multifactorial.[25,26] To date, there are no other studies assessing pulmonary vascular properties in sarcoidosis. Domingo et al. showed worse outcomes on pulmonary arterial stiffness and lower percentage WT in ILD patients (no sarcoidosis patients) compared to COPD patients.[21] The results imply that pulmonary arteries in COPD are less stiff and have more functional reserve capacity, possibly explained by higher amounts of collagen fibers in pulmonary arteries of ILD patients. Hoffmann et al. confirmed different molecular mechanisms for pulmonary vascular remodeling in COPD and Idiopathic Pulmonary Fibrosis patients.[27] In PAH, there is a high correlation between perivascular inflammation and pulmonary vascular remodeling and mean PAP.[28] Persistent inflammation is also a major contributor for PH in CTD patients, and PAH patients without CTD showed slightly better pulmonary vascular properties.[19] In sarcoidosis, local vascular abnormalities might induce vascular remodeling contributing to PH. An autopsy study showed granulomatous vascular involvement in all sarcoidosis patients, with destruction of elastic fibers and healed lesions interrupted with fibrous tissue replacement.[1] Granulomas in the elastic pulmonary artery were found in only 30% of the cases. Healed lesions were more often observed in patients treated with steroids. Steroid treatment in sarcoidosis associated PH showed improvement in functional and haemodynamic outcomes in previous case series.[29,30] Vascular involvement and venous predisposition of granulomatous infiltration was also seen in a histopathologic study of Nunes et al.[30] investigating five pairs of transplanted lungs of sarcoidosis patients, and also in two lung biopsy studies.[11,12] An interesting finding in our data was the upper lobe predominance of abnormalities in percentage WT and pulmonary vascular properties. In contrast, a histopathologic study from 1958 showed more pronounced wall hypertrophy in lower lobes in physiological circumstances.[31] It was thought to be attributed

to higher hydrostatic pressure in upright position. Additionally, Bresolette et al. studied 30 patients with predominantly PH due to left heart disease and showed significantly higher percentage WT in lower lobes compared to upper lobes (17.1 ± 5.7% vs 14.3 ± 6.1%, p=0.01).[17] Our findings might be explained by the upper lobe predominance of sarcoidosis related abnormalities, as shown on chest-CT[2], and suggest vascular involvement leading to pulmonary vascular remodeling as one of the mechanisms of PH in sarcoidosis. This might be an interesting finding for future therapies. However, upper lobe predominance of vascular involvement could not be confirmed in an autopsy study on sarcoidosis patients.[1]

Previous IVUS studies of the pulmonary vasculature described no complications. In our study two patients developed a pulmonary embolism after the procedure despite correct use of low molecular weight heparin peri-procedural. A causative relation with IVUS cannot be confirmed or excluded. Sarcoidosis patients are known for an increased risk of venous thromboembolisms.[32] Therefore, less invasive methods to evaluate pulmonary vascular properties may be preferred especially in this subgroup of patients.

Limitations and future research

The present study investigates a group of sarcoidosis patients with and without PH, defined by a mean PAP of ≥25mmHg. This cut-off value is open for debate since mean PAP in healthy persons rarely exceeds 20mmHg,[33] and new definitions for precapillary PH (mean PAP >20mmHg and PVR ≥3 Wood Units) have been proposed.[34] We decided to follow the 2015 ESC/ERS PH guideline[25] since new definitions are not officially stated, and this cut-off is used in previous literature which allows us to make comparisons. Our study lacks a healthy control group. Due to the small sample size we were not able to perform corrections on other factors that might influence vascular remodeling, such as age. The 45Mhz catheter allowed us to analyse lumen diameters up to 6.2mm. More proximal parts of the pulmonary artery could not be imaged, while larger elastic pulmonary arteries may also contribute to the development of PAH.[35] Lower frequency IVUS catheters should be used for larger pulmonary arteries, however compromising in image quality. We did not study differences in distal or proximal segments. Previously it was shown that there was no difference in haemodynamics or pulmonary stiffness indices between distal and proximal remodeling subtypes, however distal remodeling subtype showed worse survival.[19] Furthermore, other studies take into account other stiffness indices less dependent of distending pressures and more representative for intrinsic changes of the elastic PA, such as elastic membrane or stiffness index β. These were also significantly increased in PAH patients.[19,20] In our study we did not capture this data, however granulomatous vascular involvement in sarcoidosis might have signifi-

cant effects on intrinsic vascular properties. IVUS measurements are time consuming and need specific analysis software, however some measurements can be taken during the procedure. Further research is needed for validation of measurements since there are currently no specific cut-off values for wall thickness or pulmonary vascular properties.

IVUS is an invasive investigation. Cardiac magnetic resonance imaging previously showed to be able to reliably predict mean PAP and PVR in the ASPIRE registry.[36] Additionally, in a same day RHC and phase contrast cardiac magnetic resonance study, Sanz et al. found increased values of pulmonary artery stiffness in patients with PH compared to patients without PH.[37] Cardiac magnetic resonance imaging might develop as a substitute for invasive diagnostic tools to detect early pulmonary vascular disease.

Conclusion

IVUS is able to investigate the more distal pulmonary vasculature in sarcoidosis patients, and showed an upper lobe predominance of increased wall thickness, decreased distensibility and compliance in sarcoidosis patients with PH. This finding correlates with typical patterns of sarcoidosis related abnormalities on chest-CT, and suggest the presence of sarcoidosis related vasculopathy as a contributor to the development of PH. Early recognition of pulmonary vascular changes might change the treatment regimen in the future. Further research is needed to establish cut-off values for IVUS measurements in the pulmonary circulation.

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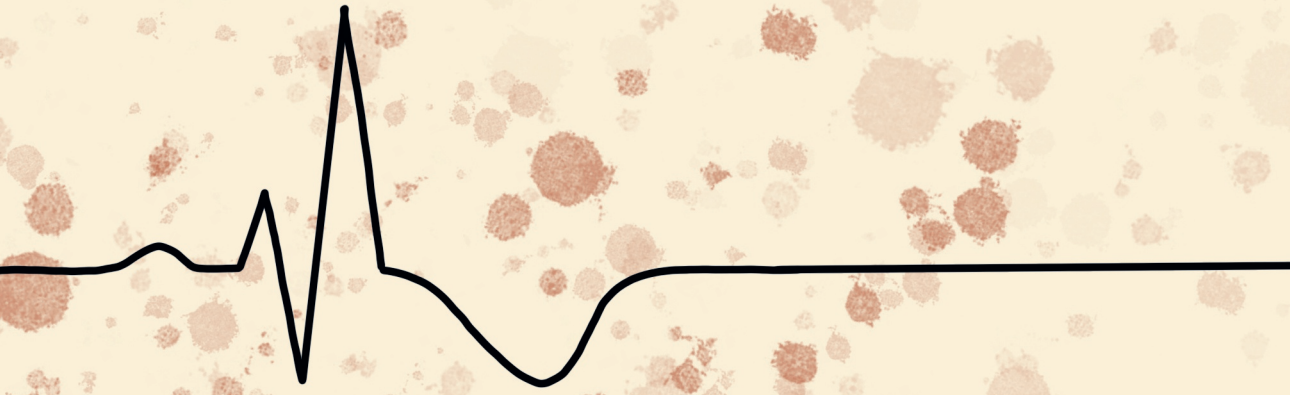
PART II

DIAGNOSIS



CHAPTER 5

Predicting pulmonary hypertension in sarcoidosis; value of PH probability on echocardiography

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Abstract

Background: Pulmonary hypertension (PH) is a well-recognised complication of sarcoidosis. Non-invasive diagnosis is challenging due to limited accuracy of echocardiography in interstitial lung disease.

Methods: This study evaluates the value of echocardiographic PH probability for diagnosing PH in pulmonary sarcoidosis. All consecutive patients between August 2015 and November 2018 were prospectively screened for PH, and classified as low, intermediate or high PH probability. Patients with intermediate or high PH probability were referred for right heart catheterisation. PH was defined as a mean pulmonary artery pressure of ≥25mmHg. Additional data on pulmonary function and chest-CT was collected.

Results: Of all 479 patients, PH was present in 17 and absent in 19 patients. Six patients refused right heart catheterisation. PH was present in 33% and 75% of patients with intermediate and high PH probability respectively (n=36). TRV max was measurable in 46% of all patients. Measurability did not correlate with FVC% predicted or presence of significant fibrosis. In intermediate and high PH probability, TRV max <2.9m/s successfully ruled out PH whereas a TRV max >3.4 confirmed PH in all patients. If TRV max was absent or in between 2.9 and 3.4, secondary echocardiographic signs were not able to improve the diagnostic accuracy.

Conclusion: PH is unlikely in patients with a TRV max <2.9m/s on echocardiography, whereas PH is highly suspected in a TRV max >3.4m/s. Discrimination is challenging if the TRV max is between 2.9–3.4m/s or absent. Additional secondary signs do not improve discrimination. Decision making for further investigations should be made by an expert team.

Introduction

Sarcoidosis is an inflammatory systemic disease with formation of granulomas in one or multiple organs, most often involving the pulmonary system.[1] Pulmonary hypertension (PH) is a well-known complication of pulmonary sarcoidosis[2] presenting in 3–74% of the patients, depending on the severity and stage of disease.[3–5] It is associated with a significant increase in mortality and morbidity.[6] The diagnosis PH is established by the gold standard right heart catheterisation (RHC), defined by a mean pulmonary artery pressure (PAP) of at least 25mmHg.[6] However, RHC is invasive, costly and resource limited. Transthoracic echocardiography is a commonly used method for non-invasive classification of PH probability. The 2015 ESC/ERS guideline uses the tricuspid regurgitation maximal velocity (TRV max) together with measurements of secondary echocardiographic signs for PH in order to classify patients into low, intermediate and high PH probability.[7] However, the accuracy of this guideline has not been validated extensively, especially in patients with interstitial lung diseases such as sarcoidosis. Also, correlations between invasively measured systolic PAP versus echocardiographic estimates of the pulmonary artery pressure in interstitial lung diseases vary.[8,9]

This prospective cohort study prospectively investigates the value of intermediate and high PH probability on echocardiography for detecting PH in a large consecutive group of sarcoidosis patients in a tertiary centre for both sarcoidosis and PH.

Methods

Study design and population

This is a prospective cohort study investigating PH probability on echocardiography in patients with pulmonary sarcoidosis. Between August 2015 and November 2018, all consecutive sarcoidosis patients referred to the pulmonology department of the St. Antonius Hospital Nieuwegein, a tertiary centre for both sarcoidosis and PH, were invited for PH screening. Furthermore, patients visiting the outpatient clinic with symptoms or signs of PH were referred for PH screening. Inclusion criteria were an age of 18 years or above and a (history of) histologically confirmed or confident clinical diagnosis of pulmonary sarcoidosis as stated by an expert team. Written informed consent was obtained in all participating patients. The study was in compliance with the principles outlined in the Declaration of Helsinki, and its ethics aspects were reviewed and approved by the MEC-U Institutional Review Board (NL49594.100.14).

Ethnicity was self-reported by patients. The pulmonary function test with the closest date to PH screening was assessed. Predicted values were calculated according to the American Thoracic Society and ERS guidelines.[10] An independent radiologist assessed the available chest X-rays and chest-CT's. Scadding classification on chest X-ray was used to classify patients into Scadding stage 0 (no nodal enlargement or parenchymal disease), I (hilar and mediastinal nodal enlargement only), II (nodal enlargement and parenchymal disease), III (parenchymal disease only), or IV (pulmonary fibrosis).[11] On chest-CT, presence of significant fibrosis was defined as >20%.

Echocardiography

As shown in Figure 5.1, screening consisted of thorough history taking, physical examination and echocardiography by the same experienced physician. Patients were classified into low, intermediate and high PH probability according to the 2015 ESC/ERS PH guideline for PH.[7] An echocardiogram was considered inconclusive if image quality was too poor or in presence of pulmonary valve stenosis. As shown in Table 5.1, the classification was based on the tricuspid regurgitation maximum velocity (TRV max) and/or secondary signs for PH on echocardiography. TRV max was measured if the signal was considered to be interpretable, e.g. a complete envelope or a partial envelope prone to extrapolation.[12] 'Secondary PH signs' was defined as one or more secondary PH signs of at least two different categories as shown in Figure 5.2.[7] Figure 5.2 illustrates the right heart metrics, measured according to the guideline for Echocardiographic Assessment of the Right Heart in Adults,[13] including right sided dimensions (mid- and basal right ventricular diameter, subcostal wall thickness, right ventricular outflow tract on long axis and short axis, right atrial dimension), right ventricular systolic function (tricuspid annular plane systolic excursion (TAPSE), pulsed Doppler peak velocity at the annulus) and other parameters (PA acceleration time, pulmonary regurgitation velocity, vena cava inferior dimension).

Table 5.1: Classification of pulmonary hypertension

ESC classification	Tricuspid regurgitation velocity	Secondary signs
Low probability	<2.9m/s	<2
	Absent	<2
Intermediate probability	<2.9m/s	≥2
	Absent	≥2
	2.9–3.4m/s	<2
High probability	2.9–3.4m/s	≥2
	>3.4m/s	<2 or ≥2

Classification of the PH probability as adapted from the ESC/ERS guideline for PH. Based on both the tricuspid regurgitation velocity and secondary signs for pulmonary hypertension on echocardiography patients are classified into low, intermediate or high probability of pulmonary hypertension.

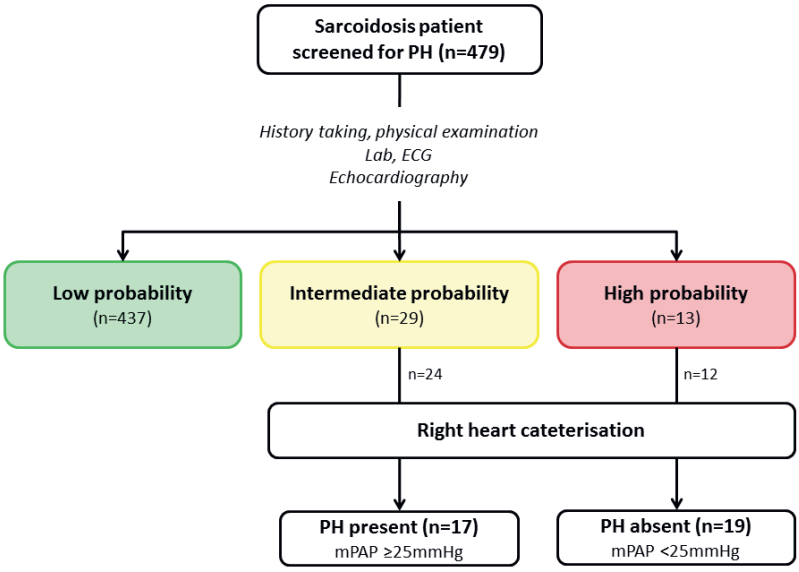


Figure 5.1: Flowchart pulmonary hypertension screening.

Haemodynamic

Patients with intermediate or high PH probability were referred for RHC, performed by one experienced interventional cardiologist. Haemodynamic data were collected, including mean PAP, right atrial pressure, pulmonary capillary wedge pressure or left ventricular end diastolic pressure, cardiac output and pulmonary vascular resistance (PVR). PH was defined as a mean PAP of at least 25mmHg. A post capillary component was suspected in case of an elevated pulmonary capillary wedge pressure or left ventricular end diastolic pressure of at least 15mmHg. All patients with PH were discussed in a multidisciplinary PH team for the final diagnosis.

Statistical analysis

Data were stored in the webbased datamanager REDCap. All statistical analyses were performed using IBM SPSS Statistics 24. Descriptive statistics were used for both continuous and categorical variables. The chi-squared test was used to compare categorical variables. The Student's t-test or Mann–Whitney U test was used to compare mean values of continuous variables. A two-tailed p-value of <0.05 was considered significant. Pearson correlation coefficient was calculated to determine correlations between variables.

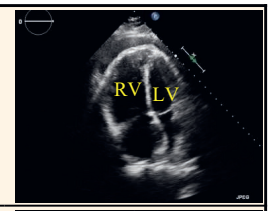
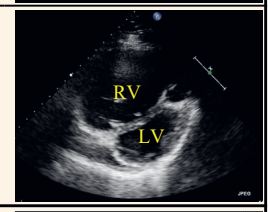
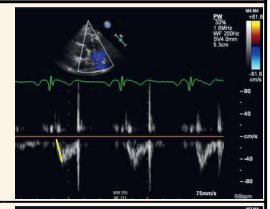
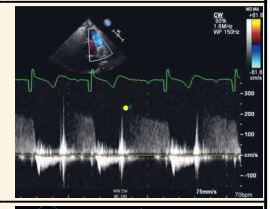
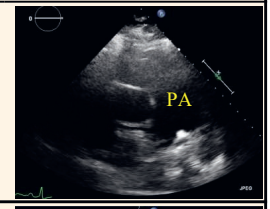
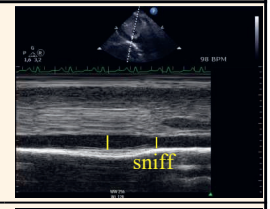
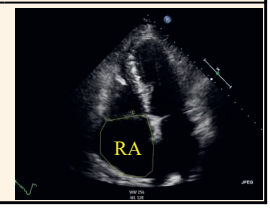
Ventricles	Right ventricle/left ventricle basal diameter ratio >1.0,	
	Flattening of the interventricular septum	
Pulmonary artery	Right ventricular outflow Doppler with acceleration time <105ms or mid-systolic notching	
	Early diastolic pulmonary regurgitation velocity >2.2m/s,	
	Pulmonary artery diameter >25 mm	
Inferior vena cava & right atrium	Inferior vena cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)	
	Right atrial area (end-systole) >18 cm^2	

Figure 5.2: Examples of right heart metrics measured on echocardiography, in accordance to Rudski et al.[13]

Results

PH screening

479 patients were screened for PH. Low, intermediate and high PH probability was present in 437, 29 and 13 patients respectively. Five patients with intermediate PH probability and one with high PH probability refused further diagnostic evaluation by RHC. In total, 36 patients with intermediate or high PH echocardiographic probability and available RHC were analysed (27.8% female, mean age 57.6±11.9 years). Using 25mmHg as a cut-off value for the mean PAP, PH was confirmed in 17 patients and ruled out in 19 patients. Baseline characteristics are given in Table 5.2.

Table 5.2: Baseline data and comparison between PH present and PH absent

	Low probability	Intermediate and high probability		p-value
	n=437	PH absent n=19	PH present n=17	PH absent vs PH present
Age (years)	49.4±11.5	58.7±12.9	58.7±12.9	0.601
Sex (female)	40.3	23.5	23.5	0.590
Ethnicity (caucasian)	89.7	88.2	88.2	0.306
Scadding stage (on X-ray)				0.431
0	0	0		
1	11.8	11.8		
2	23.5	23.5		
3	0	0		
4	64.7	64.7		
History of sarcoidosis (years)	6.8 (0.0–48.8)	13.4 (0.1–32.6)	13.4 (0.1–32.6)	0.050
Immunosuppressants (%)	60.0	68.8	68.8	0.983
FVC (% predicted)	96.3±18.7	75.5±17.2	75.5±17.2	0.001
FEV1 (%predicted)	87.8±20.9	61.6±16.3	61.6±16.3	<0.001
DLCO SB (% predicted)	74.4±16.1	54.0±20.5	54.0±20.5	0.023
Extend of disease on Chest-CT				0.223
<5%	5.9	5.9		
5–20%	23.5	23.5		
>20%	70.6	70.6		
RA pressure (mmHg)	-	6.7±2.4	6.7±2.4	0.024
Mean PAP (mmHg)	-	32.2±9.9	32.2±9.9	<0.001
PCWP (mmHg)	-	10.0±4.0	10.0±4.0	0.272
CO (L/min)	-	6.3±1.8	6.3±1.8	0.739
PVR (WU)		4.2±3.2	4.2±3.2	0.001

Data is expressed a percentage and as mean±standard deviation or median + range where appropriate. CO = cardiac output; DLCO SB = diffusion lung capacity for carbon monoxide single breath; forced expiratory volume in 1 second; FVC = forced vital capacity; PA = pulmonary artery; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RA = right atrium; RHC = right heart catheterisation; TTE = transthoracic echocardiography.

Echocardiography

In patients with intermediate PH probability PH was present in 33% of the patients, as for 75% in patients with a high PH probability. TRV max was measurable in 46% of all patients (n=479), and in 83% of patients who underwent RHC (n=36). If measurable, TRV max correlated good with systolic PAP (r=0.687, p<0.001) and mean PAP (r=0.721, p<0.001) (Figure 5.3). FVC% predicted was not significantly associated with the ability to measure TRV max (mean FVC% predicted 93.7%±18.7% if not measurable versus 97.1%±19.6% if measurable, p=0.058). The presence of >20% fibrosis on chest-CT (n=360) did not affect the measurability.

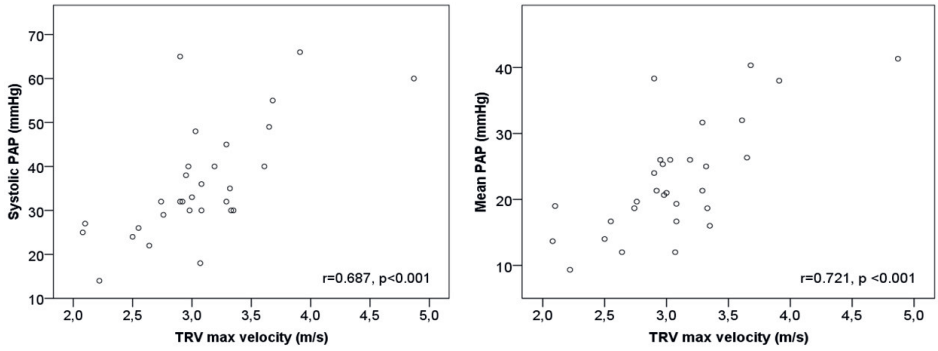


Figure 5.3: Scatter plot correlation TRV max versus systolic PAP and mean PAP (n=30).

Figure 5.4A distinguishes the different subgroups for intermediate and high PH probability. It shows that PH was absent in all patients with a TRV max <2.9 m/s, and PH was present in all patients with a TRV max >3.4m/s. The diagnostic challenge is apparent in the subgroup of patients with an absent TRV max or a TRV max between 2.9 and 3.4m/s (n=23). In these patients, PH was ruled out in 48%. In Figure 5.4B, a sub analysis was made using 20mmHg as a cut-off value for the mean PAP, which has recently been suggested as a new cut-off for normal pulmonary artery pressures.[14] This shows the same results for a TRVmax <2.9m/s or an absent TRVmax. However, in patients with a TRV max between 2.9 and 3.4m/s, the majority of the patients showed a mean PAP ≥20mmHg.

As shown in Table 5.3, none of the secondary signs differed significantly between PH present and PH absent. Also, taking secondary signs as a group (Figure 5.2), there were no differences for the ventricles, pulmonary artery and atria group. Following the ESC guideline, presence of at least two secondary signs in at least two different groups showed no difference between groups. Outcomes for all echocardiographic right heart metrics are given in a supplemental file (Table S5.1). Only right atrial length differed significantly between PH present and PH absent. Non-significant differences between

PH present and PH absent were found for TAPSE (20.9±4.1 vs 24.1±5.1, p=0.082), PA acceleration time (92.9±24.0 vs 105.3±18.1, p=0.094) and IVC diameter (16.0±4.5 vs 17.3±4.1, p=0.072). There was a significant correlation between mean PAP and TAPSE (r=-0.389, p=0.021) as well as PA acceleration time (r=-0.349, p=0.046). For the subgroup of patients in whom TRV max was absent or between 2.9–3.4m/s (n=23), none of the secondary signs for PH differed significantly between PH present and PH absent.

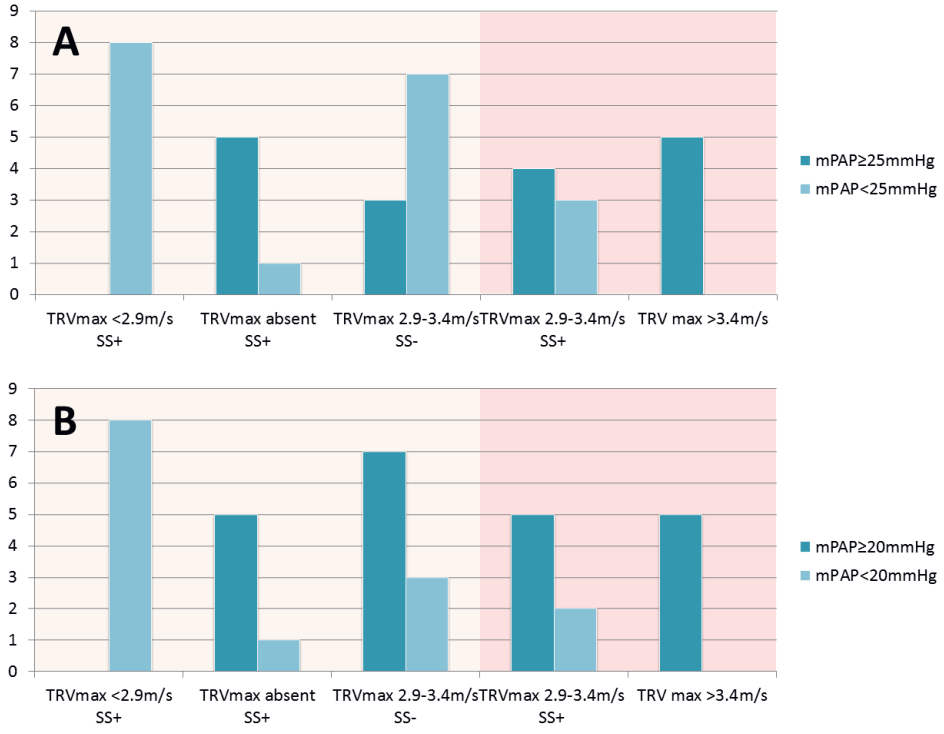


Figure 5.4: Elaboration of echocardiographic PH probability.
A: With the predinfed cut-off of a mean PAP of 25mmHg for diagnosing PH, in patients with an intermediate PH probability with a TRVmax <2.9m/s, abstaining from further investigation by right heart catheterisation safely excludes PH. a TRV max >3.4m/s has a high accuracy for diagnosing PH. If TRV max is absent or between 2.9–3.4m/s, the diagnostic accuracy of echocardiography is limited, even when adding secondary signs (SS).
B: When changing the mean PAP cut-off value to 20mmHg (the normal upper range), a TRV max between 2.9–3.4m/s has improved ability to predict elevated pressures

Discussion

Over the past decennia, predicting PH in sarcoidosis has been challenging, since symptoms and signs of PH and pulmonary sarcoidosis overlap. Echocardiography is one of the most used modalities for non-invasive estimation of the pulmonary artery pressure, but limitations and inaccuracies are frequently described. The diagnosis is

Table 5.3: Echocardiographic characteristics predicting PH

	PH absent n=19	PH present n=17	P-value
TRVmax (m/s)			
Absolute value	2.8±0.4m/s	3.5±0.6m/s	
Not measurable	5.3%	29.4%	
<2.9m/s	42.1%	0%	
2.9–3.4m/s	52.6%	41.2%	
>3.4m/s	0%	29.4%	
Ventricles	52.6%	47.1%	0.738
Right ventricle/left ventricle basal diameter ratio >1.0	31.6%	23.5%	
Flattening of the interventricular septum	26.3%	47.1%	
Pulmonary artery	61.1%	87.5%	0.082
RV outflow Doppler acceleration time <105ms or midsystolic notching	55.6%	78.6%	
Early diastolic pulmonary regurgitation velocity >2.2m/s	5.3%	23.5%	
Pulmonary artery diameter >25mm	15.8%	17.6%	
Inferior vena cava /right atrium	73.7%	62.5%	0.478
Inferior cava vein diameter >21mm with decreased inspiratory collapse	0%	0%	
Atrial area (end-systole) >18cm^2	73.7%	62.5%	

Secondary signs were not able to discriminate for the presence of PH. None of the abovementioned variables had a p-value <0.005. PH = pulmonary hypertension. The first column shows the percentage if at least one of the secondary signs is present for that group. The second column presents the percentages of that particular secondary sign. RV = right ventricle; TRV = tricuspid regurgitation velocity.

made by the gold standard RHC. However, this investigation is invasive, costly and resource limited.

Measuring TRV max can be challenging, especially in patients with interstitial lung diseases. For example, Arcasoy et al.[8] reported a measurable TRV max in 44% of the patients with advanced lung disease. Similarly, Nathan et al.[9] was able to measure TRV max in 40% of patients with idiopathic pulmonary fibrosis. Amsallem et al.[15] studied 192 patients with advanced lung disease versus 50 healthy controls in order to evaluate whether right heart metrics help to detect PH in advanced lung disease. TRV max was measurable in 52% of the patients with advanced lung disease, compared to 90% in healthy controls. Although they did not elaborate this finding, it might be suggested that severe lung disease could affect the acoustic windows on echocardiography. Compared to other interstitial lung diseases, disease extend in sarcoidosis can be less. With a measurability of TRV max in 46%, our cohort of 479 sarcoidosis patients showed

the same results as in other interstitial lung diseases. Since there was no significant association between FVC% predicted or the presence of >20% fibrosis on chest-CT with the ability to measure TRV max, the reason of this mechanism remains unclear. In patients who underwent RHC (n=36), TRV max was measured in 83%. This can be explained by selection bias since TRV max is one of the determents for intermediate or high PH probability.

If TRV max is measurable, the correlation with invasively measured pulmonary artery pressure may vary. In PAH a very strong correlation with systolic PAP has been described.[16–18] However, for patients with severe lung diseases results are inconsistent, ranging from weak to no correlation[8, 19] up to good correlation.[15] In our study we found a good correlation of TRV max with systolic PAP (r=0.687, p<0.001) and mean PAP (r=0.721, p<0.001). Accurate measurement of the TRV max signal on echocardiography is highly important in order to minimise the discrepancy.[15]

In our cohort a TRV max >3.4m/s confirmed PH in all patients. Keir et al.[20] investigated 265 consecutive ILD patients suspected for PH with confirmed PH in 73%. A TRV max >3.4m/s was associated with PH in 86% of the patients. In the cohort of Amsallem et al.[15] PH was present in 97% of the patients with a TRV max >3.4m/s.

In absence of pulmonary valve stenosis, a cut-off value of >3.4m/s for the TRV max seems to be highly suspicious for the presence of PH in patients with lung disease. As for a TRV max between 2.9–3.4m/s, this accuracy is less robust. In our study this subgroup showed PH in 59%. Keir et al. and Amsallem et al. found comparable rates of 69% and 54% respectively. This number increases if the cut of value for the upper range of a normal mean PAP is taken, e.g. 20mmHg.[14] Currently, there is a debate whether the definition of PH should be adjusted to this level.[21] A TRV max <2.9m/s with secondary signs safely excluded PH in our cohort of patients with intermediate or high PH probability. Due to ethical consideration, we did not performed RHC in patients with low PH probability (TRV max <2.9m/s or absent without secondary signs). Amsallem et al.[15] found PH in 17% of patients with a TRVmax <2.9m/s with positive right heart metrics. One could argue to abstain from invasive diagnosis of PH if the TRV max is below 2.9m/s.

The value of secondary signs for PH in order to improve the prediction of PH has not been studied vigorously. Most studies adapt the ESC/ERS PH guideline since not all measurements are available due to the retrospective study design. Keir et al.[20] used the 'modified' ESC criteria (TRV max and right ventricular dilatation or function). This showed significant differences between patient with or without PH, however it was not able to improve the diagnostic accuracy. Amsallem et al.[15] measured TRV max,

right ventricular dimension and function, and right atrial dimension. Indexed right atrial volume and TAPSE were associated with PH. However, the presence of right heart metrics were also not able to improve the detection of PH. Our prospective study focussed on obtaining complete echocardiographic data, and therefore there was no need to adapt the measurements as presented in the ESC/ ERS PH guideline. However, none of secondary signs was able to discriminate for the presence of PH. Therefore, it seems that secondary echocardiographic signs alone are insufficient for improving the PH probability classification on echocardiography. Adding other clinical parameters (such as cardiac biomarkers or findings on chest-CT) in this subgroup might help to distinguish for the presence of PH. To date, no solid clinical predictors have been found which could be incorporated in the screening protocol. The need for further investigation should be made by a multidisciplinary expert team on case by case basis, taking into account possible treatment options.

This study has several limitations. First, we acknowledge that we were only able to include a limited number of patients with PH, since sarcoidosis and PH are both rare diseases. Retrospective analysis would increase the number of inclusions, however due to the prospective study design we were able to guarantee qualitative and complete data. No firm conclusions can be made on a cohort of this size. This study aims to be hypothesis generating and emphasises the limited accuracy of echocardiography to discriminate for the presence of PH. Second, this study was performed in a tertiary centre for PH, with long-standing experience. Correct measurement of the TRV max can be challenging,[12] therefore outcomes might differ in non-specialised centres. Furthermore, using contrast is known to increase the ability to measure the TRV max. However, we did not use any contrast agents in this study.

Conclusion

In this prospective cohort study, PH is unlikely in patients with a TRV max <2.9m/s on echocardiography, whereas PH is highly suspected in a TRV max >3.4m/s. Discrimination for the presence of PH is more challenging if the TRV max is between 2.9–3.4m/s or absent. Additional secondary signs on echocardiography are not able to further discriminate for the presence of PH in this subgroup. Decision making for further investigations should be made on a case by case basis in a multidisciplinary expert team.

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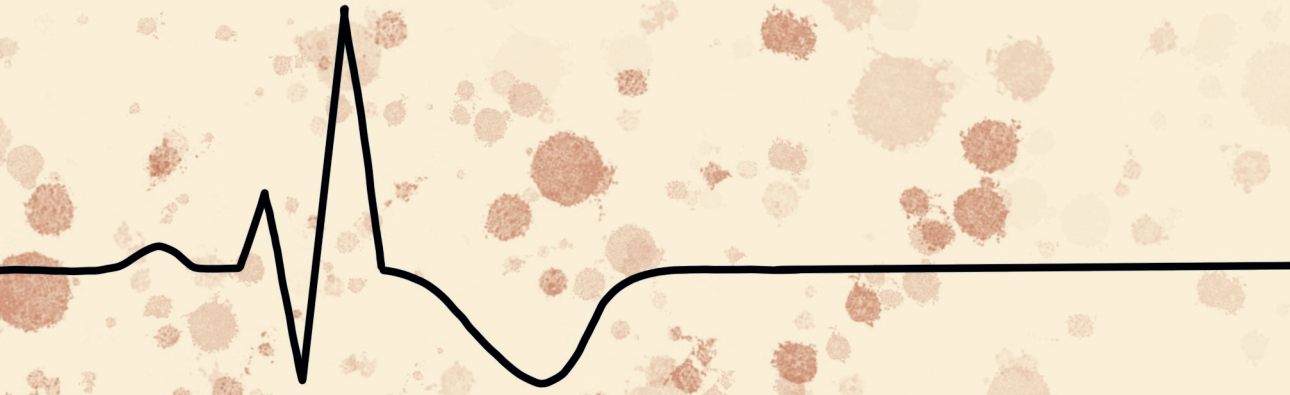
Appendix

Supplementary Table S5.1: Outcomes of all echocardiographic right heart metrics

Echocardiographic measurement	n	PH present n=19	PH absent n=17	p-value	Pearson correlation with mean PAP
Right ventricular dimensions					
Right ventricular diameter basal (cm)	33	4.5±0.6	4.5±0.7	0.715	0.028
Right ventricular diameter mid (cm)	26	2.9±0.4	2.8±0.4	0.623	0.330
RVOT long axis (mm)	36	31.9±3.8	34.3±6.1	0.176	-0.256
RVOT short axis proximal (mm)	35	33.3±5.9	34.8±5.2	0.540	-0.235
RVOT short axis distal (mm)	31	27.0±4.5	27.4±4.0	0.721	-0.083
Pulmonary trunk (mm)	8	28.6±7.7	23.8±5.6	0.297	0.575
Right atrium measurements					
RA area (cm^2)	34	19.1±5.1	20.6±4.3	0.334	-0.214
RA major (mm)	34	50.9±7.8	56.2±5.6	0.019	-0.242
RA minor (mm)	33	42.7±8.5	42.9±6.5	0.914	-0.234
RA volume indexed (mL/m^2)	34	28.0±16.0	29.0±12.9	0.270	-0.231
Right ventricular function					
TAPSE (cm/s)	35	20.9±4.1	24.1±5.1	0.082	-0.389
Pulsed Doppler peak velocity at the annulus (m/s)	34	11.9±3.4	12.9±2.7	0.641	-0.305
Other measurements					
PA acceleration time (ms)	33	92.9±24.0	105.3±18.1	0.094	-0.349
Maximum pulmonary regurgitation velocity (m/s)	10	2.0±0.4	1.7±0.4	0.394	0.657
End diastolic pulmonary regurgitation velocity (m/s)	9	1.4±0.4	1.1±0.2	0.221	0.814
Inferior vena cava diameter (mm)	29	16.0±4.5	17.3±4.1	0.072	-0.226

Right heart metrics in 36 patients with intermediate and high PH probability. PA = pulmonary artery; RA = right atrium; RVOT = right ventricular outflow tract; TAPSE = tricuspid annular plane systolic excursion.



CHAPTER 6

Echocardiographic estimate of pulmonary artery pressure in sarcoidosis patients – real world data from a multi-national study

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Abstract

Introduction: Echocardiographic measurement of the right ventricular systolic pressure (RVSP) is commonly used for estimating systolic pulmonary artery pressure (PASP) measured during right heart catheterisation (RHC) in patients suspected for pulmonary hypertension (PH). Generally, there seems to be a strong correlation. However, this has been reported as less robust in sarcoidosis. We aim to investigate the correlation between RVSP and RHC measurements using real world data and analysed factors influencing the relationship between RVSP and PASP in sarcoidosis.

Methods & Results: Data of patients with and without sarcoidosis associated PH who had both a measurable echocardiographic RVSP and invasive PASP were collected from the RESAPH registry, PULSAR study and Cincinnati Sarcoidosis Clinic database (n=173, 60.1% female, mean age 56.0±9.5 years). Among them, 124 had PH confirmed by RHC. There was a strong correlation between RVSP and PASP (r=0.640). This correlation was significant in both male and female, white or non-white, forced vital capacity (FVC) >60%, and presence of fibrosis (p<0.001). However, it was less robust in patients with FVC of 50% or less. RVSP was considered inaccurate if the difference with PASP was >10mmHg. Inaccurate echocardiographic estimation of the invasive PASP occurred in 50.8%, with overestimation mostly in patients without PH, and underestimation in patients with severe PH. An RVSP>50mmHg was associated with worse survival.

Conclusions: In this real world multicenter cohort of sarcoidosis patients, we found a significant correlation between RVSP as determined by echocardiography and invasive PASP. Over- or underestimation of PASP occurred frequently. Therefore, echocardiographic RVSP measurement alone to screen for PH in sarcoidosis should be used with caution.

Introduction

Pulmonary hypertension (PH) is a well-known complication of sarcoidosis, and is related to a significant increase in mortality and morbidity.[1,2] The diagnosis PH can be established by the gold standard right heart catheterisation (RHC), defined by a mean pulmonary artery pressure (mPAP) of at least 25mmHg, as defined by the 2015 ESC/ERS guideline.[3] However, RHC is invasive, costly and resource limited. A good non-invasive estimation of the pulmonary artery pressure might lower the burden of RHC. Transthoracic echocardiography is a commonly used method for noninvasive estimation of the pulmonary artery pressure. By using the simplified Bernoulli equation on the tricuspid regurgitation maximal velocity (TRV max) added by the right atrial pressure (RAP), the right ventricular systolic pressure (RVSP) can be calculated. Furthermore, echocardiography provides additional information about the heart dimension and function.[4]

In pulmonary arterial hypertension (WHO group 1) there is generally a strong correlation between echocardiographic RVSP and systolic pulmonary artery pressure (PASP) as determined by RHC, especially under controlled study conditions.[5-7] However, the relationship has been reported as much less robust in sarcoidosis patients and other interstitial lung diseases. In clinical practice, differences between RVSP and PASP of 10mmHg or more are frequently encountered.[8-11]

In the present study, we aimed to investigate the correlation between RVSP and RHC measurements in using real world data and analysed factors that may influence this relationship. We recruited patients with sarcoidosis associated PH (SAPH) from the ReSAPH database, which reports on data from many different sites all over the world. Besides these patients, we retrieved data on sarcoidosis patients without PH but with both echocardiographic as invasive haemodynamic data from the PULSAR study and the Cincinnati Sarcoidosis database.

Materials and Methods

Study design and population

This is a retrospective multinational study with real world data investigating the association and factors which may influence the echocardiographic estimate of RVSP compared to PASP, including parenchymal lung disease. Data of patients with sarcoidosis associated PH were collected from the REgistry for SArcoidosis associated Pulmonary Hypertension (RESAPH), a large international multicenter registry, aiming to enroll

patients with SAPH from different regions of the world. Reports on baseline characteristics were published previously.[12] The ReSAPH registry is registered as NCT01467791 (https://clinicaltrials.gov). Databases of the PULSAR study (NTR5295 www. trialregister.nl), a large prospective study investigating the presence of PH in sarcoidosis patients in a Dutch tertiary centre,[13] and Cincinnati Saroidosis Clinic (an in-hospital registry for heamodynamic data collected in sarcoidosis patients) were examined in order to add additional sarcoidosis patients without PH as confirmed by RHC (Figure 6.1).

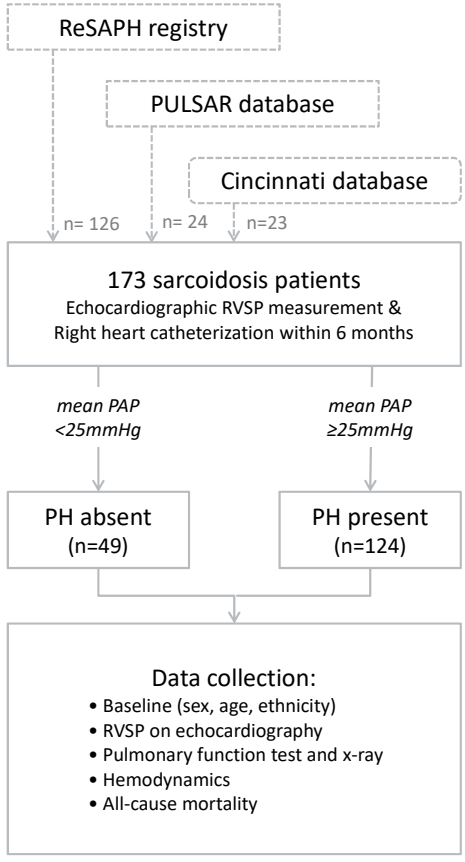

Figure 6.1: Flowchart of patient selection and data collection.

Patients were included if they had undergone both RHC and echocardiography with RVSP estimation within a timeframe of six months. Furthermore, we collected data on sex, age, ethnicity, Scadding stage,[14] forced vital capacity percent predicted (FVC%), and presence of fibrosis on chest imaging within this timeframe. Not all of the patients had recorded data on spirometry or imaging. Data on survival was collected and scored as alive or the composite endpoint dead/transplanted at the last day of visit.

Haemodynamics

RHC data on RAP, systolic, mean and diastolic PAP, pulmonary capillary wedge pressure, cardiac output and pulmonary vascular resistance were collected. PH was defined as a mPAP ≥25mmHg. A mPAP between 25mmHg and 35mmHg was considered as mild to moderate PH, whereas a mPAP ≥35mmHg was considered severe PH.[15]

As for transthoracic echocardiography, measurement of the TRV max was recorded. As shown in Figure 6.2, RVSP was calculated using the simplified Bernoulli equation (PASP = 4 X TRV max^2 + RAP), with RAP estimated based on the size and collapse of the inferior vena cava.[4] No data was captured on the use of contrast methods during echocardiography nor other contributing factors such as volume status for the measurement of the TRV.

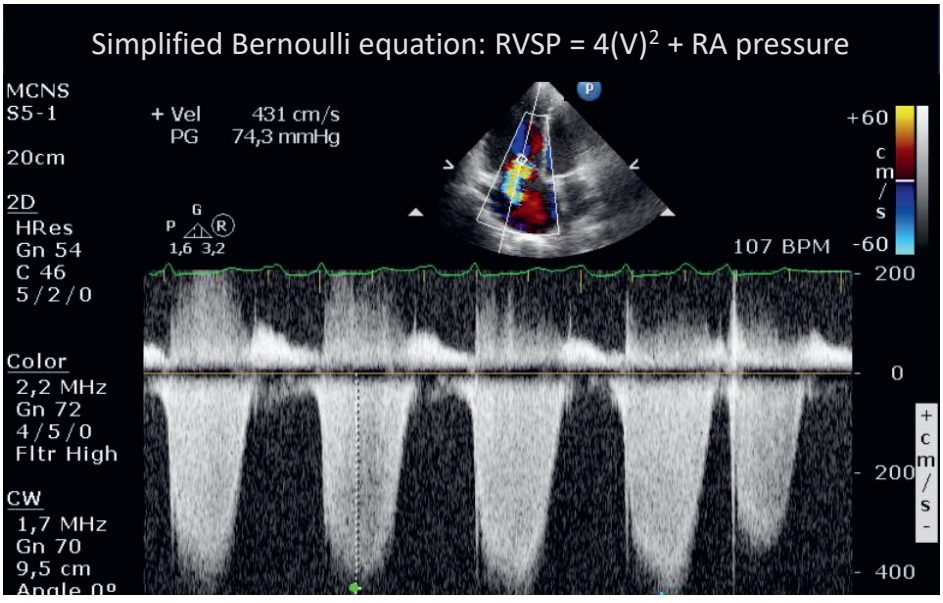

Figure 6.2: Echocardiographic measurement of the tricuspid regurgitation velocity and calculation of RVSP using the simplified Bernoulli equation.

Statistics

Comparison between groups was made using Student T-test, Mann Whitney U test and Chi-squared test where appropriate. Pearson correlations were determined for the overall group and for different subgroups. Bland-Altman analyses were performed to evaluate the agreement between echocardiography derived RVSP and PASP on RHC. Survival was compared between groups using Kaplan-Meier curves including log rank test. Hazard ratio's (HR) including 95% confidence interval (CI) were calculated using

Cox regression analysis. Regardless the total time of follow up, patients who were still alive at time of the analysis were censored as alive for further analysis. Statistics were calculated using IBM SPSS Statistics 24.

Results

Baseline characteristics

A total of 274 patients with sarcoidosis were identified from the three databases who had both RVSP measurements on echocardiography and invasive RHC measurements between June 2002 and September 2018. In 101 patients, the date difference between echocardiography and RHC exceeded our pre-determined maximum time interval of six months. Of the remaining 173 patients (mean time interval between echo and RHC of 52 days, ranging from 0 to 183 days), 124 had confirmed PH. The other 49 patients had no PH. After recalculation of the mPAP in all patients, two of the RESAPH patients turned out to have a mPAP <25mmHg. Baseline characteristics of patients are presented in Table 6.1.

Haemodynamic assessment

Haemodynamic characteristics are listed in Table 6.1. Among patients with PH, 32 had a pulmonary capillary wedge pressure >15mmHg. As shown in Figure 6.3, there was only a moderate correlation between RVSP versus PASP and mPAP (r=0.640 and 0.626 respectively, p<0.0001).

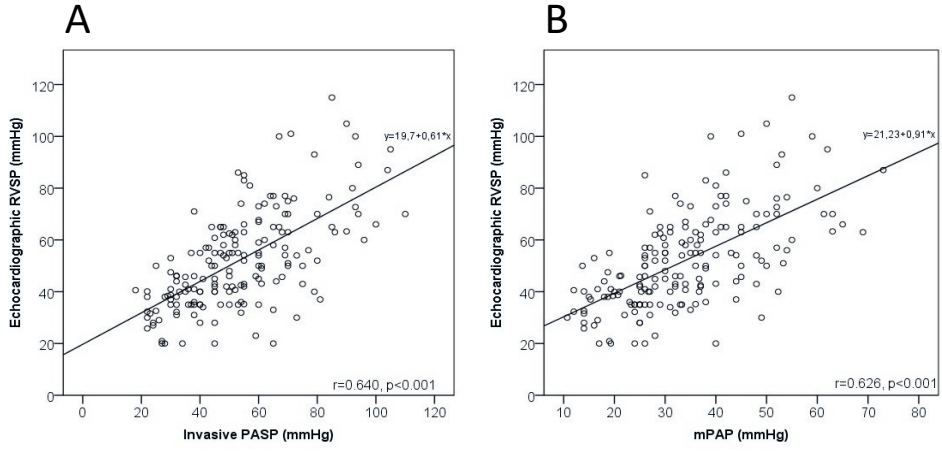

Figure 6.3: Scatter plot RVSP versus PASP (A) and mPAP (B), showing a moderate correlation between measurements.

Table 6.1: Baseline characteristics

Baseline parameters	All patients (n=173)	PH present (mPAP≥25mmHg) (n=124)	PH absent (mPAP<25mmHg) (n=49)	p-value PH present vs PH absent
Sex (% female)	60.1	62.9	53.1	0.234
Age (years)	56.0±9.5	56.4±9.2	55.2±10.3	0.524
Ethnicity (%)				0.003
White	43.4	35.5	63.3	
Black	40.5	47.6	22.4	
Other	16.2	16.9	14.3	
Scadding stage (%)				0.009
0	4.2	2.5	8.3	
I	8.3	5.0	16.7	
II	12.5	11.7	14.6	
III	14.9	13.3	18.8	
IV	60.1	67.5	41.7	
Fibrosis on chest CT >20% (%)	60.3	64.2	51.1	0.123
FVC (% predicted)	66.6±21.4 (n=151)	61.2±18.5	79.9±22.6	0.067
DLCO (% predicted)	50.7±51.4 (n=123)	45.9±19.9	48.5±26.4	0.034
RVSP (mmHg)	52.0±18.7	57.5±18.4	38.2±10.3	<0.001
MPAP (mmHg)	32.5±12.1	37.9±10.3	19.3±4.1	<0.001
PASP (mmHg)	53.2±19.3	61.8±16.3	32.0±7.3	<0.001
Cardiac output (L/min)	5.7±1.7 (n=172)	5.5±1.6	6.1±1.7	0.442
PCWP (mmHg)	11.7±6.7 (n=172)	12.7±7.2	9.0±3.9	<0.001
PVR (wood units)	4.3±3.2 (n=172)	5.2±3.3	1.9±1.2	<0.001

Data is expressed a percentage and as percentage or mean±standard deviation. DLCO = diffusion lung capacity for carbon monoxide; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PASP = systolic pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance.

Correlation between RVSP and PASP

We compared the RVSP and PASP including correlation based on sex, white versus non-white, FVC% greater or less than 60, 50 or 40, and presence or absence of fibrosis. Table 6.2 summarises the correlation within these subgroups. While almost all correlations were significant (p<0.001), for the small sample size of 15 patients with a FVC% of less than 40%, there was no longer a significant correlation between RVSP and PASP.

The difference between echocardiographic RVSP and invasive PASP reflects the accuracy of echocardiography for assessing invasively measured PASP. As an absolute value, the mean difference for both over- and underestimation of RVSP compared to PASP in this

cohort was 12.9±1.0mmHg. This difference did not correlate with the number of days between echocardiography and RHC (r=-0.057, p=0.455).

There was a significant correlation for the difference between RVSP and PASP compared to both PASP and mPAP with a Pearson correlation coefficient of r=-0.475 and r=-0.462 respectively (p<0.001).

Table 6.2: Pearson correlations for RVSP and PASP within specific subgroups

	Female	White	FVC≤60%	FVC≤50%	FVC≤40%	Fibrosis>20%
Yes	n=104 (r=0.541)	n=75 (r=0.634)	n=59 (r=0.544)	n=34 (r=0.520)†	n=15 (r=0.404)††	n=94 (r=0.560)
No	n=69 (r=0.692)	n=98 (r=0.559)	n=98 (r=0.559)	n=115 (r=0.607)	n=134 (r=0.616)	n=62 (r=0.569)

FVC = forced vital capacity; RVSP = right ventricular systolic pressure p<0.001 for all, except for †p=0.02; ††p=0.135.

Figure 6.4 shows the difference between RVSP and PASP values compared to invasively measured PASP. The green line reflects the acceptable variance of 10mmHg between measurements.[8,10,11] Taking this into account, echocardiographic over- and underestimation of PASP occurred in 23.7% and 27.2% respectively. Therefore, within a 10mmHg variance limit, RVSP on echocardiography correctly reflects the invasive PASP in only 49.1% of the patients. Overestimation tended to occur mostly in lower PASP values, whereas underestimation mainly occurred in higher PASP values. FVC% predicted or presence of >20% fibrosis on chest CT did not correlate significantly with the difference between RVSP and PASP (Figure 6.3B and C).

Figure 6.5 shows the number of patients expected to have PH based on different cut-off values for RVSP in each of the subgroups 'no PH (n=49), 'mild to moderate PH' (n=56) and 'severe PH' (n=68). The figure shows that, for example using an RVSP cut-off value of 40mmHg (which is frequently used in literature), it tremendously overestimates the presence of PH in group A (no PH with mPAP <25mmHg), whereas a cut off value of 60mmHg significantly underestimates the presence of PH in group C (severe PH >35mmHg). Based on these results, there is no clear cut off value for RVSP to predict the presence of PH and therefore it cannot be used as a diagnostic tool.

Survival

Data on survival, defined as alive or dead/ transplanted on the last day of visit, was available for 167 patients, with a mean follow up of 3.5±3.2 years. Figure 6.6A displays the overall survival of all patients up to a maximum follow up of ten years. Patients

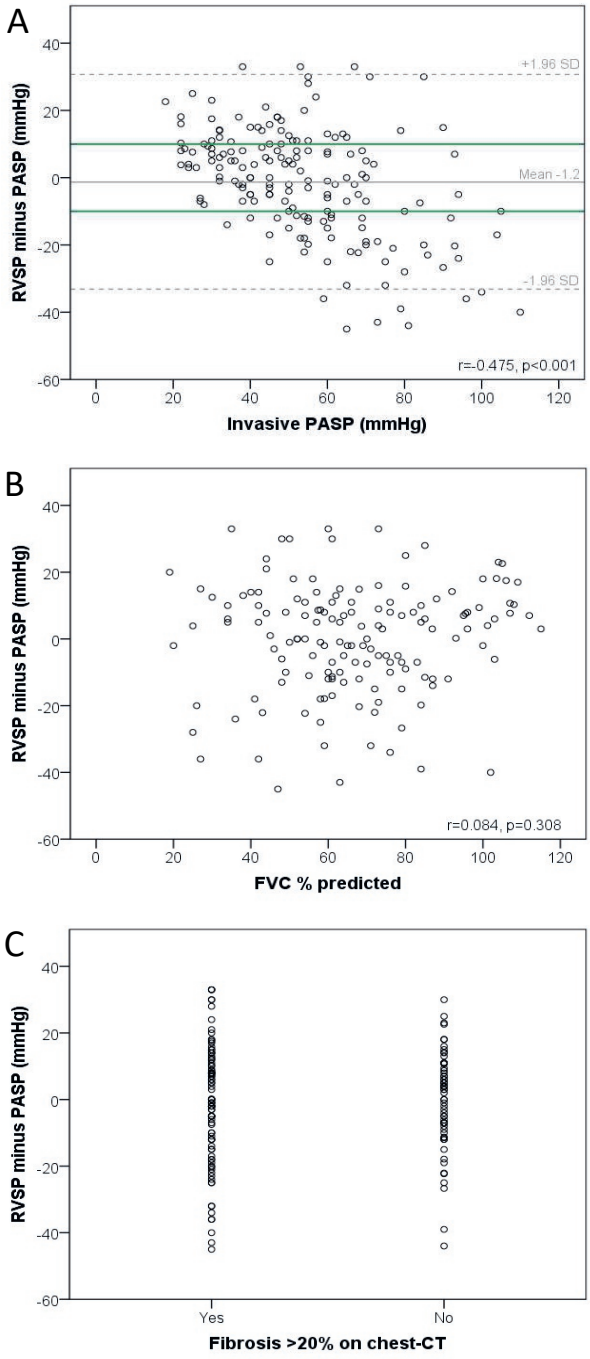

Figure 6.4: A. Bland Altman analysis for the difference in RVSP versus PASP compared to the PASP (r=-0.475, p<0.001). Grey lines: mean ±1.96SD. Green lines: reference line for acceptable variance of 10mmHg; **B.** Scatterplot for the difference between RVSP and PASP compared to FVC% predicted. There is no significant correlation; **C.** Plot for difference between RVSP and PASP related to presence of significant fibrosis on chestCT with a cut- off value of 20%. This figure shows no significant difference.

with PH had significantly worse outcomes (p=0.009) with a 1, 2, 5 and 10 year survival of 87.5%, 71.4%, 47.8% and 32.4% for patients with PH. Figure 6.6B further divides the group into no PH (mPAP <25mmHg), mild to moderate PH (mPAP ≥25 and <35mmHg), and severe PH (mPAP ≥35mmHg), with a significant difference in survival between these groups (p<0.001). Survival was comparable between patients without PH and mild to moderate PH. However, for those with severe PH, survival was significantly worse (HR 3.1; 95% CI 1.835–5.115; p<0.001). There was no significant difference in survival based on sex, age or ethnicity. A significant difference in survival using Cox Regression analysis was found for mPAP (HR per percent 1.04; 95% CI 1.02–1.06; p<0.001), FVC% (HR per percent 1.02; 95% CI 1.01–1.04; p=0.002), DLCO% predicted (HR per percent 1.011, 95% CI 1.003–1.019, p=0.004) and RVSP (HR per percent 1.02; 95% CI 1.004–1.03; p=0.11). An RVSP>40mmHg was not significantly associated with worse mortality (HR 1.75; 95% CI 0,983.07; p=0.06) (Figure 6.6C). For an RVSP of >50mmHg, a significant difference in mortality was found (HR 2.2; 95% CI 1.33–3.74, p=0.002).

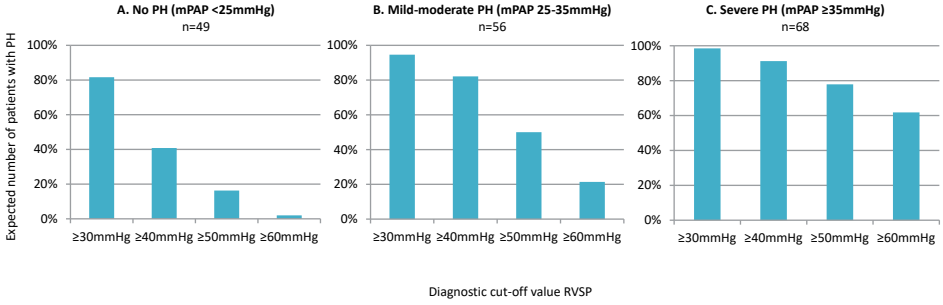

Figure 6.5: Overview of the number of patients expected to have PH (Y-axis) based on different cut-off values for RVSP (X-axis) within the subgroups no PH **(A)**, mild to moderate PH **(B)** and severe PH **(C)**. This figure shows that echocardiographic RVSP overestimates the presence of PH in patients with no PH (group A), whereas it underestimates the presence of PH in patients with severe PH (group C).

Discussion

PH in sarcoidosis is associated with increased mortality and morbidity. RVSP measurement on echocardiography is widely used for non-invasive estimation of the PASP. In this study, we focused on the relationship between echocardiographic RVSP and invasive PASP using real world data, including possible factors by which this relationship might be influenced. As a result, the correlation between RVSP and PASP in our cohort of 173 sarcoidosis patients was moderate (r=0.640; p<0.001). Over- or underestimation by echocardiography occurred in the majority of patients. Survival was significantly worse in sarcoidosis patients with an invasive mean PAP of ≥35mmHg. An RVSP of 40 mmHg or higher tended to be associated with worse survival.

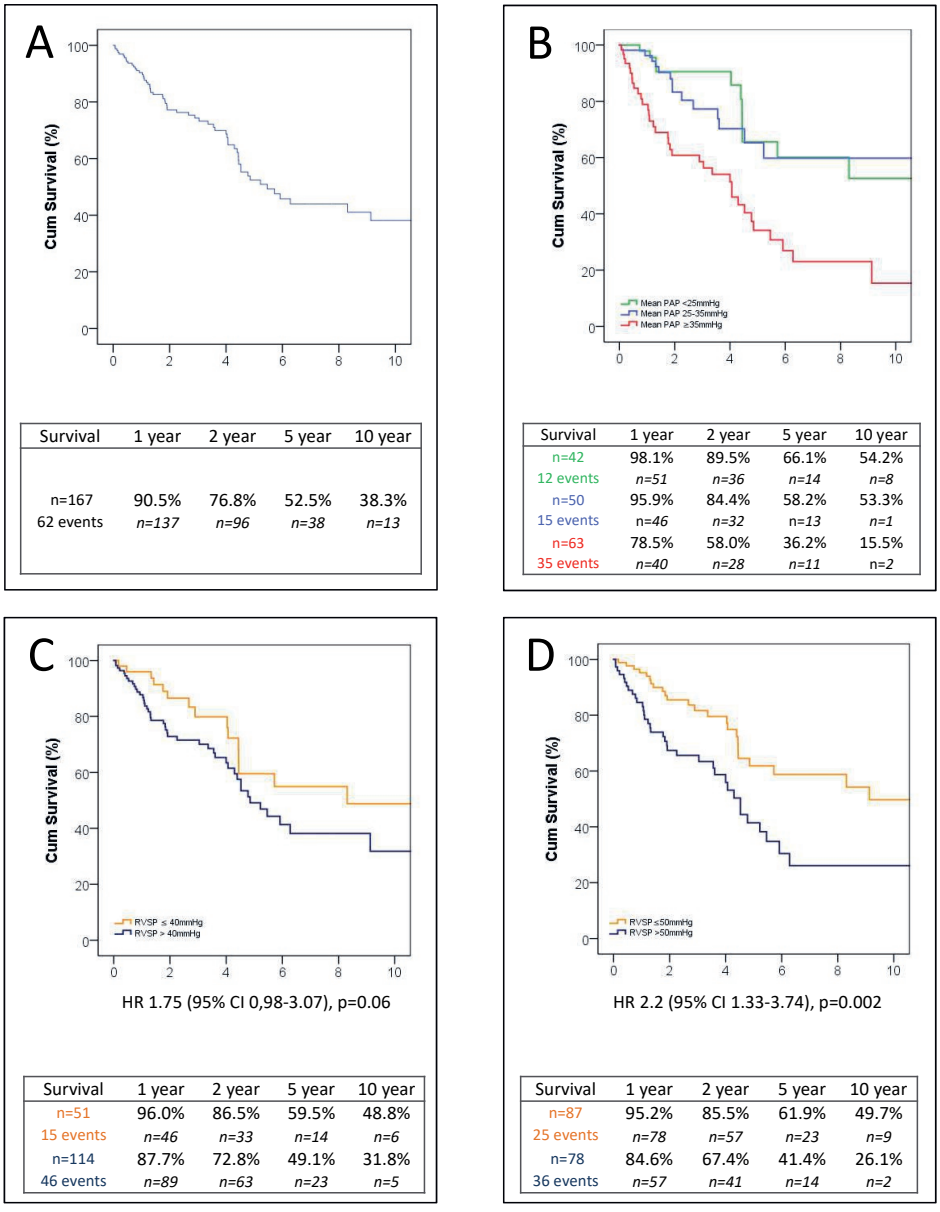

Figure 6.6: Kaplan Meier survival curves with comparison between different subgroups.
A. All patients; **B.** Divided by severity of PH (no PH, mild-moderate PH and severe PH), with a significant decrease in survival for severe PH ; **C.** RVSP>40mmHg (no significant difference in survival); **D.** RVSP>50mmHg (significant difference in survival).

Under controlled study circumstances, a strong correlation of RVSP with PASP has been described.[5-7] A meta-analysis conducted in 2011[16] demonstrated an overall strong correlation in PH patients (r=0.70, 95% CI 0.67–0.73). In line with our findings, this

meta-analysis also showed that the correlation decreased in patients with high PASP and different lung diseases, varying between r=0.48 to r=0.69, depending on the type and stage of lung disease.[8,17,19] Part of the inaccuracy might be explained by incorrect measurement of the tricuspid regurgitation velocity signal, where measurement of the "chin" or "beard" of the tricuspid regurgitation signal can make a significant difference.[18] Amsallem et al.[20] re-measured all TRV signals in a standardised manner,[21] resulting in a very strong correlation of r=0.88 ($p<0.0001$) in a cohort of 192 patients with advanced lung disease. In our cohort of sarcoidosis patients, the correlation weakened if FVC% predicted decreased. In a small cohort of patients with FVC% predicted <40%, the correlation was no longer significant.

The ability of RVSP to accurately correlate with the PASP is disputable. Differences up to 10 mmHg between echocardiographic RVSP and invasive PASP have been marked as an acceptable range between both measurements in previous studies.[8,10,11] Following this cut-off value in our cohort, over- and underestimation using RVSP on echocardiography occurred in 23.7% and 27.2% of the patients respectively. This is in line with other studies, describing differences of 10 mmHg or more in up to 50% of patients with or without interstitial lung disease.[8,10,11,19] In our cohort, a difference of more than 10 mmHg was more likely in patients with higher PASP values, mostly due to underestimation. This finding is in line with a study of Rich et al.[11] and could be due to equalisation of right ventricular and right atrial pressures due to severe tricuspid regurgitation.[22] On the other hand, overestimation of PASP values in patients without PH may lead to unnecessary invasive diagnostic investigations.

Another limitation of echocardiography is that RVSP measurements frequently cannot be obtained, especially in patients with lung disease. The present study did not capture this data, however several studies have reported that Doppler tricuspid regurgitation signal for measuring RVSP is interpretable in only 30–50% of patients with advanced lung disease,[8,10,20] compared to 80–90% in those without advanced lung disease (20). If an adequate RVSP measurement is possible, no clear cut-off value has been established for diagnosing PH. A cut-off value of 40 mmHg is frequently used, with varying but insufficient data on accuracy in patients with lung disease.[8,10] A meta-analysis evaluating the diagnostic accuracy of echocardiography for RHC concluded that this cutoff value performed only modestly in predicting PH. Other cut-off values, ranging from 32 to 50mmHg, were not able to improve diagnostic accuracy.[16] International guidelines use other echocardiographic signs for right ventricular overload and pulmonary vascular resistance to improve the diagnostic accuracy.[3]

As for long-term outcome in SAPH, previous studies have shown SAPH to be associated with significant increase in mortality, especially in patients with severe PH.[1,23] Our study confirms this association. There was a trend to worse outcome in patients with an RVSP >40mmHg on echocardiography (HR 1.73; 95% CI 0.98–3.07; p=0.06), while an RVSP >50 mmHg was significantly associated with lung transplantation-free survival (HR 2.2; 95% CI 1.33–3.74), p=0.002).

Concluding this manuscript considering previous literature, echocardiography is an affordable and non-invasive method to screen for PH in sarcoidosis, and might be helpful in estimating prognosis in patients with SAPH. However, measurements by echocardiography have significant limitations and cannot be used as a one-on-one replacement for RHC. RVSP on echocardiography only approximates PASP. As the pulmonary disease progresses and the FVC% decreases, while simultaneously the likelihood of PH increases, RVSP measurements showed less correlation with PASP in sarcoidosis patients. Underestimation frequently occurred. Therefore, echocardiography derived RVSP should not be used as the only diagnostic tool. On the other hand, absence of an RVSP signal or a low RVSP measurement with high clinical suspicion should not refrain a clinician from further diagnostics since overestimation also occurs frequently. Furthermore, echocardiography is unable to quantitatively assess pulmonary capillary wedge pressure (PCWP) and pulmonary vascular resistance, which are important parameters in the classification of PH. However, echocardiography is able to detect left ventricular heart disease as a potential cause of an increased PCWP. Therefore, in sarcoidosis patients with a clinical suspicion for PH, RVSP measurement on echocardiography should not be the only factor to decide if further diagnostic evaluation is required.

This study has several limitations, inherent to the retrospective and multicenter registry design. First, we only included patients with a measurable RVSP. Second, since this study reflects real world data representative for the day to day practice of a health care provider with only a report of the echocardiogram available, the RVSP measurements were not standarised and based on the local protocols. It was not re-measured in a standardised manner throughout all participating centers and no data was captured for the use of contrast methods or other contributing factors such as volume status. Supposedly, there is a lot of variability in this measurement in both measurement technique and physiological circumstances influencing the correlation. Furthermore, we choose a maximum of six months' time interval between echocardiography and RHC. This is a relatively large time interval, which is also known to influence the correlation.[16,21] Also, there is no data on treatment within this time interval.

Conclusion

In this multicenter cohort of sarcoidosis patients, we found a significant correlation between RVSP as determined by echocardiography and PASP measured by RHC. Over- or underestimation was encountered in more than half of the patients. Therefore, using echocardiographic RVSP measurement alone to screen for PH in sarcoidosis should be used with caution, especially in those with severe lung disease.

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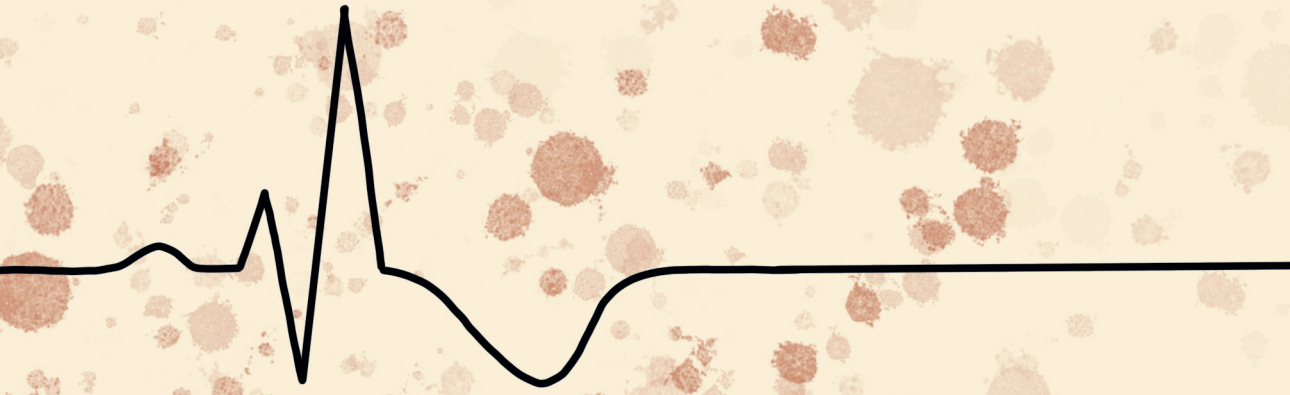

CHAPTER 7

Value of echocardiography using knowledge-based reconstruction in determining right ventricular volumes in pulmonary sarcoidosis: comparison with cardiac magnetic resonance imaging

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Abstract

Background: Right ventricular (RV) dysfunction in sarcoidosis is associated with adverse outcomes. Assessment of RV function by conventional transthoracic echocardiography (TTE) is challenging due to the complex RV geometry. Knowledge-based reconstruction (KBR) combines TTE measurements with three-dimensional coordinates to determine RV volumes. The aim of this study was to investigate the accuracy of TTE-KBR compared to the gold standard cardiac magnetic resonance imaging (CMR) in determining RV dimensions in pulmonary sarcoidosis.

Methods: Pulmonary sarcoidosis patients prospectively received same-day TTE and TTE-KBR. If performed, CMR within 90 days after TTE-KBR was used as reference standard. Outcome parameters included RV end-diastolic volume (RVEDV), end-systolic volume (RVESV), stroke volume (RVSV) and ejection fraction (RVEF).

Results: 281 patients underwent same day TTE and TTE-KBR. In total, 122 patients received a CMR within 90 days of TTE and were included. TTE-KBR measured RVEDV and RVESV showed strong correlation with CMR measurements (R=0.73, R=0.76), while RVSV and RVEF correlated weakly (R=0.46, R=0.46). Bland-Altman analyses (mean bias ±95% limits of agreement), showed good agreement for RVEDV ($\Delta RVEDV_{KBR-CMR}$, 5.67±55.4mL), while RVESV, RVSV and RVEF showed poor agreement ($\Delta RVESV_{KBR-CMR}$, 21.6±34.1mL; $\Delta RVSV_{KBR-CMR}$, -16.1±42.9mL; $\Delta RVEF_{KBR-CMR}$, -12.9±16.4%). The image quality and time between CMR and TTE-KBR showed no impact on intermodality differences and there was no sign of a possible learning curve.

Conclusion: TTE-KBR is convenient and shows good agreement with CMR for RVEDV. However, there is poor agreement for RVESV, RVSV and RVEF. The use of TTE-KBR does not seem to provide additional value in the determination of RV dimensions in pulmonary sarcoidosis patients.

Introduction

Sarcoidosis is a rare systemic inflammatory disease of unknown aetiology. It is characterised by formation of non-caseating granulomas in affected tissues. Sarcoidosis may manifest in different organs, most often the lungs and lymphatic system. Right ventricular (RV) dysfunction in sarcoidosis is associated with an increased prevalence of pulmonary hypertension (PH) and adverse outcomes.[1–3] Assessment of RV function by conventional transthoracic echocardiography (TTE) is challenging due to the complex crescent shape of the RV, which cannot be properly visualised in single two-dimensional views.[4] Cardiac magnetic resonance imaging (CMR) is the gold standard for evaluating RV volumes and function.[5,6] However, the use of CMR is limited by high costs, long procedural times and several limitations. To bridge the gap between both imaging modalities, TTE with knowledge-based reconstruction (KBR) is increasingly used for imaging the right heart. This method uses conventional TTE images to construct a RV three-dimensional image, which is compared to a database of RV shapes based on CMR. TTE-KBR correlated well with CMR in determination of RV volumes and function in both PH and congenital heart disease populations.[7–10] Also, it demonstrated good inter- and intra-observer reproducibility. However, little is known about the utility of TTE-KBR in populations with interstitial lung diseases such as sarcoidosis, with predominantly normal RV dimensions. The goal of this study is to investigate the value of TTE-KBR compared to CMR in the determination of RV volumes and function in a large pulmonary sarcoidosis population.

Methods

We performed a single-centre, prospective, cross-sectional study. The study was in compliance with the principles outlined in the Declaration of Helsinki, and was approved by the MEC-U Institutional Review Board (NL49594.100.14). Between August 2015 and November 2018, all consecutive pulmonary sarcoidosis patients who were newly referred to the pulmonary outpatient clinic of the St. Antonius Hospital, a tertiary care centre for sarcoidosis, were invited to participate in this study. Furthermore, sarcoidosis patients visiting our pulmonary outpatient clinic with symptoms or signs for PH, based on the interpretation of the treating physician, who were referred for PH screening, were invited. Written informed consent was obtained from all participating patients.

Inclusion criteria were: an age of 18 years or above, a diagnosis of sarcoidosis according to current guidelines[11] and a CMR within 90 days of TTE-KBR. Patients with a pacemaker

were excluded from TTE-KBR, since safety of this technique in patients with pacemakers had not yet been determined at the time of the study. The decision to perform a CMR was at the discretion of the treating physician, as CMR was not part of the study workup. In most cases, suspected cardiac sarcoidosis was the reason to perform a CMR. At baseline, medical history, self-reported ethnicity, New York Heart Association functional class, pulmonary function test and laboratory testing were obtained. Both TTE and TTE-KBR were performed prospectively. Predicted values of the pulmonary function test were calculated according to the European Respiratory Society guidelines.[12] PH was defined as mean pulmonary artery pressure ≥25 mmHg measured by right heart catheterisation.[13]

Echocardiography and KBR

All TTE and TTE-KBR acquisition and analysis were performed and analysed by the same experienced physician (M.P.H). The echocardiogram was considered inconclusive if image quality was too poor, or in case of a pulmonary valve stenosis. TTE images were acquired using standard ultrasound equipment (iE33 system and S5 transducer; Philips Medical Systems). Right heart metrics were measured according to Rudski et al.[14] TTE-KBR images were made according to the VentriPoint user guide, by adding a magnetic localiser attached to the S5 transducer and a magnetic field generator hanging above the patient (VentriPoint Diagnostics Ltd. Seattle, USA). Before each study, the optimal ultrasound depth for the visualisation of all relevant structures were determined and pre-set in the specialised console. Throughout the imaging protocol, the patients remained entirely stationary in the left lateral decubitus position. A series of standard and nonstandard TTE views were obtained: parasternal long and short axis, RV inflow and outflow tract, standard apical four-chamber and focused RV apical. Each acquisition consisted of two or three heartbeats during breath holds, preferably end-expiratory. Image analysis was performed using the VentriPoint software. End-diastolic and end-systolic time point was selected as the time at which RV volume was the largest and smallest respectively. The same end-diastole to end-systole interval was applied to all other acquisitions. A minimum of nine points corresponding to several predefined anatomic landmarks were required for a reconstruction model of the right heart and placed in both end-diastole and end-systole. RV endocardial points were placed at the base of trabeculations. A proprietary algorithm, KBR (VentriPoint Diagnostics Ltd), processes the images into a three-dimensional model of the right ventricle at end-diastole (Figure 7.1). This model is compared with a database of RV shapes based on CMR. TTE images with superimposed outlines of the three-dimensional model were reviewed by adding and deleting points as needed and reprocessed. In cases of obvious

border misalignment (suggesting shifts in the patients position), all points were deleted and the images were excluded from the model. For end-systolic measurements the same procedure was executed, resulting in both an end-diastolic and end-systolic model. Finally, a nested view of both models was reviewed to confirm appropriate alignment of tricuspid and pulmonic annular planes. RV end-diastolic volume (RVEDV), end-systolic volume (RVESV), stroke volume (RVSV) and ejection fraction (RVEF) were calculated using these models.

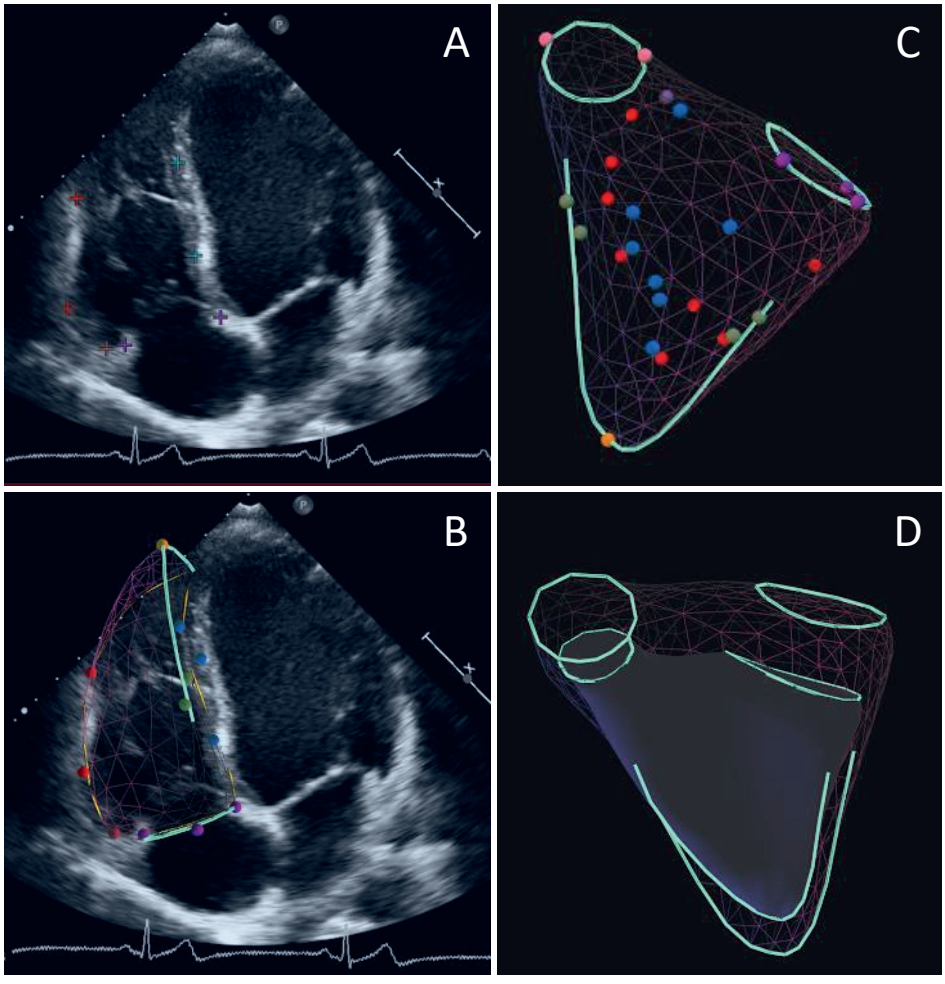

Figure 7.1: Transthoracic echocardiographic images of the standard apical four-chamber view with points placed to define anatomic landmarks **(A)** and borders of the three-dimensional model **(B)**. Three-dimensional model of the right ventricle at end-diastole. The two circles represent the position of the tricuspid and pulmonary valves **(C)**. Nested view of the end-diastolic and end-systolic RV model **(D)**. Different colors represent different anatomic landmarks: red = RV endocardium, blue = RV septum, brown = basal bulge, violet = tricuspid annulus, pink = pulmonic annulus, green = RV septal edge, orange = RV apex.

CMR acquisition and analysis

CMR was performed using a 1.5T Philips MRI scanner with an eight-element phased-array cardiac coil. A vector electrocardiographic system was used for cardiac gating. A stack of short-axis cine slices of both the RV and left ventricle (8-mm thickness, no gap) from the base to the apex of the entire heart were acquired. Cine images were obtained during end-expiratory breath holds. Analysis was performed offline on a workstation using Philips Intellispace Portal® software (version 10.1). Based on the short axis cine slices, ventricular volumes and EFs were calculated using Simpson's method of disks. Endocardial RV borders were traced manually at end-diastole and end-systole, which were identified by the largest and smallest RV cavity areas, respectively. SV was the difference between EDV and ESV. EF was calculated as (SV/EDV) × 100%. RV dysfunction was defined as an EF <40% in males and <45% in females.[15] All measurements were performed by a single experienced observer (F.A.) who was blinded to TTE and TTE-KBR results.

Statistical analysis

Data were stored in the web-based datamanager REDCap. All statistical analyses were performed using SPSS Statistics, version 26.0 for Windows (Armonk, NY:IBM Corp). Descriptive statistics were used for both continuous and categorical variables. All continuous data were expressed as mean ± standard deviation or median [interquartile range]. The chi-squared test and Fisher's Exact Test were used to compare categorical variables. The student's paired t-test was used to compare TTE-KBR and CMR-derived RV dimensions. The student's unpaired t-test or Mann-Whitney U test was used to compare means or medians of unpaired variables. A two-tailed p-value of <0.05 was considered significant. The relationship between variables was evaluated using Pearson or Spearman correlation analysis. A correlation coefficient >0.7 was considered strong, between 0.5–0.7 moderate and <0.5 weak. In addition, Bland-Altman analysis was performed to assess intermodality agreement, in terms of mean bias (average difference between measurements) and 95% limits of agreement.

Results

Figure 7.2 shows the flowchart for patient selection. Image quality of TTE-KBR was sufficient for 265 of 281 patients, resulting in a feasibility of 94.3%. In total, 122 patients had a CMR within 90 days of TTE-KBR and were included for analysis. Baseline characteristics are shown in Table 7.1. Sarcoidosis diagnosis was biopsy proven in

78.7%. In 21.3% a clinical diagnosis was made based on clinical, laboratory and radiological findings. Cardiac involvement was diagnosed in 9.8% of patients. Compared to patients who did not undergo CMR within this timeframe, included patients had a significantly higher prevalence of obstructive sleep apnea (22.1% vs 11.2%, p=0.016), higher tricuspid annulus velocity as measured by tissue Doppler imaging (12.7cm/s vs

Table 7.1: Baseline characteristics

Variable	Value (n=122)
Age (years)	50.9±12.0
Male	54.1%
Body mass index (m^2/kg)	27.8±4.6
Body surface area (m^2)	2.01±0.21
Caucasian ethnicity	87.7%
Biopsy-confirmed sarcoidosis	78.7%
Duration of disease (years)	2.3 [0.6–8.3]
Immunosuppressive therapy Steroid monotherapy Non-steroid monotherapy Combination therapy	41.8% 18.9% 18.0% 4.9%
Scadding stage (0 / I / II / III / IV)	25.0 / 22.4 / 21.6 / 2.6 / 28.4% (n=116)
NYHA functional class (I, II, III, IV)	23.0 / 52.5 / 24.5 / 0%
LVEF measured by CMR (%)	58.2±7.1
Pulmonary function, laboratory testing	
FVC % of predicted	96.4±18.2
FEV1 % of predicted	87.3±19.6
$DLCO_{SB}$ % of predicted	73.7±17.1
NT-proBNP (pg/mL)	54.0 [28.0–97.5]
Comorbidities	
Hypertension	22.1%
Prior coronary artery disease	4.1%
Obstructive sleep apnea	22.1%
Pulmonary hypertension	4.1%
Cardiac sarcoidosis	9.8%
Echocardiography	
TAPSE (mm)	22.4±4.2 (n=120)
Tricuspidal annulus velocity by TDI (cm/s)	12.7±2.2 (n=115)
Right ventricular systolic pressure (mmHg)	28.4±8.4 (n=60)

$DLCO_{SB}$ = diffusing capacity for carbon monoxide, single breath; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; NT-proBNP = N-terminal pro brain natriuretic peptide; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging.

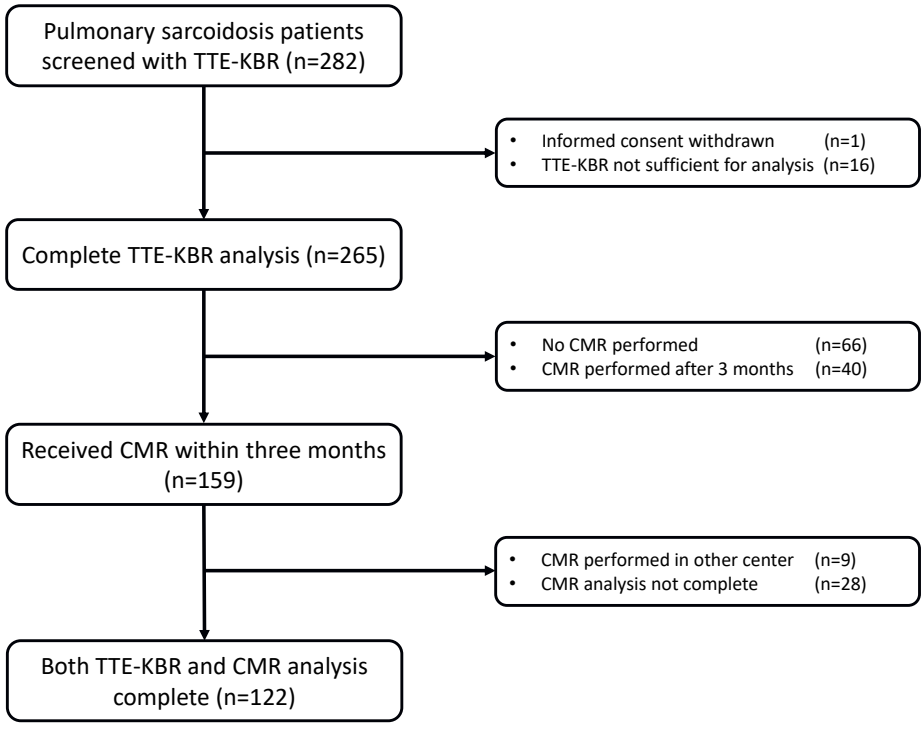

Figure 7.2: Flowchart showing patient selection.

12.2cm/s, p=0.042) and a higher New York Heart Association functional class (24.5% vs 11.9% in class III, p=0.007) (Supplementary Table S7.1). TTE-KBR measurements did not differ between both groups.

Accuracy of TTE-KBR

Mean time between TTE-KBR and CMR was 37.8±22.2 days. Image quality of TTE-KBR was bad, moderate and good in 9.8%, 45.1% and 45.1% of patients respectively. Table 7.2 shows the comparison of RV volumes and EF between TTE-KBR and CMR. All RV parameters showed significant differences. As Figure 7.3 shows, correlation was strong for both RVEDV (R=0.73) and RVESV (R=0.76) and weak for both RVSV (R=0.46) and RVEF (R=0.46). Comparison of the TTE-KBR and CMR results with Bland-Altman statistics are shown in Figure 7.4. There was good agreement for RVEDV with a marginal overestimation ($\Delta RVEDV_{KBR-CMR}$, 5.67±55.4mL), and poor agreement for RVESV with a large overestimation ($\Delta RVESV_{KBR-CMR}$, 21.6±34.1mL). For both RVSV and RVEF there was a large underestimation ($\Delta RVSV_{KBR-CMR}$, -16.1±42.9mL; $\Delta RVEF_{KBR-CMR}$, -12.9±16.4%). RV dysfunction was present in 4.9% of patients based on CMR. No impact on the intermodality

Table 7.2: Right ventricular dimensions measured by TTE-KBR and CMR

	TTE-KBR (n=122)	CMR (n=122)	p-value Paired t-test	Pearson rho
EDV (mL)	155.9±39.5	150.2±37.5	0.028	0.732
ESV (mL)	84.1±25.8	62.4±24.0	<0.001	0.758
Stroke volume (mL)	71.7±20.6	87.8±21.5	<0.001	0.461
Ejection fraction (%)	46.3±7.7	59.2±8.4	<0.001	0.463

CMR = cardiac magnetic resonance imaging; EDV = end-diastolic volume; ESV = end-systolic volume; TTE-KBR = transthoracic echocardiography with knowledge-based reconstruction.

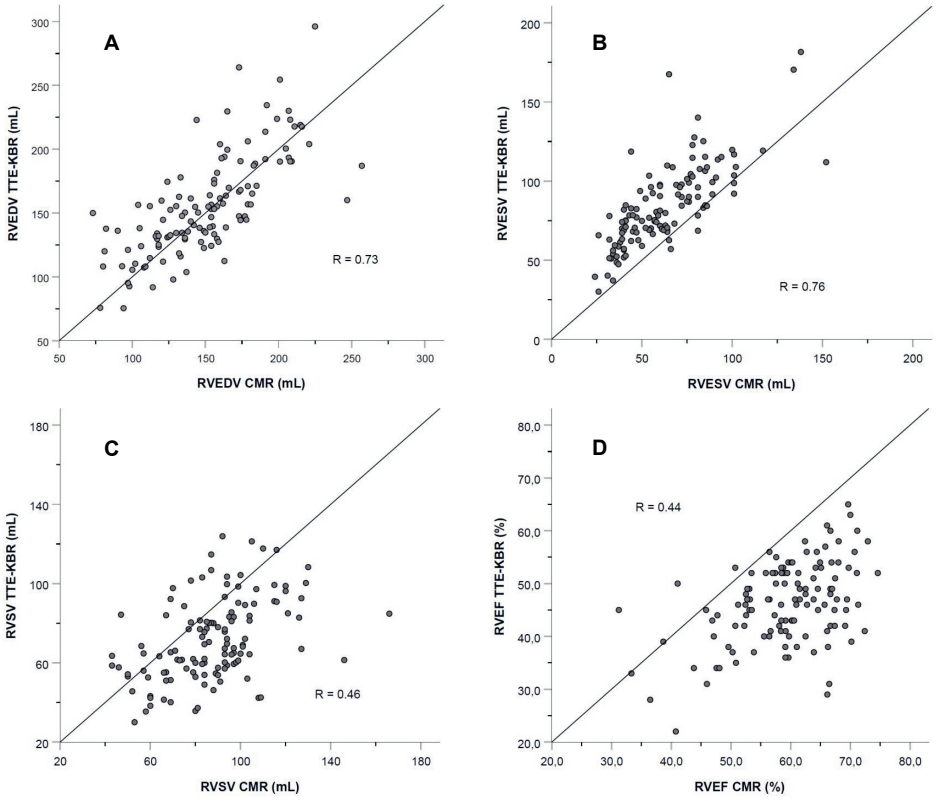

Figure 7.3: Correlation plots of RVEDV (A), RVESV (B), RVSV (C) and RVEF (D) measured by TTE-KBR versus CMR.

differences was seen when taking only patients with at least moderate image quality or time between TTE-KBR and CMR <30 days into account and there were no signs of a possible learning curve. Comparison between patients with and without PH or with and without CS showed no significant differences in RV dimensions of both TTE-KBR and CMR (Supplementary Tables S7.2 and S7.3). Although there was a trend towards a higher RVESV (median 71.0 vs 58.0mL, p=0.08) and lower RVEF (median 57.0% vs 60.0%,

p=0.09) on CMR in patients with PH. Echocardiographic RV parameters, pulmonary function values, laboratory testing (including NT-proBNP), pulmonary artery diameter on chest CT, Scadding stage and functional class all showed a weak or no correlation with both TTE-KBR and CMR derived RV dimensions. Supplementary Tables S7.4 and S7.5 show all correlation values.

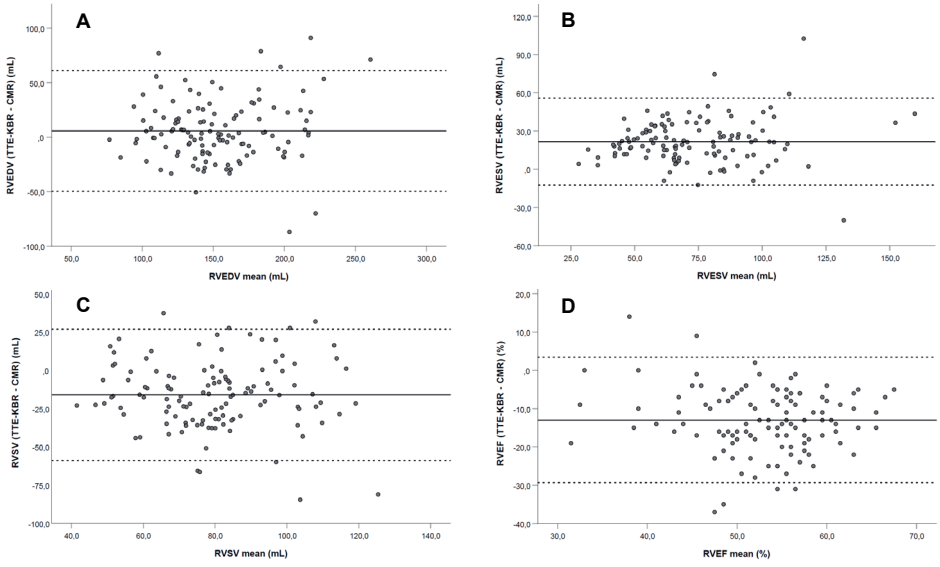

Figure 7.4: Bland-Altman analysis of bias (black solid line) and 95% limits of agreement (dashed line) for TTE-KBR versus CMR quantification of RVEDV (A), RVESV (B), RVSV (C) and RVEF (D).

Discussion

To our knowledge, this is the first study using echocardiography with KBR in patients with pulmonary sarcoidosis to determine RV volumes and function. The main finding of the study is that only TTE-KBR derived RVEDV shows good agreement with CMR. TTE-KBR is highly feasible, but significantly overestimates RVESV and underestimates RVSV and RVEF compared to the gold standard CMR.

TTE-KBR has not been described in populations with interstitial lung diseases, such as sarcoidosis. Nevertheless it has been validated in PH and congenital heart disease populations showing favorable results in determination of RV volumes and function compared to CMR.[7–10] However, most studies were small and investigated less than fifty patients. Dragulescu et al. were one of the first to describe the usage of TTE-KBR in patients after tetralogy of Fallot repair. They studied thirty patients and found good

intermodality agreement with a small underestimation of RVEDV and RVESV, with low intra- and interobserver variability.[9] Neukamm et al. observed similar results in patients with tetralogy of Fallot, although they found poor agreement for RVEF (r=0.38).[10] Bhave et al. studied 27 patients with PH and found a slight overestimation of RVEDV, RVESV and RVSV, while RVEF was slightly underestimated.[7] They concluded that TTE-KBR was accurate and reproducible in patients with PH, which was also stated by Knight et al. who investigated twenty-eight PH patients.[8] The differences between our findings and the previously mentioned studies are not explained by the time between TTE-KBR and CMR, image quality or a possible learning curve. First, the poor intermodality agreement for both RVSV and RVEF can be explained by the significant overestimation of the RVESV, as RVSV and RVEF are both calculated using RVESV. A possible explanation for the differences in intermodality agreement with previous reported studies is our unselected pulmonary sarcoidosis population in which many patients had normal RV function and dimensions. In other studies, patients had known congenital heart disease or PH. The KBR algorithm takes the impact of the underlying disease on the RV morphology into account, so knowledge of underlying cardiac pathology is beneficial.[16] As we screened pulmonary sarcoidosis patients for PH without further data on RV function, all RV shapes were compared by the KBR algorithm to 'regular' right ventricles in the CMR reference data library. This could explain the intermodality differences, as 4.1% of patients was diagnosed with PH and these patients were not compared to a library of RV shapes of PAH patients. Furthermore, it is unknown whether this reference library contains patients with (cardiac) sarcoidosis, which could also explain the differences with our findings. Finally, the difference between acquisition positioning of TTE-KBR and CMR might impact our findings. TTE-KBR was performed in left lateral decubitus position, while CMR was performed in supine position.

Limitations

An important limitation of our study is that CMR acquisition was not part of standard study protocol. As screening for cardiac sarcoidosis was the main reason for CMR in many patients, there is a risk for referral bias with patients with more profound cardiac symptoms, abnormal cardiac biomarker results, electrocardiogram abnormalities or echocardiographic abnormalities. However, there were no significant differences between TTE-KBR derived values between patients with and without CMR within 90 days. In addition, TTE-KBR and CMR were not performed on the same day, with a mean time difference of 35 days. Nevertheless, analysis of patients with CMR <30 days only, showed no change in the differences between both modalities. Also, our population had mainly normal RV size and function, therefore the results cannot be generalised

to patients with RV involvement in (cardiac) sarcoidosis. Furthermore, it is unknown whether the used reference library contains patients with (cardiac) sarcoidosis. All echocardiographic images were acquired using a transducer without 3D features. Therefore, KBR could not be compared to RV models created by 3D echocardiography. Lastly, a single observer performed all TTE-KBR studies and intra-, inter- and test-retest variability could therefore not be determined, which may limit generalisability. Previous studies have shown no significant intra- and inter-observer test-retest variability for both RV volumes and function.[7,8]

Conclusion

TTE-KBR is convenient, feasible and shows good agreement with CMR for RVEDV. However, there is poor intermodality agreement for RVESV, RVSV and RV function with a significant overestimation of RVESV and underestimation of RVSV and RVEF. The use of TTE-KBR does not seem to provide additional value in the determination of RV dimensions in pulmonary sarcoidosis patients.

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Appendix

Supplementary Table S7.1: Baseline characteristics of patients with complete TTE-KBR analysis who received CMR within 90 days (included in the study) and did not receive CMR within 90 days

Variable	Included in study (n=122)	Not included in study (n=143)	p-value
Age (years)	50.9±12.0	49.9±11.7	0.506
Female sex	45.9%	35.7%	0.090
Body mass index (m^2/kg)	27.8±4.6	27.6±5.5	0.756
Body surface area (m^2)	2.01±0.21	2.01±0.25	0.847
Caucasian ethnicity	87.7%	89.5%	0.644
Biopsy confirmed sarcoidosis	78.7%	79.0%	0.947
Duration of disease (years)	2.3 [0.6–8.3]	4.0 [0.8–10.1]	0.303
Immunosuppressive therapy Steroids Non-steroids	41.8% 23.8% 22.1%	43.4% 28.7% 25.2%	0.799 0.367 0.562
Scadding stage (0 / I / II / III / IV)	25.0 / 22.4 / 21.6 / 2.6 / 28.4% (n=116)	19.3 / 17.8 / 22.2 / 9.6 / 31.1% (n=135)	0.142
NYHA functional class (I, II, III, IV)	23.0 / 52.5 / 24.5 / 0.0%	29.4 / 58.7 / 11.9 / 0.0%	0.019
Pulmonary function, laboratory testing			
FVC % of predicted	96.4±18.2	93.3±19.5	0.192
FEV1 % of predicted	87.3±19.6	85.7±21.1	0.520
$DLCO_{SB}$ % of predicted	73.7±17.1	72.4±16.4	0.554
NT-proBNP (pg/mL)	54.0 [28.0–97.5]	48.0 [22.0–103.8]	0.760
Comorbidities			
Hypertension	22.1%	28.0%	0.322
Prior coronary artery disease	4.1%	1.4%	0.253
Obstructive sleep apnea	22.1%	11.2%	0.016
Pulmonary hypertension	4.1%	2.1%	0.477
Cardiac sarcoidosis	9.8%	9.8%	0.990
Echocardiography			
TAPSE (mm)	22.4±4.2 (n=120)	23.0±4.3 (n=142)	0.239
Tricuspidal annulus velocity by TDI (cm/s)	12.7±2.2 (n=115)	12.2±1.9 (n=142)	0.042
Right ventricular systolic pressure (mmHg)	28.4±8.4 (n=60)	26.7±10.9 (n=60)	0.337

$DLCO_{SB}$ = diffusing capacity for carbon monoxide, single breath; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; NT-proBNP = N-terminal pro brain natriuretic peptide; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging.

Supplementary Table S7.2: RV volumes and EF by TTE-KBR and CMR in PH vs no PH

	No PH (n=117)	PH + (n=5)	p-value
TTE-KBR EDV (mL)	150.0 [130.2–175.3]	199.6 [142.9–219.3]	0.100
TTE-KBR ESV (mL)	78.4 [68.0–97.8]	102.8 [76.6–139.7]	0.129
TTE-KBR SV (mL)	67.4 [56.6–84.6]	68.2 [62.4–97.9]	0.427
TTE-KBR EF (%)	47.0 [41.5–52.0]	45.0 [34.5–51.0]	0.473
CMR EDV (mL)	150.0 [122.5–173.5]	179.0 [138.5–206.5]	0.123
CMR ESV (mL)	58.0 [41.0–78.0]	71.0 [65.5–115.0]	0.075
CMR SV (mL)	88.0 [74.5–99.0]	94.0 [57.5–114.0]	0.887
CMR EF (%)	60.0 [53.5–66.0]	57.0 [36.0–61.5]	0.094

CMR = cardiac magnetic resonance imaging; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; PH = pulmonary hypertension; RV = right ventricular; SV = stroke volume; TTE-KBR = transthoracic echocardiography with knowledge-based reconstruction.

Supplementary Table S7.3: RV volumes and EF by TTE-KBR and CMR in patients with cardiac sarcoidosis vs without cardiac sarcoidosis

	No CS (n=110)	CS + (n=12)	p-value
TTE-KBR EDV (mL)	149.5 [121.0–178.3]	155.0 [133.8–165.5]	0.747
TTE-KBR ESV (mL)	60.0 [41.0–78.0]	59.0 [50.5–77.5]	0.205
TTE-KBR SV (mL)	87.0 [73.8–100.0]	93.5 [71.0–98.5]	0.331
TTE-KBR EF (%)	60.0 [53.8–66.0]	61.0 [52.3–65.0]	0.089
CMR EDV (mL)	150.2 [130.3–187.1]	154.9 [131.7–174.5]	0.966
CMR ESV (mL)	78.3 [67.4–98.8]	89.7 [76.2–106.0]	0.976
CMR SV (mL)	69.2 [57.4–84.9]	60.3 [55.4–80.2]	0.724
CMR EF (%)	47.0 [42.0–52.0]	43.0 [35.3–48.5]	0.931

CMR = cardiac magnetic resonance imaging; CS = cardiac sarcoidosis; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; PH = pulmonary hypertension; RV = right ventricular; SV = stroke volume; TTE-KBR = transthoracic echocardiography with knowledge-based reconstruction.

Supplementary Table S7.4: Correlations of RV volumes by TTE-KBR

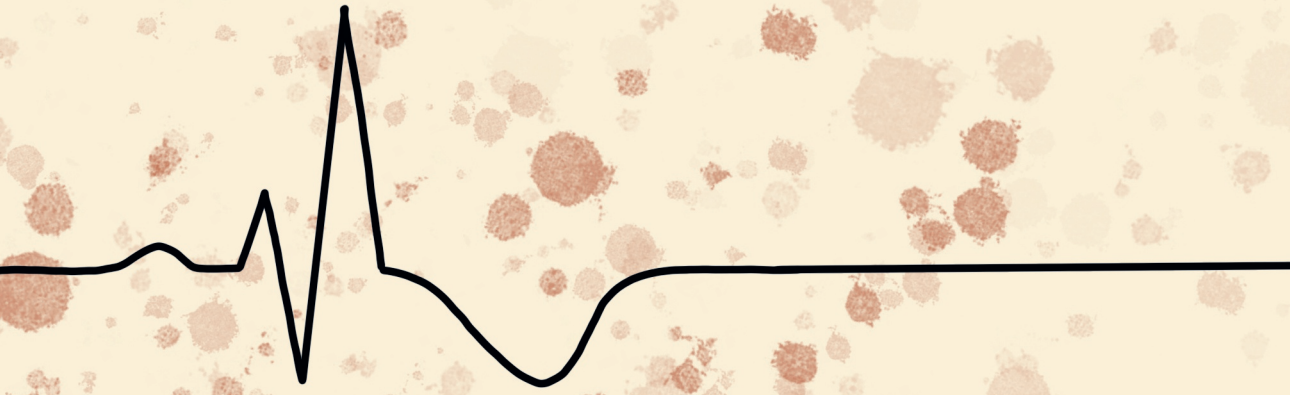
	RV EDV	RV ESV	RV SV	RV EF
Pearson *rho*				
Age	-0.161	-0.095	-0.191	-0.045
Body mass index	0.362	0.291	0.332	0.015
Body surface area	0.690	0.647	0.519	-0.179
TAPSE (mm)	0.231	0.047	0.374	0.320
Tricuspidal annulus velocity (TDI)	0.223	0.072	0.330	0.226
RV systolic pressure	0.128	0.157	0.061	-0.083
FVC % of pred	0.048	-0.079	0.192	0.294
FEV1 % of pred	0.058	-0.071	0.201	0.283
$DLCO_{SB}$ % of pred	0.322	0.203	0.365	0.145
NT-proBNP	-0.062	-0.034	-0.075	-0.047
Log NT-proBNP	-0.156	-0.157	-0.099	0.052
Mean PA diameter	0.222	0.283	0.080	-0.196
Mean PA diameter indexed for BSA	-0.278	-0.209	-0.258	-0.022
Spearman *rho*				
Scadding stage	-0.083	0.006	-0.162	-0.131
NYHA functional class	-0.130	-0.083	-0.194	-0.119

BSA = body surface area; $DLCO_{SB}$ = diffusing capacity for carbon monoxide, single breath; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; NYHA = New York Heart Association; NT-proBNP = N-terminal pro brain natriuretic peptide; PA = pulmonary artery; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging.

Supplementary Table S7.5: Correlations of RV volumes by CMR

	RV EDV	RV ESV	RV SV	RV EF
Pearson *rho*				
Age	-0.392	-0.279	-0.372	0.067
Body mass index	0.121	0.084	0.117	0.017
Body surface area	0.632	0.524	0.516	-0.224
TAPSE (mm)	0.107	-0.030	0.213	0.180
Tricuspidal annulus velocity (TDI)	0.104	0.001	0.177	0.087
RV systolic pressure	-0.050	0.089	-0.196	-0.226
FVC % of pred	0.104	-0.041	0.227	0.218
FEV1 % of pred	0.139	-0.048	0.295	0.260
$DLCO_{SB}$ % of pred	0.368	0.205	0.409	0.049
NT-proBNP	-0.044	-0.070	0.002	0.087
Log NT-proBNP	-0.227	-0.225	-0.145	0.152
Mean PA diameter	0.264	0.318	0.110	-0.262
Mean PA diameter indexed for BSA	-0.232	-0.091	-0.306	-0.097
Spearman *rho*				
Scadding stage	-0.167	-0.067	-0.297	-0.093
NYHA functional class	-0.241	-0.160	-0.247	-0.030

BSA = body surface area; $DLCO_{SB}$ = diffusing capacity for carbon monoxide, single breath; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; NYHA = New York Heart Association; NT-proBNP = N-terminal pro brain natriuretic peptide; PA = pulmonary artery; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging.



CHAPTER 8

Pulmonary artery diameter to predict pulmonary hypertension in pulmonary sarcoidosis

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European Respiratory Journal. 2016;47(2):673–676

To the Editor:

Pulmonary hypertension (PH) is a known complication of pulmonary sarcoidosis with a prevalence ranging from 5% to 74%.[1] The aetiology of PH in sarcoidosis is not fully understood. Usually, it is attributed to the destruction of the distal capillary bed by lung fibrosis and/or chronic hypoxaemia. However, the severity of PH does not correlate consistently with the degree of pulmonary fibrosis, and PH exists in sarcoidosis patients without fibrosis, suggesting a multifactorial mechanism. The presence of PH is associated with a poor prognosis, and early diagnosis and treatment might improve outcome.[1] Echocardiography should always be performed when PH is suspected.[2] However, the accuracy of echocardiography in patients with interstitial lung diseases is often limited due to poor image quality and unreliable tricuspid regurgitation signal to measure the right ventricular systolic pressure (RVSP).[3] Further invasive investigation with the gold standard, right heart catheterisation (RHC), is often required. In order to optimise the noninvasive diagnostic approach, there is a need for more accurate predictors of PH. Computed tomography (CT) may raise suspicion of PH in symptomatic patients or those examined for unrelated indications by showing an increased pulmonary artery (PA) diameter (≥29 mm) and PA diameter/ascending aorta diameter (AAD) ratio (≥1.0).[2] Similarly, PA diameter indexed to body surface area (BSA) has been suggested as possible predictor of PH. However, these parameters have never been investigated in pulmonary sarcoidosis specifically.

In this study, PA diameter measurements on chest CT were retrospectively evaluated as predictors of PH. Patients suspected of PH and referred for analysis between November 2007 and May 2014 were included in cases with a consensus diagnosis of pulmonary sarcoidosis, aged ≥18 years, with availability of chest CT within 1 year of PH analysis. The analysis protocol was based on the European PH guideline,[2] and consisted of an ECG, laboratory testing, and echocardiographic assessment of RVSP and secondary parameters. Subsequently, patients were classified as "PH likely" (RVSP >50mmHg), "PH possible" (RVSP of 36–50mmHg or presence of secondary signs with normal/absent RVSP signal) or "PH unlikely" (RVSP <36mmHg or absence of signal without secondary signs). RHC was performed if PH was possible or likely. PH was defined as an invasively measured mean PA pressure (mPAP) ≥25mmHg. Patients were divided into three groups: "PH confirmed by RHC", "no PH confirmed by RHC" and "no PH based on echocardiography".

A radiologist, specialised in interstitial lung diseases and blinded to haemodynamic data, reviewed the chest CT performed most recently to the echocardiographic analysis. The

PA diameter was measured at the level of the bifurcation along the line from the centre of the adjacent ascending aorta perpendicular to the main PA axis.[4] As a derivative, the PA diameter was indexed to BSA[5] and calculated as a ratio with AAD. Furthermore, the percentage of fibrosis of the total lung area was described as "not significant" (<5%), "intermediate" (5–20%) or "severe" (>20%).

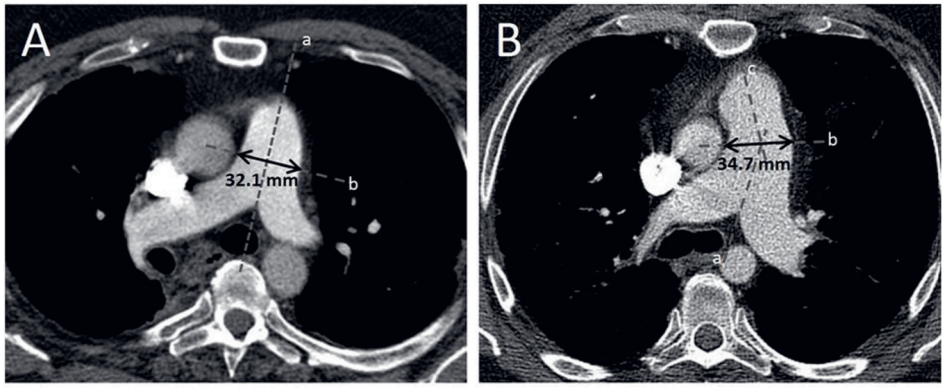

Figure 8.1: Kaplan Meier survival curves with comparison between different subgroups.
The main pulmonary artery diameter (MPAD) was measured at the level of the bifurcation along the line that originates from the center of the adjacent ascending aorta perpendicular to the axis of main pulmonary artery **(A)**. If the trunk was too curved, measurements were made using the second method **(B)**.

In total, 89 out of 103 pulmonary sarcoidosis patients referred for PH analysis were eligible for inclusion. The estimated prevalence of PH was 28.1%. Table 8.1 shows the baseline characteristics and outcomes. 16 patients had been referred as a result of a dilated PA. After excluding these patients, PA measurements remained highly significant. PA diameter indexed to BSA and PA diameter/AAD ratio correlated moderately with RHC-derived mPAP (r=0.51 and r=0.52, respectively).

Receiver operating curve analysis showed a good accuracy for PA diameter indexed to BSA and PA diameter/AAD ratio (area under the curve (AUC) of 0.88 and 0.81, respectively; p<0.001). Optimal cut-off values were calculated for PA diameter (30.6mm), PA diameter indexed to BSA (16.02mm·m^{-2}) and PA diameter/AAD ratio (1.06). PA diameter indexed to BSA showed the best positive and negative predictive value for diagnosing PH (70% and 93.2%, respectively) followed by PA diameter/AAD ratio (64.3% and 88.5%, respectively).

In a subanalysis, we evaluated patients classified as "PH possible" (n=18). Only PA diameter indexed to BSA was able to significantly discriminate between the presence

Table 8.1: Baseline characteristics and outcomes

	PH_{RHC} (n=25)	no PH_{RHC} (n=12)	no PH_{echo} (n=52)	p-value PH_{RHC} vs no PH_{RHC}	p-value PH_{RHC} vs no $PH_{RHC/echo}$
Demographics					
Sex (male)	16 (64.0)	9 (75.0)	35 (67.4)	0.79	0.81
Age (years)	55.8±9.0	48.3±10.0	50.5±12.0	0.131	0.77
BSA (m^2)	1.9±0.2	2.0±0.3	2.1±0.2	0.194	0.02
NYHA functional class (I/II/III/IV)	0/6/15/4	1/2/8/0	12/29/9/2	0.518	<0.001
NT-pro-BNP (log)	5.5±1.8	3.9±1.1	4.0±0.8	0.001	<0.001
Sarcoidosis related					
Sarcoidosis related fibrosis (stage 4)	25 (100)	7 (58.3)	30 (57.7)	0.02	0.001
Sarcoidosis treatment	18 (72.0)	10 (83.3)	34 (65.4)	0.766	0.46
Oxygen therapy	7 (28.0)	0	1 (1.9)	0.009	<0.001
Pulmonary function					
FVC	2.29±0.89	3.19±1.32	3.63±1.10	0.054	<0.001
FVC%	57.6±18.1	73.71±24.00	83.83±18.00	0.050	<0.001
FEV1	1.45±0.79	2.35±1.13	2.54±0.83	0.011	<0.001
FEV1%	46.4±17.2	66.94±31.02	73.08±19.72	0.018	<0.001
FVC%/FEV1%	1.78±0.81	1.45±0.49	1.47±0.39	0.213	0.80
DLCO%	41.4±15.4	53.38±22.34	58.15±18.21	0.216	0.01
FVC%/DLCO%	1.73±0.72	1.63±0.59	1.54±0.44	0.896	0.348
Heamodynamics					
RVSP (mmHg)	62.6±21.4	31.9±5.3	29.6±4.2	<0.001	<0.001
Systolic PAP (mmHg)	61.8±16.9	28.9±5.5	-	<0.001	-
Mean PAP (mmHg)	39.2±9.9	17.5±3.4	-	<0.001	-
Diastolic PAP (mmHg)	26.0±7.4	11.7±2.8		<0.001	-
PCWP (mmHg)	12.9±6.8	8.8±2.6	-	0.012	-
TPG (mmHg)	26.1±10.9	8.6±3.4	-	<0.001	-
DPG (mmHg)	13.0±2.8	8.7±2.9	-	<0.001	-
PVR (WU)	5.6±2.9	1.3±0.7	-	<0.001	
Chest-CT parameters					
PA diameter (mm)	33.1±4.1	29.2±3.5	28.8±3.8	0.001	<0.001
PA indexed for BSA (mm/m^2)	17.7±2.3	14.5±1.8	14.2±1.8	<0.001	<0.001
PA ratio with AAD	1.1±0.2	0.9±0.1	1.0±0.2	<0.001	<0.001
Fibrosis (extend)				0.13	0.001
<5%	3 (12.0)	5 (41.7)	23 (44.2)		
5–20%	2 (8.0)	1 (8.3)	9 (17.3)		
>20%	20 (80.0)	6 (50.0)	20 (38.5)		

Data are presented as n, n(%) or mean. AAD = ascending aorta diameter; BSA = body surface area; DLCO = diffusing capacity for carbon monoxide; DPG = diastolic pulmonary gradient; FVC = forced vital capacity; FEV1 = forced expiratory volume in one minute; NT-pro-BNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association functional class; PA = pulmonary artery; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; TPG = transpulmonary pressure gradient; RVSP = right ventricular systolic pressure.

and absence of PH (17.0 versus 14.3mm·m^{-2}, respectively; p<0.006), with a high diagnostic accuracy (AUC 0.91) using a cut-off value of 15.2mm·m^{-2}. This was notably higher than PA diameter/AAD ratio (AUC 0.71).

Finally, we evaluated the correlation of PA measurements with the presence of fibrosis. PA diameter and PA diameter indexed to BSA had a weak but significant correlation with the extent of fibrosis (r=0.32 and r=0.42, respectively).

This is the first study to investigate chest CT parameters for predicting PH only in patients with pulmonary sarcoidosis. The results implicate that PA diameter indexed to BSA is the most reliable predictor of PH for both the general pulmonary sarcoidosis population and for the "PH possible" subgroup, classified by echocardiography. Therefore, PA measurement on chest CT might be valuable to further optimise PH analysis in pulmonary sarcoidosis.

Besides hypoxaemia, mechanisms for PH in sarcoidosis include specific vasculopathy of the vessel wall, perivascular fibrosis, external compression of the PA by severe lymphadenopathy, mediastinal fibrosis and left heart disease.[1] PA dilatation in PH can be due to chronically elevated PA pressure.[6] Similarly to aortic diameter, PA size may vary among individuals, depending on age, sex and BSA.[7] It has been suggested that indexing PA to BSA might lead to a higher accuracy that PA diameter/AAD ratio, since BSA influences both PA and aortic diameters.[8]

Many studies describe positive correlations for mPAP with PA measurements in different subgroups of PH, especially for PA diameter indexed to BSA and PA diameter/AAD ratio.[9] Only few studies assessed these parameters in interstitial lung diseases, most reporting positive correlations.[10–12] Unfortunately, PA diameter indexed to BSA has not been evaluated in interstitial lung disease. Furthermore, two studies were unable to obtain positive correlations. Zisman et al.[13] studied 65 idiopathic pulmonary fibrosis (IPF) patients and found no significant correlation of PA diameters with mPAP, including PA diameter indexed to BSA. However, in that study, a mean mPAP of 26.1 mmHg might have been too low in order to cause dilatation. Similarly, Devaraj et al.[14] found no correlation of mPAP with PA diameter or PA diameter/AAD ratio in 30 patients with pulmonary fibrosis, of whom 11 had sarcoidosis. PA dilatation occurred in the absence of significant PH; however, this was unrelated to the extent of fibrosis. Our study involves the largest group of sarcoidosis patients studied and supports the hypothesis that the mechanism of PH in sarcoidosis is not fully explained by pulmonary fibrosis. Compared to patients with IPF, pulmonary fibrosis in sarcoidosis is characterised by a chronic course, often involving the upper lobe, and is predominantly of the nonhoneycombing

type. Conversely, IPF progresses quickly, is mostly located peripherally or in the lower lobe, with a predominance of honeycombing.[15] This might lead to increased traction on the PA in IPF. For PH in sarcoidosis, the exact mechanism of PH and PA dilatation remains unknown, and requires further investigation.

Measurements of PA diameter and AAD are highly reproducible, with an excellent inter- and intraobserver variability.[7] Limitations of this study were mostly due to its retrospective nature, resulting in different types of CT and echocardiography equipment with variable time intervals. Second, not all patients underwent RHC, which might have led to underdetection of PH. Last, this study was conducted in a tertiary care centre.

In conclusion, our study demonstrates that measurement of PA diameter indexed to BSA is the most accurate predictor of PH on chest CT in patients with pulmonary sarcoidosis. Prospective research in a large, predefined group of sarcoidosis patients is warranted for further validation and clinical implementation.

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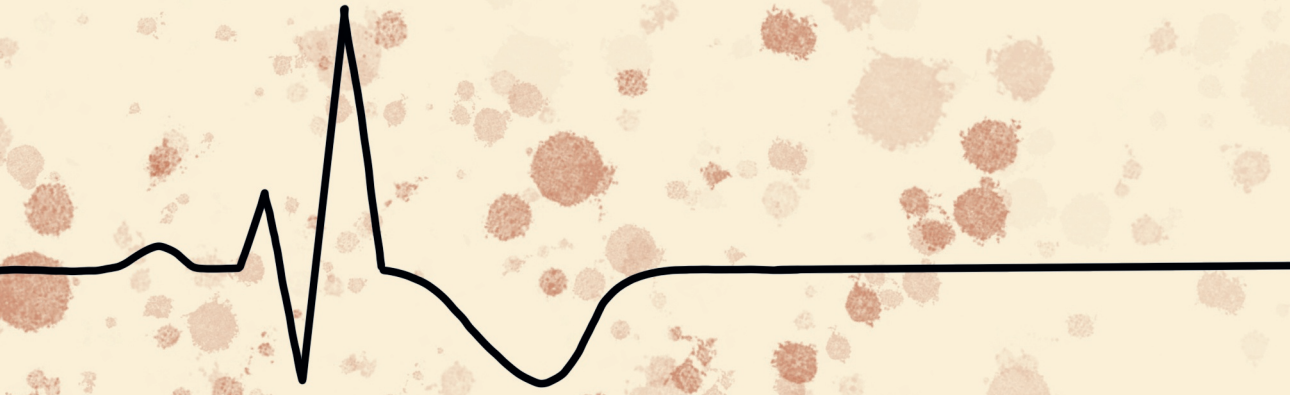
PART III

TREATMENT AND OUTCOMES



CHAPTER 9

Safety of macitentan in sarcoidosis-associated pulmonary hypertension: a case series

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Abstract

Background: Pulmonary hypertension (PH) is a known complication of pulmonary sarcoidosis and is associated with higher morbidity and mortality. Currently, there are no approved PH-targeted therapies for sarcoidosis-associated pulmonary hypertension (SAPH). Macitentan is frequently used as treatment for pulmonary arterial hypertension, but no results are known in the SAPH population. The aim of this study was to investigate the safety and effect of macitentan as treatment for SAPH.

Methods: We retrospectively reviewed our patient database for all SAPH patients receiving macitentan as treatment, with a minimum follow-up of twelve months for monitoring safety. Safety outcomes included reported side effects, hospitalisations and mortality. Furthermore, six-minutes walking distance, New York Heart Association functional class and NT-proBNP levels were collected.

Results: Six cases (three men) with a median age of 64 years (range 52–74 years) were identified. During macitentan treatment, one patient experienced side effects and aborted therapy after five days of treatment and died 16 months later. Three patients were hospitalised during treatment for congestive heart failure. Four patients showed improvement of their functional class and three patients in exercise capacity after 12 months of therapy.

Conclusion: Macitentan was well tolerated in five out of six cases with severe pulmonary sarcoidosis and PH. Functional capacity improved in four cases. Prospective controlled trials are warranted before therapeutic recommendations can be made.

Introduction

Pulmonary hypertension (PH) is a known complication of pulmonary sarcoidosis. Prevalence numbers range from 3% in early stage pulmonary sarcoidosis, up to 70% in patients awaiting lung transplantation.[1,2] Sarcoidosis-associated pulmonary hypertension (SAPH) is associated with increased morbidity and mortality.[3,4] The underlying pathophysiological mechanism of SAPH remains unclear. Hypothesised mechanisms include destruction of the pulmonary vascular bed by pulmonary fibrosis, granulomatous vasculopathy, extrinsic compression from thoracic lymphadenopathy, mediastinal fibrosis and cardiac involvement.[4–6] Currently, there are no approved PH-targeted treatments for SAPH. Although endothelin receptor antagonists are well used in pulmonary arterial hypertension, studies have shown mixed results in SAPH.[7,8] To our best knowledge, the safety and effect of the endothelin receptor antagonist macitentan in SAPH patients has not been evaluated. We report the results of a single centre case-series.

Methods

The St. Antonius hospital is a tertiary referral centre for sarcoidosis and PH. We retrospectively reviewed our patient database between 2014–2018 to include all patients aged ≥18 years, diagnosed with both sarcoidosis and PH, who received macitentan as treatment (mono- or dual therapy), and had at least 12 months of follow-up for monitoring safety outcomes. The diagnosis of sarcoidosis was based on current clinical diagnostic guidelines.[9] PH was confirmed by right heart catheterisation (RHC) and defined as a resting mean pulmonary artery pressure (mPAP) ≥25mmHg. The decision to start treatment was made by a multidisciplinary team. Safety outcomes included side effects leading to (temporarily) aborting therapy, hospitalisation for heart failure or dyspnoea, and death.

Baseline was defined as the start of PH-targeted treatment. At baseline, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, forced vital capacity (FVC), New York Heart Association (NYHA) functional class were determined and a six-minute walking distance (6-MWD) was obtained. Macitentan was administered at a dose of 10mg/day. If applicable, sildenafil was dosed 20mg three times daily. All outcome parameters were obtained by chart review. Written informed consent was obtained in all cases. The study was approved by the local institutional review board.

Results

Figure 9.1 shows the flowchart of case selection. In total, 27 patients with SAPH were identified between 2014–2018. Of these patients, 8 were treated with macitentan. Of these, 6 patients had a follow-up of at least twelve months, while the other two patients were recently started on macitentan. The baseline characteristics and outcome parameters of all cases are shown in Table 9.1. Six patients (three men) with a median age of 64 years (range 52–74 years) were identified. All cases were Caucasian patients with biopsy confirmed sarcoidosis. RHC showed a median mPAP of 49 (27–66) mmHg and the pulmonary vascular resistance (PVR) was >3 Wood Units (WU) in all cases.

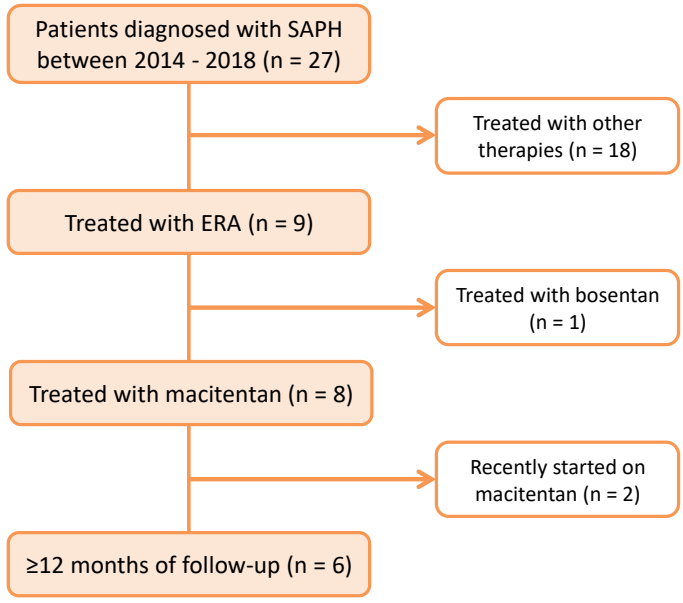

Figure 9.1: Flowchart of case selection.

Case 1 was a 60-year old female with suspected fibrosing pulmonary sarcoidosis and severe PH. Macitentan was started after PH diagnosis. After two months, sarcoidosis was proven on biopsy and immunosuppressive therapy with methotrexate 15mg/week was initiated due to active disease on FDG-PET (fluorodeoxyglucose-positron emission tomography) with compression of the pulmonary artery. At three months, echocardiography showed improved right ventricular function and sildenafil was added. At 7 months, immunosuppressive therapy was switched to azathioprine 100mg/day due to side effects of methotrexate. At one year, there was an improvement of mPAP (47mmHg), PVR (5.0WU), 6-MWD, and NYHA functional class. NT-proBNP levels and

the FVC remained stable. During 3.5 years of follow-up, macitentan was well tolerated with no reported side effects.

Case 2 was a 74-year old male with fibrosing pulmonary sarcoidosis. RHC showed severe PH and macitentan was started. After four weeks, he was admitted for pneumonia and congestive heart failure. After recovery, sildenafil was added. At 12 months, no side effects were reported. NT-proBNP levels had increased, while NYHA functional class and FVC remained stable. A 6-MWD was not performed during follow-up due to persisting disabilities after a cerebrovascular event.

Case 3 was a 64-year old male with pulmonary sarcoidosis. After PH diagnosis, macitentan and sildenafil were started with good effect on NYHA functional class at 12 months while other outcome parameters remained stable or showed mild improvement. Macitentan was well tolerated.

Case 4 was a 52-year old female, with recently diagnosed pulmonary sarcoidosis and severe PH. Macitentan treatment was started with initial good effect on functional capacity. At 10 months, she was hospitalised due to congestive heart failure. After recovery, RHC was repeated which showed a mPAP of 58 mmHg and a PVR of 12.5WU. Sildenafil was added and after 24 months all outcome parameters improved, while FVC remained stable. After 3.5 years of follow-up, macitentan was well tolerated and the patient remained clinically stable.

Case 5 was a 69-year old female patient with fibrosing pulmonary sarcoidosis and severely reduced exercise capacity. Dual treatment with macitentan and sildenafil was started. The FDG-PET showed enhanced inflammatory activity, and high-dosage prednisone was started at 6 weeks. At 12 months, there was an improvement in 6-MWD (340 vs 145m), NT-proBNP and NYHA functional class. FVC also improved during treatment (74.0% vs 50.4%). Echocardiography showed improvement in right ventricular function after 12 months. No side effects were reported during follow-up.

Case 6 was a 65-year old male patient with fibrosing pulmonary sarcoidosis. After PH diagnosis, initial treatment with sildenafil was started. After 12 months of treatment, RHC showed a mPAP of 47mmHg with no subjective improvement. FDG-PET revealed no signs of inflammatory activity and macitentan was initiated. Macitentan was not well tolerated and aborted after five days due to severe muscle aches and fatigue. Several days later, this patient was hospitalised for increasing dyspnoea and sildenafil was aborted due to no clinical improvement. The patient was discharged home with oxygen therapy and diuretics and died sixteen months later due to right ventricular failure.

Table 9.1. Case characteristics

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Demographics						
Age (years)	60	74	64	52	69	65
Male / female	Female	Male	Male	Female	Female	Male
Time since sarcoidosis diagnosis (years)	8,3	4,3	20	0,2	22,5	12,2
Pulmonary function						
FEV1 % predicted	75.9	90.0	49.0	54.9	36.9	25.6
FVC % predicted	104.1	88.0	69.0	62.5	50.4	75.0
DLCO SB % predicted	76.4	25.0	-	40.3	13.9	57.1
Fibrosis on HRCT	Yes	Yes	No	No	Yes	Yes
Heamodynamics						
sPAP / dPAP (mmHg)	110/40	60/32	43/19	96/49	85/35	76/30
mPAP (mmHg)	63	37	27	66	55	43
PAWP (mmHg)	6	11	10	18	5	12
PVR (Wood Units)	10.3	10.4	3.2	11.3	13.9	7.2
Cardiac output (L/min)	5.6	2.5	5.3	4.3	3.6	4.6
Sarcoidosis treatment						
Supplemental oxygen use	No	Yes	Yes	Yes	Yes	No
Immunosuppressive treatment	No	Yes	Yes	Yes	No	Yes
Escalation of immunosuppressive treatment during follow-up	Yes	No	No	No	Yes	No

Table 9.1. *Continued*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
PH treatment						
Initial PH-targeted therapy	Macitentan	Macitentan	Dual	Macitentan	Dual	Sildenafil
Time before start dual treatment (months)	3	1	-	10	-	15
Follow-up duration (months)	42	12	12	42	36	18
Outcome parameters						
NYHA functional class at baseline	III	III	III	III	IV	III
NYHA functional class at 12 months	II	III	II	II	III	III
NYHA functional class at 24 months	II	III	II	II	III	IV
6-MWD at baseline (meters)	327	365	445	364	145	341
6-MWD at 12 months (meters)	439	-	457	367	340	244
6-MWD at 24 months (meters)	456	-	-	422	243	-
NT-proBNP at baseline (pg/mL)	136	959	52	3382	5875	346
NT-proBNP at 12 months (pg/mL)	110	1516	45	3512	343	688
NT-proBNP at 24 months (pg/mL)	38	-	-	1543	210	-

6-MWD = six minute walking distance; DLCO SB = diffusing capacity of the lung for carbon monoxide single breath; dPAP = diastolic pulmonary artery pressure; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high resolution chest tomography; mPAP = mean pulmonary artery pressure; NYHA = New York Heart Association; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; sPAP = systolic pulmonary artery pressure.

Discussion

To the best of our knowledge, this is the first case series describing the safety and effect of macitentan, either as monotherapy or as dual treatment with sildenafil, as treatment for SAPH in predominantly patients with fibrosing pulmonary sarcoidosis. We found that macitentan was well tolerated in five patients, but one patient aborted macitentan therapy due to side effects and died sixteen months later.

Judson et al. investigated the role of the endothelin receptor antagonist ambrisentan as treatment for SAPH. They found that 11 out of 21 patients aborted ambrisentan therapy, mostly due to increasing dyspnoea.[7] In our case series, no patients aborted therapy due to dyspnoea. However three patients were hospitalised for dyspnoea due to congestive heart failure, but recovered with diuretic treatment. A known side effect of a pulmonary vasodilator in parenchymal lung disease is the possible worsening of ventilation/perfusion mismatch, which could lead to increasing dyspnoea.[10,11] Unfortunately, we were not able to evaluate the effect of macitentan on gas exchange before and during treatment due to missing data for arterial blood gas analyses. The found rate of adverse events are in line with the MUSIC trial. This study showed that 12 months of macitentan therapy was well tolerated in patients with idiopathic pulmonary fibrosis, with 12.6% of patients aborting therapy due to adverse events.[12]

Furthermore, in four patients functional class improved and in three patients exercise capacity improved after 12 months of therapy. A possible confounder for this improvement is the escalating immunosuppressive treatment for increased sarcoidosis activity. It is known that immunosuppressive treatment can improve FVC in pulmonary sarcoidosis patients.[13] This could explain the functional improvement in case 5 as this was the only case with an improved FVC during follow-up. In all other cases the FVC remained stable.

In conclusion, this is the first case-series describing the safety and effect of macitentan therapy in SAPH. Macitentan was well tolerated in five out of six cases with severe pulmonary sarcoidosis and PH. Functional capacity improved in four out of six cases. However, results of this case series need to be interpreted with caution. Prospective controlled trials are warranted before therapeutic recommendations can be made.

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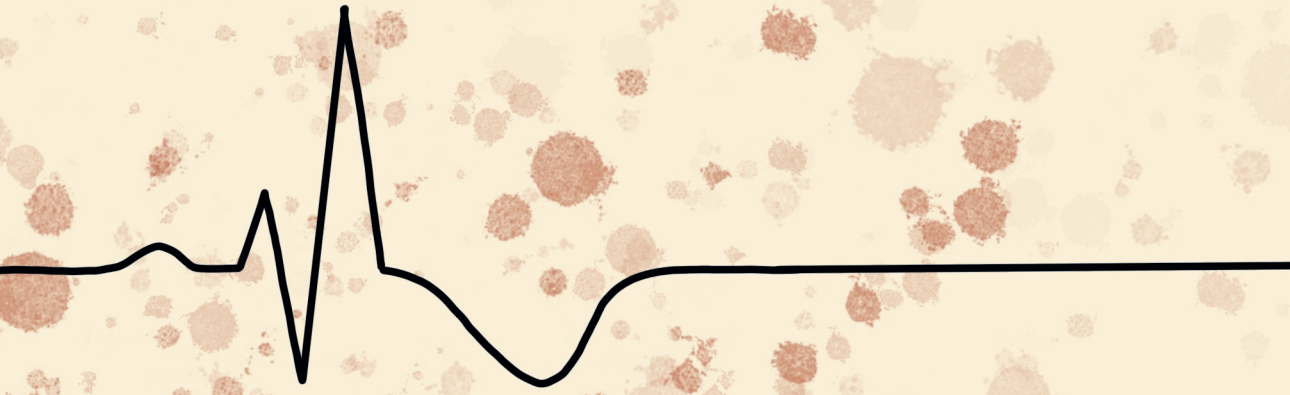

CHAPTER 10

Four-year survival rate in pulmonary sarcoidosis with extensive pulmonary hypertension screening

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Abstract

Background: Sarcoidosis is a systemic disease of unknown aetiology with significant morbidity and mortality. The PULSAR study prospectively performed cardiac analysis including systematic pulmonary hypertension screening in sarcoidosis patients newly referred to a tertiary sarcoidosis center. In this manuscript we studied the four-year mortality of this population.

Methods and main findings: Between August 2015 and October 2017, 399 patients (58% male, mean age 49.4 years, 90.5% Caucasian) were included and followed for a mean period of 4.3±0.7 years. In total, 10 patients had died at the time of analysis. 1-, 2-, 3- and 4-year survival rate was 100% (n=399), 99.0% (n=399), 98.2% (n=399) and 96.4% (n=276). Most patients died of respiratory failure, other causes were heterogeneous including cardiac, neurological and non-sarcoidosis origin. A low CPI score or modified Walsh score was associated with higher mortality, similar for high PH probability on echocardiography and elevated right ventricular systolic pressure.

Conclusion: This study highlights that elevated RVSP and presence of PH on echocardiography and progression of fibrotic disease with subsequent decline in pulmonary function test are important factors for mortality in sarcoidosis patients.

Introduction

Sarcoidosis is a systemic disease of unknown aetiology which may result in chronic disease with significant morbidity and mortality, depending on disease stage and severity.[1–7] Previous studies have never performed systematic cardiac analysis including pulmonary hypertension (PH) screening. In 2019, the PULmonary hypertension in pulmonary SARcoidosis (PULSAR)-study showed a PH prevalence of 3%.[8] We present four-year follow-up data on mortality of this well-defined group of pulmonary sarcoidosis patients.

Methods

The PULSAR study is a cross sectional prospective cohort study performing systematic cardiac evaluation in a large well-defined cohort of mainly Caucasian pulmonary sarcoidosis patients newly referred to a national center of excellence for both sarcoidosis and PH. An extensive description of study design can be found in the previously published article.[8]

All patients underwent transthoracic echocardiography (TTE), and were referred for right heart catheterisation (RHC) in case of intermediate or high PH probability as defined by the ESC/ERS guideline.[9] PH was defined as a mean pulmonary artery pressure (PAP) ≥25mmHg by RHC, and absence of PH as a mean PAP <25mmHg or a low PH probability on TTE. Patients with reduced left ventricular ejection fraction, elevated cardiac biomarkers, ECG abnormalities or symptoms suggestive for cardiac sarcoidosis (CS) were evaluated by cardiac magnetic resonance imaging and 24-hour ECG monitoring and FDG PET/CT, and classified as CS unlikely/possible/probable by a multidisciplinary team according to the Heart Rhythm Society consensus statement.[10] Furthermore, data was collected on demographics, imaging and pulmonary function test. Composite Physiologic Index (CPI), Walsh and modified Walsh algorithm scores were calculated.[5,11] Data on mortality of all patients were obtained from the Dutch national death registration (consultation date 26-02-2021). The cause of death was determined by chart review and if necessary by consulting the general practitioner. Survival was analysed using Kaplan Meier analysis, with the Log-Rank test for comparison between curves. Predictors for mortality were analysed using Univariate Cox regression. Event numbers were too low for multivariate analysis.

Results

Between August 2015 and October 2017, 399 patients (57.9% male, mean age 49.4±11.6 years, 90.5% Caucasian) were included in the PULSAR study,[8] and followed for a mean period of 4.3±0.7 years. During follow-up, ten (2.5%) patients died and none were transplanted.

Main findings between the groups 'alive' and 'death' are displayed in Table 10.1. The overall 1-, 2-, 3- and 4-year survival rate was 100% (n=399), 99.0% (n=399), 98.2% (n=399) and 96.4% (n=276). The main cause of death was respiratory failure (n=5), of whom one due to COVID-19. One patient with concomitant CS died due to end stage heart failure. One patient was found dead at home with unknown cause. Another patient died in palliative setting due to neurological paralysis, possibly related to neurosarcoidosis. Furthermore, two patients died from non-sarcoidosis related comorbidities. As shown in Table 10.1, patients who had died were significantly older and were more likely to be on immunosuppressive or oxygen therapy. Troponin T was more often elevated in deceased patients. The FVC% predicted and DLCOcSB% predicted was lower in the deceased group. The alive patients had a significantly lower CPI score and modified Walsh algorithm score. For the Walsh algorithm there was a trend towards significance. Low, intermediate and high PH probability was present in 368, 22 and 6 patients respectively. 28 patients underwent RHC. Among the deceased patients, one had confirmed PH due to chronic thrombo-embolic pulmonary embolisms and severe fibrotic pulmonary sarcoidosis. Seven patients had a low PH probability on echocardiography. In the other two patients PH was excluded by RHC. Right ventricular systolic pressure (RVSP) was significantly higher in deceased patients. A high PH probability on TTE was associated with increased mortality (HR 8.7; 95% CI 1.1–69.1, p=0.042). All deceased patients had a normal left ventricular function at baseline. CS was diagnosed as 'probable' in 9.3% of the alive and 10.0% of the deceased patients.

Discussion

This study shows that the four-year mortality rate in pulmonary sarcoidosis patients, newly referred to a tertiary sarcoidosis center, is low with a four-year survival rate of 96.4%. Especially compared to studies with a more severely diseased population,[5,7,11–13] showing an increased mortality in patients with more severe lung disease with 5 year survival rates of 91.5%,[6] and with PH (3–5 year survival rates around 55%).[4,7]

Table 10.1: Baseline characteristics

Parameter	Alive (n=389)	Deceased (n=10)	p-value	Hazard ratio
Age (years)	49.0 [40.4–56.9]	64.0 [46.1–72.8]	0.005	HR 1.08 [95% CI 1.02–1.14]
Male sex	58.4%	40.0%	0.238	-
Caucasian ethnicity	90.2%	100%	0.302	-
Duration of disease (years)	2.31 [0.66–7.60]	4.97 [0.53–24.04]	0.084	-
Immunosuppressive therapy at baseline	37.0%	80.0%	0.006	HR 6.5 [95% CI 1.4–30.8] p=0.018
Oxygen therapy	0.8%	10.0%	0.002	HR 12.6 [95% CI 1.6–99.4] p=0.016
NYHA functional class			0.306	-
I	30.1%	20.0%		
II	56.6%	50.0%		
III	13.4%	30.0%		
High sensitive troponin T >0.014 (ug/L) (n=386)	7.2%	33.3%	0.004	HR 6.1 [95% CI 1.5–24.4] p=0.011
NT-proBNP (pg/mL)	48.0 [24.0–91.5]	79.0 [32.0–373.5]	0.277	-
Scadding stage (n=374)			0.790	-
0	27.2%	30.0%		
I	21.2%	10.0%		
II	26.1%	30.0%		
III	5.8%	0.0%		
IV	19.8%	30.0%		

Table 10.1 continues on next page.

Table 10.1: ***Continued***

Parameter	Alive (n=389)	Deceased (n=10)	p-value	Hazard ratio
FVC % predicted (n=381)	100.0 [88.0–110.0]	83.5 [60.3–104.0]	0.021	HR 0.96 [95% CI 0.93–0.99]
FEV1 % predicted (n=383)	92.0 [78.0–104.0]	76.5 [61.3–99.3]	0.149	-
DLCOcSB % predicted (n=345)	77.0 [66.1–86.0]	56.5 [39.0–80.8]	0.006	HR 0.95 [95% CI 0.92–0.99]
CT MPAD (mm) (n=316)	27.0 [25.0–30.0]	28.0 [25.0–30.0]	0.306	-
CT MPAD/BSA ratio (n=316)	13.5 [12.4–15.0]	15.3 [11.9–15.8]	0.097	-
CT MPAD/AAD (n=316)	0.88 [0.79–0.96] (n=306)	0.84 [0.71–0.98]	0.376	
CT total disease extend (n=311)			0.613	-
<5%	42.4%	40.0%		
5–20%	18.1%	30.0%		
>20%	39.5%	30.0%		
RVSP (mmHg) (n=193)	25.3 [21.2–30.2]	33.3 [27.9–45.0]	0.004	HR 1.07 [95% CI 1.02–1.11]
Echocardiographic PH classification			0.046	HR 8.7 (high vs low)
Low	93.5%	80.0%		[95% CI 1.1–69.4]
Intermediate	5.2%	10.0%		p=0.042
High	1.3%	10.0%		
LV ejection fraction impaired <50% (n=397)	5.8%	0.0%	0.893	-

Table 10.1: *Continued*

Parameter	Alive (n=389)	Deceased (n=10)	p-value	Hazard ratio
Diastolic function normal (n=385)	92.2%	100.0%	0.680	-
TAPSE (mm) (n=392)	22.0 [20.0–25.0]	20.0 [17.9–24.3]	0.179	-
CPI (n=345)	19.9 [11.9–27.6]	34.6 [13.6–59.8]	0.002	-
CPI >40 (n=345)	8.9%	50.0%	<0.001	HR 9.6 [95% CI 2.4–38.5] p=0.001
Walsh algorithm poor prognosis (n=284)	22.1%	50.0%	0.063	HR 3.4 [95% CI 0.86–13.7] p=0.081
Modified Walsh algorithm poor prognosis (n=284)	18.8%	50.0%		HR 4.2 [95% CI 1.05–16.8] p=0.042

BSA = body surface area; CPI = Composite Physiologic Index; CT = computed tomography; DLCOSB = diffusing capacity for carbon monoxide single breath; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; HR = hazard ratio; LV = left ventricle; MPAD = mean pulmonary artery diameter; NT-proBNP = N-terminal pro brain natriuretic peptide; NYHA = New York Heart Association; PH = pulmonary hypertension; RVSP = right ventricular systolic pressure; TAPSE = tricuspid annular plane systolic excursion.

In our study, we found that the Modified Walsh algorithm, elevated RVSP and presence of PH on echocardiography, treatment with immunosuppressive agents, need for oxygen therapy, and decreased FVC% and/or DLCOcSB% predicted were significant predictors for mortality. These findings are in line with previous population based and clinical studies, which have identified several potential predictors for increased mortality, such as age,[3] presence of PH,[3–6] severity of pulmonary fibrosis on chest CT[3,5] or Scadding stage IV disease[3,4] and risk scores like CPI, Walsh or modified Walsh algorithm.[5,11] In our cohort CPI score was significantly higher in the deceased patients. The Walsh algorithm showed a trend towards significance between alive and deceased patients. However, the Modified Walsh algorithm incorporating the pulmonary artery diameter corrected for body surface area, was a significant predictor for mortality with a HR of 4.2. The Walsh algorithm was validated by Walsh et al. and showed to be a strong predictor for mortality with a HR of 4.91.[11] In the study by Jeny et al., poor prognosis by the Walsh algorithm and especially the Modified Walsh algorithm was a powerful predictor with a HR of 5.54 and 11.0 respectively.[5] In contrast to the present study, only patients with Scadding stage IV sarcoidosis were included and there was a higher prevalence of non-white patients, higher CPI scores and worse pulmonary function tests. Presence of PH on echocardiography, defined as an RVSP >35mmHg, was a significant predictor with a HR of 3.42. Kirkil et al. studied a more similar population, with Scadding Stage IV in 17.3% of the patients and comparable pulmonary function tests and CPI scores, but a higher prevalence of black patients (30.1%).[3] In this study the Walsh algorithm poor prognosis was associated with increased mortality with a HR of 3.21. PH, defined as a mean PAP ≥25mmHg during RHC, was a significant predictor for mortality with a HR of 8.96. Our study was the first to perform prospective cardiac evaluation including extensive PH screening in all patients, showing a high PH probability on echocardiography as predictor for mortality during follow-up with a HR of 8.7 (high vs low PH probability). This is in line with other studies, however it should be noted that other studies often use non-guideline definitions for PH and no systematic screening for PH was performed. Furthermore, this study showed that the cause of death is highly variable and can be either due to pulmonary, cardiovascular or neurologic complications of sarcoidosis.

This study has several limitations. Due to a study population with less severe disease compared to other studies, event numbers are relatively low and therefore robust statistical analysis including multivariate analysis could not be performed. Furthermore, not all patients underwent RHC and/or cardiac magnetic resonance imaging and therefore the prevalence of PH or CS might be underestimated.

Conclusion

In this well-defined cohort of pulmonary sarcoidosis patients newly referred to a tertiary center, overall 4-year survival was 96.4%. This study highlights that elevated RVSP and presence of PH on echocardiography and progression of fibrotic disease with subsequent decline in pulmonary function test are important factors for mortality in sarcoidosis patients.

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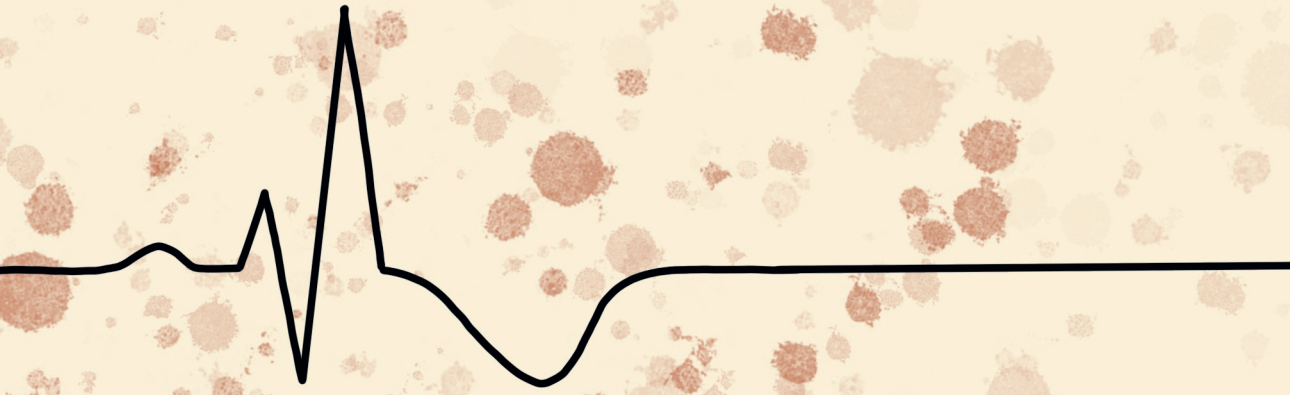
PART IV

RECOMMENDATIONS



CHAPTER 11

WASOG statement on the diagnosis and management of sarcoidosis-associated pulmonary hypertension

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Abstract

Sarcoidosis-associated pulmonary hypertension (SAPH) is an important complication of advanced sarcoidosis. Over the past few years, there have been several studies dealing with screening, diagnosis and treatment of SAPH. This includes the results of two large SAPH-specific registries. A task force was established by the World Association of Sarcoidosis and Other Granulomatous disease (WASOG) to summarise the current level of knowledge in the area and provide guidance for the management of patients. A group of sarcoidosis and pulmonary hypertension experts participated in this task force. The committee developed a consensus regarding initial screening including who should undergo more specific testing with echocardiogram. Based on the results, the committee agreed upon who should undergo right heart catheterisation and how to interpret the results. The committee felt there was no specific phenotype of a SAPH patient in whom pulmonary hypertension-specific therapy could be definitively recommended. They recommended that treatment decisions be made jointly with a sarcoidosis and pulmonary hypertension expert. The committee recognised that there were significant defects in the current knowledge regarding SAPH, but felt the statement would be useful in directing future studies.

Introduction

Pulmonary hypertension (PH) is haemodynamically defined by right-heart catheterisation (RHC) by a mean pulmonary artery pressure (mPAP) above 20mmHg. Post-capillary PH is characterised by a pulmonary artery wedge pressure (PAWP) above 15mmHg while pre-capillary PH is defined by PAWP ≤15mmHg and pulmonary vascular resistance (PVR) >3 Wood's units (WU). Right ventricle (RV) remodelling and dysfunction induced by increased afterload results in exercise limitation and death. The purpose of the recently updated PH 6th World Symposium clinical classification was to categorise clinical conditions associated with PH based on similar pathophysiological mechanisms, clinical presentation, haemodynamic characteristics and therapeutic management. Sarcoidosis-associated pulmonary hypertension (SAPH) can be caused by different and sometimes overlapping mechanisms and it has remained in Group 5 of the clinical classification of PH. SAPH is a significant cause of morbidity and mortality in patients with advanced sarcoidosis[1,2] The reported incidence of SAPH has been around 5% in studies from across the world. Higher incidences were reported in patients who had persistent dyspnoea or who were being evaluated for lung transplantation (Figure 11.1).[3–16] Over the past few years, there has been increasing recognition of the prevalence of this major complication of sarcoidosis, as well as studies regarding screening/early detection, diagnosis and treatment.

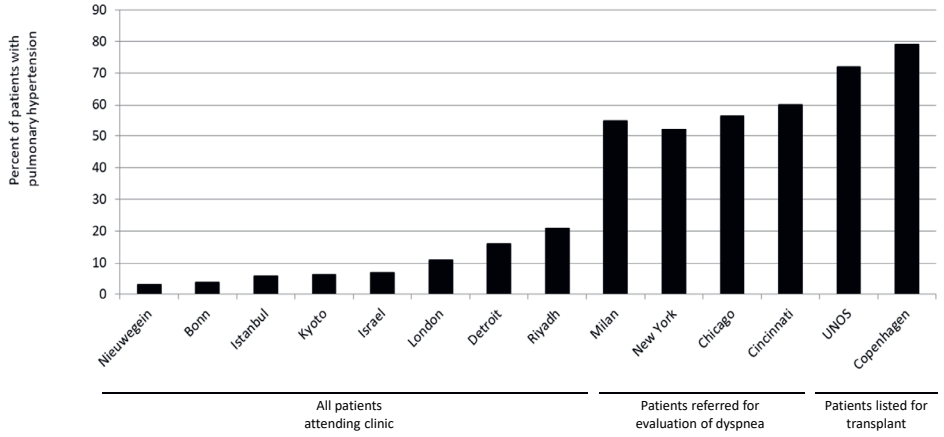

Figure 11.1: The reported incidence of SAPH from various centres across the world.
The city or country of origin of the study is indicated. A higher incidence of SAPH was found for patients being evaluated for persistent dyspnoea or lung transplantation.[3–16] SAPH = sarcoidosis-associated pulmonary hypertension; UNOS = United Network Organ Sharing.

Based on the increasing evidence and the need for better awareness of SAPH, a task force was established by the World Association of Sarcoidosis and Other Granulomatous diseases (WASOG) and the Foundation for Sarcoidosis Research (FSR). This global task force was chaired by three international experts: two of sarcoidosis (RP Baughman, AU Wells) and one of PH (M Humbert). The committee met physically and virtually over 3 years (2019–2021). The committee acknowledges that the present recommendations were for the most part based on limited information available for SAPH. Many organisations such as the European Respiratory Society use the GRADE method and PICO questions (patient, intervention, comparison, outcomes)[17] for clinical practice guidelines. We decided not to use this approach because there were too few well-designed large multicentre SAPH registries and randomised clinical trials. The committee therefore focused on specific areas regarding screening, diagnosis and treatment and made specific comments (Table 11.1). The comments were based on a literature review and a series of polls of the committee members to provide answers where there was consensus among the committee members. Consensus was defined as >70% of voting members agreeing on an individual statement. This Statement is narrative and pragmatic rather than systematic and is further complemented by a description of usual clinical practice and the experience of the panel members.[18] This Statement summarises the current state of knowledge and it does not make formal recommendations for clinical practice.

Table 11.1: Summary of Task Force comments

1.	Presence of SAPH is associated with significant symptomatology and morbidity, as evidenced by increased WHO FC, decreased 6MWD or desaturation and increased oxygen use.
2.	Pulmonary hypertension is an independent predictor of mortality in patients with sarcoidosis.
3.	Since the cause of SAPH is multi-factorial, the committee commented that the current recommendation to keep SAPH in Group 5 was reasonable. The committee considered that patients with left ventricular disease either due to sarcoidosis or other conditions should be treated as WHO Group 2. The committee felt it was important to identify a dominant cause for SAPH on an individual basis, as it is likely to have treatment implications.
4.	The suggestions of who should undergo transthoracic echocardiogram are summarised in Figure 11.3.
5.	The committee's suggestions regarding who should undergo RHC are summarised in Figure 11.5.
6.	The committee suggested that the right heart catheterisation results should be interpreted by a multidisciplinary team with at least a sarcoidosis and PH expert and decisions should be made as summarised in Figure 11.6.
7.	Evaluate for pulmonary artery stenosis or mediastinal compression by chest imaging.
8.	In SAPH, treatment decision and follow-up should be made by a multidisciplinary team with a sarcoidosis and a PH expert. Off label use of PAH medical therapy may be considered for symptomatic patients on a case by case basis (Figure 11.7).
9.	Patients who have failed to respond to treatment for PH should be referred for lung transplant evaluation, if they are deemed otherwise to be appropriate candidates.

SAPH clinical outcomes

Is SAPH associated with increased morbidity?

The presence of PH in sarcoidosis is associated with greater supplemental oxygen requirements[10,12,15,19,20] as exemplified by an analysis of 363 patients with sarcoidosis listed for lung transplantation, in which subjects with SAPH required more supplemental oxygen (2.7±1.8 versus 1.6±1.4L·min^{-1}) compared with those without PH.[15] In the ReSAPH registry analysis of 176 patients, most desaturated during the 6-min walk test (6MWT), with a median degree of desaturation of 5%.[20] Similarly, in the French Registry cohort of 126 patients with moderate-to-severe SAPH followed over a 10-year period, 54% were on long-term oxygen.[21] Presence of SAPH also increases the burden on functional capacity,[10,22–24] employment status and need for caregiver assistance.[19] In the French Registry, 83% of the patients with SAPH reported World Health Organisation (WHO) functional class (FC) III–IV symptoms.[21] In the Duke cohort of 95 patients followed for 11 years, almost all patients (99%) were symptomatic with activity (WHO FC II–IV symptoms) and 77% of the cohort reported WHO FC III/IV symptoms.[22] In a small British cohort of 24 patients, 48% had WHO FC III symptoms, while 42% had WHO FC IV symptoms.[23] Moreover, objective assessment of functional capacity supports subjectively reported decreased exercise tolerance in patients with SAPH. The 6-min walk distance (6MWD) was consistently found to be reduced in several studies, with mean values ranging between 305 and 320 metres.[20,21,24] The French Registry analysis which captured dyspnoea assessed by the Borg scale found it to be elevated at 4.0±2.3[21] during the performance of the 6MWT.

Summary

Presence of SAPH is associated with significant symptomatology and morbidity, as evidenced by increased WHO FC, decreased 6MWD or desaturation and increased oxygen use.

Is SAPH an independent predictor of mortality?

Several studies have assessed the presence of RV dysfunction in patients with SAPH. In the Duke cohort, the median N-terminal pro-brain natriuretic peptide (NT-proBNP) level at the time of initial evaluation was 910 pg·mL^{-1} (Q1–Q3: 225–2807). On transthoracic echocardiogram, the majority (59%) of patients had either moderate or severe RV enlargement and 55% had moderate or severe RV dysfunction.[22] Interestingly, in this cohort, neither baseline echocardiographic nor haemodynamic characterisation of RV function were associated with outcomes, but follow-up NT-proBNP levels were higher in those who died or were hospitalised (1258.0 versus 262.0 pg·mL^{-1}, p=0.007).

The mortality implications of any PH, both pre- and post-capillary, in the context of sarcoidosis are also profound, with a 10-fold increase in mortality and an estimated 5-year survival of only 59%.[1,14,25] Figure 11.2 shows the 1-, 3-, and 5-year survival reported from several centres across the world.[7,13,21,23,24] In the Duke cohort, the median time from diagnosis of SAPH to either death or hospitalisation was 6 months (Q1–Q3: 3.0–12.0 months).[22] Patients with SAPH are more likely to be listed for lung transplant and also have a greater likelihood of succumbing while on the waiting list.[15,26] In the British cohort, the rate of mortality or transplantation was 41.2% with the median survival without transplantation being 5.3 years. In that study, more patients who died or underwent transplantation during follow-up had baseline RV dysfunction (80%).[23] The ReSAPH registry analysis of 159 patients with pre-capillary SAPH demonstrated the 1-, 3- and 5-year transplant-free survival to be 83.7%, 70.6% and 58.5%, respectively. Severe gas transfer impairment (diffusing lung capacity for carbon monoxide (D_{LCO}) <35% predicted) and 6MWD <300m were strong predictors of decreased survival (p=0.0151 and p<0.0001, respectively).[24] These results were similar to the French Registry, which demonstrated 3- and 5-year survival rates of 74% and 55%, respectively.[21]

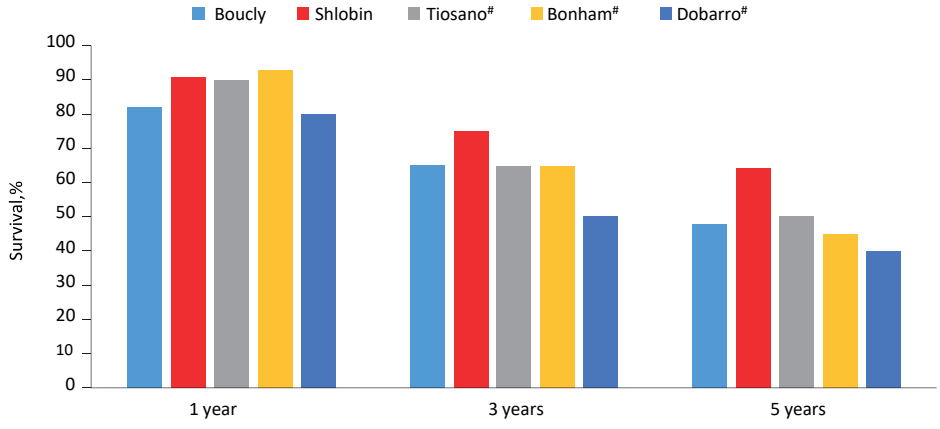

Figure 11.2: The 1-, 3- and 5-year survival from sarcoidosis-associated pulmonary hypertension.[7,13,21,23,24]
For three of the studies,[7, 13, 23] the survival was estimated based on the Kaplan–Meier survival curves presented in the papers.

In patients with SAPH from the French Registry, univariate analysis showed that WHO FC IV, 6MWD and reduced forced vital capacity (FVC) or D_{LCO} were associated with a poor survival.[21] In multivariate analysis, only 6MWD remained independently associated with mortality.[21] It is still not clear if patients with SAPH are succumbing because of PH or in the presence of PH. In one study, which demonstrated that SAPH was associated with mortality, the only haemodynamic factor that remained predictive of mortality

after multivariable analysis was the right arterial pressure.[26] In another study of a small cohort of 24 patients, presence of right ventricular dysfunction on echocardiography was the most powerful predictor of death or transplantation (OR 83.1, 95% CI 2.2–31.02, p=0.017).[23] This evidence of right-sided heart failure implies that patients with SAPH are indeed dying from their PH, rather than the PH being an epiphenomenon.

In two multi-regression analyses PH has been found to be an independent risk factor for mortality.[1,2] In evaluating patients awaiting lung transplant the final prediction model for mortality included mPAP.[19] In an analysis of fibrotic sarcoidosis patients, presence of PH by echocardiography had a hazard ratio for mortality of 3.42. In the study by Kirkil et al.,[1] haemodynamically confirmed pre-capillary SAPH had a hazard ratio of 8.96 and, along with fibrosis >20% by high-resolution computed tomography (HRCT) and age, remained an independent predictor of mortality by Cox modelling.

Summary

PH is an independent predictor of mortality in patients with sarcoidosis

Classification/cause of SAPH

Should SAPH be divided into various subclasses

SAPH can be caused by a variety of mechanisms (Table 11.2). Due to the predilection of granulomas for the lymphatics, which are found in the bronchovascular bundles and the interlobular septae, pulmonary vascular granulomatous involvement typically occurs on both the arterial and venous sides of the circulation. In one study of organ explants from patients with sarcoidosis undergoing lung transplantation, features of venous involvement were identified in addition to arterial disease.[25] An increased incidence of pulmonary emboli is frequently encountered in sarcoidosis patients,[27–29] and chronic thromboembolism can potentially lead to Group 4 PH.[30] Interstitial changes are also highly associated with the development of PH.[20,21]

Although more than half of patients with SAPH have clinical fibrotic lung disease, most studies confirm that up to 20% of patients with SAPH have no radiographic evidence of parenchymal lung disease.[12,20,31] Alveolar hypoxia, most frequently in the setting of parenchymal involvement, may also contribute to the development of PH. Hilar adenopathy compressing the pulmonary arteries and veins can also lead to PH. However, compression usually has to be of multiple vessels to lead to significant PH. In a study of 156 patients with SAPH, significant compressive hilar adenopathy leading

to PH was identified in only two patients.[21] Fibrosing mediastinitis due to sarcoidosis can also contribute to PH.[32–34] In the French Registry, 3 of 156 patients with SAPH had fibrosing mediastinitis as the identified cause.[21] In a prospective study of 72 patients with SAPH from a single institution, eight patients were found to have vascular compression/distortion. In all eight patients, stenting was successful in reducing pulmonary artery pressure.[35]

Table 11.2: Causes of pulmonary hypertension in sarcoidosis patients

Condition	Potential treatments
Vascular disease	
Vasculitis	Glucocorticoids and other anti-inflammatory treatments Pulmonary vasodilators
Granulomatous vascular involvement	Glucocorticoids and other anti-inflammatory treatments Pulmonary vasodilators
Veno-occlusive disease	Glucocorticoids and other anti-inflammatory treatments Careful use of pulmonary vasodilators
Pulmonary embolism (CTEPH)	Anticoagulation Balloon pulmonary angioplasty Pulmonary endarterectomy Pulmonary vasodilators
Interstitial lung disease	
Parenchymal lung disease due to granulomas	Glucocorticoids and other anti-inflammatory treatments
Parenchymal lung disease due to fibrosis	Anti-fibrotic agents
Hilar and mediastinal distortion	
Pulmonary artery/vein extrinsic compression	Glucocorticoids and other anti-inflammatory treatments Dilation and/or stenting of compressed vessels
Fibrosing mediastinitis	Dilation and/or stenting of compressed vessels
Extrapulmonary disease	
Left ventricular systolic dysfunction	Glucocorticoids and other anti-inflammatory treatments Diuretics, afterload reduction
Left ventricular diastolic dysfunction	Diuretics
Sleep apnoea	CPAP, oxygen and other measures
Liver disease	Glucocorticoids and other anti-inflammatory treatments

CTEPH = chronic thromboembolic pulmonary hypertension; CPAP = continuous positive airway pressure.

Left ventricular disease can lead to development of post-capillary PH. In one study, approximately 20% of patients with SAPH demonstrated elevated PAWP, consistent with left ventricular failure.[14] Sarcoidosis patients may have comorbid coronary artery disease. This can be a cause of significant morbidity in sarcoidosis.[36] Evaluation

of patients with elevated pulmonary artery pressure should exclude left ventricular disease as the basis of either ischaemic or nonischaemic heart disease. Granulomatous inflammation can also cause an infiltrative cardiomyopathy often leading to left heart failure.[37] However, in some cases, the left ventricular ejection fraction may be normal or only mildly impaired but still have a less compliant left ventricle.[38,39]

Sleep-related breathing disorders can contribute to PH,[40,41] and patients with sarcoidosis have an increased incidence of obstructive sleep apnoea syndrome (OSAS).[42–44] Of note, chronic use of corticosteroids increases the risk for OSAS in sarcoidosis patients, regardless of gender of patient.[44] If OSAS is diagnosed, treatment with continuous positive airway pressure (CPAP) should be initiated.

Although the liver is one of the most commonly affected organs in sarcoidosis,[45,46] severe liver disease is relatively uncommon[47,48] and portopulmonary hypertension is rarely seen.

Summary

Since the cause of SAPH is multifactorial, the committee commented that the current recommendation to keep SAPH in Group 5 was reasonable. The committee considered that patients with left ventricular disease either due to sarcoidosis or other conditions should be treated as WHO Group 2. The committee felt it was important to identify a dominant cause for SAPH on an individual basis, as it is likely to have treatment implications.

Screening and diagnosis of SAPH

Who should get a transthoracic echocardiogram?

Screening is defined as the systematic use of a test, or tests, in at-risk individuals to identify disease before symptom onset. Previous studies have shown that screening allows earlier management and better clinical outcome in patients with systemic sclerosis-associated pulmonary arterial hypertension (PAH).[49] While the consequences of SAPH screening remains unknown, the task force felt that it is desirable to improve awareness of this severe complication of sarcoidosis in an attempt to diagnose it earlier when functional impairment and haemodynamics are less severely compromised. Therefore, screening (in asymptomatic patients) and early diagnosis (when symptoms and functional impairment are present) have the potential to identify SAPH at an early stage. It has been previously recommended using GRADE methodology that a tran-

sthoracic echocardiogram should be performed in those patients with sarcoidosis in whom PH is suspected (conditional recommendation).[50]

The task force evaluated what factors would lead to the decision to perform a transthoracic echocardiogram in patients with sarcoidosis and identified several features which were likely to be associated with SAPH (Figure 11.3). The task force felt the presence of one or more of these features should lead to echocardiography. RHC should be performed when echocardiography gives a high or intermediate probability of PH (according to the ESC/ERS PH guidelines) (Figure 11.4)[51] and for all patients being considered for lung transplant. For those patients, the RHC should be followed by left catheterisation and coronairiography because of the potential implication of the results for the patient's management and on future lung transplantation in eligible cases (timing of transplantation, lung or heart-lung transplantation, need of extracorporeal circulation). Over 70% of sarcoidosis patients undergoing lung transplant will have SAPH and presence of SAPH increases the indication for transplant.[16,19] However, SAPH was not associated with higher mortality after transplant.[52] While a recent study did not find that SAPH was associated with increased mortality for patients on the lung transplant list,[53] patients with SAPH still had significant morbidity.

Other features, ranging from chest imaging to serum biomarkers, have been associated with the presence of SAPH and therefore could be considered as part of the screening process. In three large studies, approximately half of sarcoidosis patients with persistent dyspnoea despite anti-inflammatory therapy were noted to have SAPH.[11,12,14] These studies did not identify which specific complaint or level of dyspnoea led to further evaluation. However, all three studies found that the rate of SAPH was up to ten times higher than the general sarcoidosis population. Patients with SAPH generally have a median 6MWD of <350m.[9,20,21,54] Most patients also desaturate >5% during the test.[9] It has also been noted that some patients with SAPH have elevated serum B-type natriuretic peptide (BNP) and NT-proBNP levels.[8,22,55] Chest imaging has also been shown to be abnormal in SAPH patients. Patients with SAPH are more likely to have pulmonary fibrosis than a comparable symptomatic group.[11,12] This has led to the recommendation that all sarcoidosis patients with fibrosis be screened for SAPH.[56] However, there was the concern among the committee about the variable interpretation of presence of pulmonary fibrosis on chest radiograph.[57] The presence of greater than 20% fibrosis on HRCT has proved a more reproducible assessment of fibrosis with good agreement between radiologists and clinicians.[58,59] The presence of >20% fibrosis on HRCT has been found to be associated with increased mortality in pulmonary sarcoidosis.[1,2,58] The presence of an increased pulmonary artery diameter, corrected for by either aorta

diameter or body surface area,[2,60,61] is associated with SAPH. The group also reached consensus regarding an enlarged right ventricle on a contrast computed tomography (CT) scan as an indicator for the patient to have a transthoracic echocardiogram. Cardiac MRI findings of RV dysfunction or PH have been reported in SAPH.[62,63] Cardiac MRI is useful in identifying cardiac sarcoidosis and as a result any potential treatment implications. Several studies in patients with SAPH have shown that patients with SAPH have a degree of pulmonary restriction (FVC <60% pred) and at least moderate gas transfer impairment (D_{LCO} <50% pred).[11,12,24] Patients with sarcoidosis such lung function parameters would be considered for SAPH screening. Using the paradigm of systemic sclerosis-associated PH, a K_{CO} (transfer coefficient of the lung for carbon monoxide) <60% pred or an FVC/ D_{LCO} ratio >1.6 may be parameters predicting SAPH.[49]

There was consensus that the presence of one or more of these factors should lead to echocardiography to determine the probability of PH. In addition, other features were identified by the group and consensus for screening echocardiography was achieved if there is a worsening of New York Heart Association (NYHA) functional class, a decrease >20% in the 6MWD, or a decrease >15% of the D_{LCO} when there was no significant change in lung volumes.

Summary

The suggestions of who should undergo transthoracic echocardiogram are summarised in Figure 11.3.

Who should get right-heart catheterisation?

RHC is the gold standard for diagnosing PH. It has been recognised for several years that echocardiography may over or underestimate pulmonary arterial pressure (PAP), especially in those with interstitial lung disease.[64,65] In sarcoidosis, RHC can be particularly helpful in separating pre- and post-capillary PH.[14] A transthoracic echocardiogram can estimate the probability of PH and raise suspicion, but it cannot define SAPH. The echocardiogram can provide information regarding RV function and evaluate left ventricular function may suggest post-capillary PH. However, a RHC remains the definitive test to distinguish between pre- and post-capillary PH.[14] Therefore, the committee felt the results of echocardiography should be used to determine who should undergo RHC.

The estimated RV systolic pressure based on tricuspid regurgitation velocity (TRV) is the most validated echocardiographic parameter to screen for PH. However, the echo may not be a well visualised tricuspid regurgitation (TR) jet seen on transthoracic echocardiogram. Also, other signs suggestive of PH may be seen on transthoracic echocardiogram

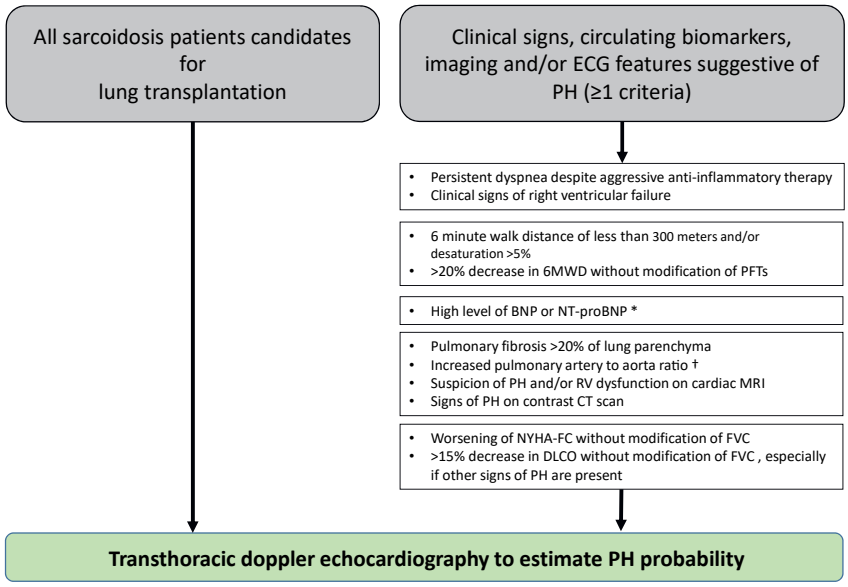

Figure 11.3: Algorithm for who should undergo transthoracic echocardiogram to evaluate for SAPH. 6MWD = 6-min walk distance; BNP = B-type natriuretic peptide; BSA = body surface area; CT = computed tomography; D_{LCO} = diffusing capacity of the lung for carbon monoxide; ECG = electrocardiogram; FVC = forced vital capacity; MRI = magnetic resonance imaging; NT-proBNP = N-terminal (NT)-pro hormone BNP = NYHA-FC = New York Heart Association functional class; PFT = pulmonary function test; PH = pulmonary hypertension; RV = right ventricle; SAPH = sarcoidosis-associated pulmonary hypertension. # Transthoracic echocardiogram recommended to assess for SAPH and left ventricular dysfunction. ¶ May be more accurate if corrected for BSA.

Echo suggestive of pulmonary hypertension	Peak tricuspid regurgitant velocity (m/s)	Presence of other echo "PH signs". See below
Low	≤ 2.8 or not measurable	No
Intermediate	≤ 2.8 or not measurable	Yes
Intermediate	2.9-3.4	No
High	2.9-3.4	Yes
High	>3.4	Not required

Presence of other echo "PH signs“		
The ventricles	**Pulmonary artery**	**Inferior vena cava and right atrium**
Right ventricle/left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or mid systolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentry index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) > 18 cm^2
	PA diameter >25 mm	

Figure 11.4: Probability of pulmonary hypertension from echocardiography findings of direct estimate of right ventricular systolic pressure and indirect evidence of right ventricular strain.
Reproduced from Galie et al.[51] PA = pulmonary artery; PH = pulmonary hypertension.

when analysing the ventricles, the pulmonary arteries, the inferior vena cava and right atrium. The ESC/ERS PH guidelines[51] have proposed a simple algorithm which allows one to incorporate both the TRV and other indirect measures (Figure 11.4) leading to a scoring of patients as having high, intermediate or low probability for PH. For SAPH, for those with low probability, the decision to proceed with a right catheterisation should be made on a case-by-case basis. For those in whom the results were inconclusive, the patient should be considered on a case-by-case basis (Figure 11.5) with a joint decision between a PH and a sarcoidosis expert. Factors which may influence the decision to perform a RHC include echocardiographic evidence for RV dysfunction (Figure 11.4), pulmonary function tests, 6MWT, BNP or NT-proBNP and imaging results. For members of the committee, there was not agreement regarding systematically performing a RHC in those with an intermediate probability of PH associated with severe interstitial lung disease. The presence of right ventricular dysfunction on echocardiogram adds further support to the decision to proceed with RHC, but there was insufficient evidence in sarcoidosis to make this a formal recommendation. Some felt this was not needed unless in the context of a lung transplant evaluation. Others felt that the decision for RHC should be made on a case-by-case basis. This ambivalence is predicated by the current literature that suggests this group may not be responsive to PAH therapies.

Summary

The committee's suggestions regarding who should undergo RHC are summarised in Figure 11.5.

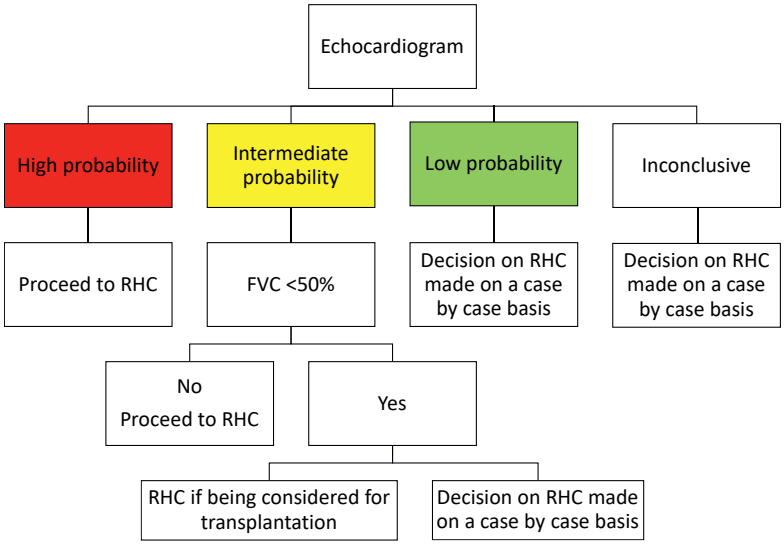

Figure 11.5: Algorithm for who should undergo RHC based on echocardiography.
FVC = forced vital capacity; RHC = right-heart catheterisation.

How should one interpret RHC in SAPH?

The committee felt that the RHC should be performed in a PH expert centre and its results (and consequences) should be interpreted by a multidisciplinary team with expertise in PH, sarcoidosis, imaging and transplantation, if available and appropriate. In some cases, the sarcoidosis and PH expert may be the same person. A cardiologist's input is needed for those with post-capillary PH to distinguish sarcoidosis-related causes from left-sided heart failure. Review of the RHC tracings may be useful in order to precisely define the pre- or post-capillary mechanisms of PH.

Figure 11.6 summarises the suggestions of the committee on assessing the RHC. For patients with an elevated mPAP (>20mmHg), the results of the PAWP measurement will determine whether this is pre- or post-capillary PH (WHO Group 2). As noted in the figure, a PAWP >15mmHg confirms a post-capillary PH. If there is any uncertainty about the validity of the PAWP measurement, then direct measurement of the left ventricular end-diastolic pressure measurement should be considered. The distinction is important for both treatment decisions as well as prognosis.[14] The committee recognised that patients might have combined pre- and post-capillary PH which can be either due to pre-capillary vascular changes due to left heart disease or due to sarcoidosis-related factors. Therefore, careful follow-up evaluation after the initial treatment decision should be undertaken for these patients in particular to ensure that the chosen treatment course is accompanied by a salutary and not a deleterious response. Pre-capillary PH due to pulmonary vascular disease is robustly defined when the PVR is ≥3WU but remains likely when the PVR is between 2 and 3.

For patients with a mean PAP of <20mmHg, the clinician should look elsewhere for the cause of symptoms and offer regular follow-up.

In patients with a PAWP 13–15mmHg, left-sided cardiac involvement can still be contributory to PH. However, a RHC occasionally with the need for provocative manoeuvres, such as fluid challenge or exercise, remains the definitive test to distinguish between pre and post-capillary PH.

The cardiac MRI may provide additional information in these cases. It may indicate cardiac involvement as the cause of increased pressures, especially for those WHO Group 2 patients. These patients should still be considered for a multidisciplinary discussion.[37] In addition, the presence of right ventricular abnormalities were prognostic factors in a population of sarcoidosis patients with suspected cardiac sarcoidosis.[66] No study has been conducted to the correlation between right ventricular sarcoidosis and the presence of PH.

Summary

The committee indicated that the RHC results should be interpreted by a multidisciplinary team with at least a sarcoidosis and PH expert and decisions should be made as summarised in Figure 11.6.

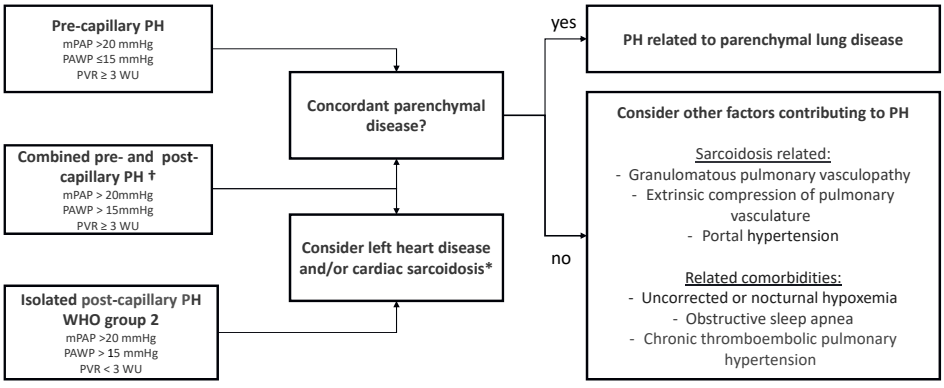

Figure 11.6: Interpretation of right heart catheterisation and subsequent treatment recommendations are made in the figure.

mPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WHO = World Health Organisation; WU = Wood's unit. *Cardiac sarcoidosis may be evident in pre-capillary PH without changing haemodynamics. †Careful evaluation should be performed by a cardiologist/PH specialist to distinguish PH due to left heart disease with subsequent pre-capillary vascular changes and sarcoidosis-associated PH.

Treatment

Should pulmonary vasculature be visualised to rule in/out narrowing

SAPH may be caused by direct compression of the pulmonary artery by either mediastinal adenopathy or fibrosis. For patients with adenopathy compressing the pulmonary arteries, anti-inflammatory therapy may lead to reduction of the size of the nodes and relief of the compression. Boucly et al.[21] identified this situation in five of their 126 (4%) patients with severe SAPH. The authors performed positron emission tomography (PET) scanning to detect this situation. Distortion of the vasculature due to mediastinal fibrosis can also lead to SAPH. In some cases, stenting of the vasculature may reduce PAP.[35,67] In a prospective study, all patients with SAPH underwent computer tomographic pulmonary angiography. Eight of 72 (11%) were found to have significant pulmonary artery stenosis and underwent successful stenting to relieve pressure.[35] A recent meta-analysis of the literature found that pulmonary artery angioplasty with or without stenting was successful in improving 6MWD.[68]

Summary

Evaluate for pulmonary artery stenosis and mediastinal compression chest imaging.

Should pre-capillary SAPH be treated?

The committee focused on treatment of pre-capillary PH. The World Symposium on Pulmonary Hypertension concluded in 2019 that there was insufficient information to make routine recommendations for therapy in SAPH.[69] The results of treatment of SAPH for individual PAH drugs are summarised in Table 11.3,[70–82] with results from the studies with the highest level of evidence for each treatment presented. To date, there have been only two double-blind, placebo controlled (DBPC) trials for SAPH.[70,71] Three studies

Table 11.3: Treatment of precapillary SAPH

	Highest level of evidence study in patients with SAPH	Total number of patients with SAPH treated	Results in sarcoidosis
Prostenoids			
Epoprostenol	Retrospective OL positive[78,79]	12	Haemodynamics improved[78,79]
Iloprost	Prospective, OL[72]	15 of 22 enrolled completed 16 weeks' therapy	In sarcoidosis, haemodynamics and QoL improved[72]
Endothelin receptor antagonists			
Bosentan	DBPC[71]	23	Haemodynamics improved, no change in 6MWD[71]
Ambrisentan	Prospective OL[73]	21	Nonsignificant improved QoL, no change 6MWD[73]
Macitentan	Retrospective OL[82]	6	WHO FC improved in 4/6 treated patients[82]
Phosphodiesterase 5 inhibitors			
Sildenafil	Retrospective OL[16]	12	Haemodynamics improved, 6MWD no changes
Tadalafil	Prospective OL[74]	12	No significant changes in 6MWD and QoL
Others			
Riociguat	DBPC[70]	16	TCW and 6MWD significantly better compared with placebo
Combination therapy	Retrospective OL positive[8,21,77]	29	Haemodynamics and 6MWD improved in some

SAPH = sarcoidosis-associated pulmonary hypertension; OL = open-label; QoL = quality of life; DBPC = double-blind, placebo-controlled; 6MWD = 6-min walk distance; WHO FC = World Health Organisation functional class; TCW = time to clinical worsening.

reported the results of prospective open label trials.[72–74] The remaining studies were retrospective case series. Initial or sequential combination therapy has been shown to be effective in treating PAH.[75,76] Three series have reported the outcome of treatment with various treatment regimens in SAPH.[8,21,77] In those studies, measuring haemodynamics before and after therapy, the majority of patients showed improvement.[8,16,21,71,72,77–79] There was only one study evaluating haemodynamics for placebo-treated patients demonstrating no significant change in pressures after 16 weeks.[71] Other end-points, including 6MWD and quality of life measures, had more mixed results. As summarised in Table 11.3, not all studies found a positive response to treatment in SAPH. To date, only one study has evaluated time to clinical worsening (TCW) with therapy.[70] That study has been published online and did find a significant improvement in TCW for riociguat compared with placebo.

Because of the limited number of randomised trials, the committee did not feel any specific recommendation could be made regarding one or other agent to treat pre-capillary PH. The committee felt that off-label use of PAH drugs may be considered on a case-by-case basis.[21,22] While not specifically studied in any of the trials, the committee felt that specific PAH therapies should be considered after taking into account the mechanisms involved in the development of PH, the severity of PH and the severity of the underlying parenchymal lung disease. Table 11.2 points out the various factors which can lead to SAPH. Therapy for pre-capillary hypertension is directed to vascular disease. Care must be taken when using these treatments in patients with veno-occlusive disease. For those with moderate-to-severe parenchymal lung disease (FVC <50% pred), treatment of SAPH may not be as effective. However, if there is evidence for RV dysfunction, treatment of SAPH may still be indicated. For patients with milder SAPH, other factors may be the major cause of patient's symptoms. A recently published study did demonstrate that treatment of mild PH in idiopathic interstitial lung disease was associated with a positive response.[80] However, that study did not include sarcoidosis patients. Worsening of ventilation/perfusion mismatch may occur with pulmonary vasodilator therapy, but in one 16 week study the frequency was similar to that seen with placebo-treated patients.[71] Another potential limitation is uncovering pulmonary veno-occlusive disease (PVOD).[79] Treatment decision and follow-up should be made by a multidisciplinary team with a sarcoidosis and a PH expert.

Summary

In SAPH, treatment decision and follow-up should be made by a multidisciplinary team with a sarcoidosis and a PH expert. Off-label use of PAH therapy may be considered for symptomatic patients on a case-by-case basis (Figure 11.7). As noted above, nearly

three-quarters of sarcoidosis patients listed for lung transplant have SAPH.[16,19] It has been observed that post-transplant survival in patients with pulmonary sarcoidosis was similar to that in patients with other indications for lung transplantation.[52,81]

Summary

Patients who have failed to respond to treatment for PH should be referred for lung transplant evaluation, if they are deemed otherwise to be appropriate candidates.

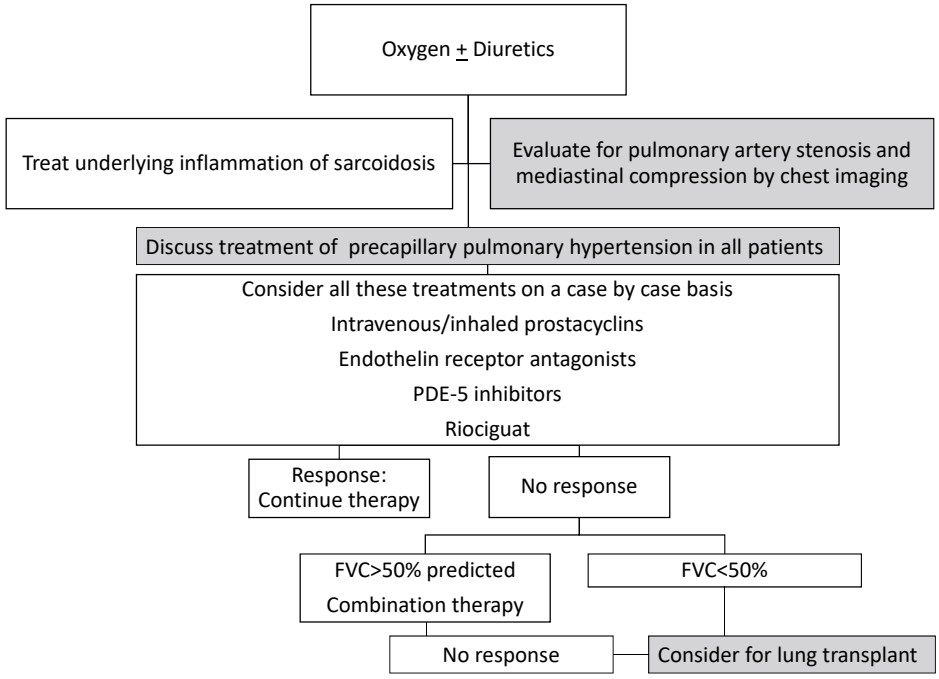

Figure 11.7: Proposed algorithm for treating pre-capillary sarcoidosis-associated pulmonary hypertension.
FVC = forced vital capacity; PDE-5 = phosphodiesterase 5.

Future research and next steps

Screening

The development of noninvasive screening tools, including serum biomarkers and MRI, need to be further evaluated in SAPH. In addition, the indications for when to repeat screening for SAPH need to be better defined.

Treatment trials

The first priority is the need to develop therapy for SAPH based on well-designed placebo controlled trials. The data summarised in this statement provide ample support for the likelihood that highly efficacious therapies will emerge and the existence of a large multinational SAPH registry indicates that the sarcoidosis community is now geared for definitive studies. The recent treprostinil data in nonsarcoid interstitial lung disease (ILD)-PH,[80] suggesting major efficacy in the short-term, is an additional spur: based on past data, there has been more basis for optimism in SAPH than in nonsarcoid ILD-PH. However, SAPH poses unique challenges in two respects.

Treatment trial phenotypes

The definition of optimal patient phenotypes for treatment trials must take into account the multiple mechanisms driving SAPH. Ideally, based on research into haemodynamic profiles, individual phenotypes will be integrated into combined phenotype trials or selectively excluded. Core phenotypes include pre-capillary vasculopathy (whether due to direct granulomatous involvement or to pathways associated with pulmonary fibrosis), vascular compression, and post-capillary pulmonary pathways (veno-occlusive processes). When SAPH coexists with cardiac disease (including cardiac sarcoidosis and comorbidities), robust algorithms will need to be developed to optimise inclusion and exclusion criteria. The distinction between SAPH resulting from end-stage lung disease and other forms of SAPH needs to be considered further, based on the definition of realistic treatment goals, short-term haemodynamic data in these patient subgroups and accumulating data on the specific effects of individual candidate therapies. Imaging assessment of the extent and distribution of parenchymal lung involvement in relation to the haemodynamic profile will also be integral to any phenotyping.

Trial end-points

Because sarcoidosis is multidimensional in its nature, with variably severe co-existent pulmonary and systemic disease, end-point selection is likely to be heavily influenced by the distinction between: 1) short-term trials designed to establish safety and proof of concept; and 2) phase 3 studies evaluating major clinical benefit. Pivotal end-point selection is not confined to the selection of the primary end-point but includes the choice of key secondary end-points. There is a need to cover the spectrum of haemodynamic effects, major clinical end-points (mortality, TCW), multidimensional functionality (6MWT data and actigraphy) and measures of quality of life, crucially including patient-reported outcomes. In short-term trials, haemodynamic effects may continue to be the primary focus but pivotal secondary end-points should cover the domains

listed above. In phase 3 trials, with clinical end-points likely to have primacy, possible strategies include the use of co-primary end-points (e.g. TCW, 6MWT data) to capture both major adverse outcomes and average cohort treatment effects. Composite end-points should be constituted by relevant clinical outcomes including but not necessarily limited to cardiopulmonary hospitalisation, mortality and categorical changes in 6MWT. In summary, whether the end-point focus is haemodynamic or primarily clinical, depending upon trial duration, all domains should be represented by pivotal secondary end-points, including the individual components of composite indices. Ongoing clinical research, defining the optimal end-point and its performance characteristics, is pivotal. Continued efforts are ongoing to identify biomarkers especially those that might identify longer-term efficacy based on short-term change.

Optimal prognostic evaluation

Clinicians now have easy access to markers of PH, in SAPH and in ILD-PH alike. Noninvasive PH markers in various forms of PH are listed in Table 11.4. More clinical research is required in SAPH to validate the prognostic significance of individual variables, with comparisons between variables of prognostic values in large well-phenotyped cohorts. These should ideally include patients with SAPH and those with less advanced disease, in order to identify earlier markers of pulmonary vasculopathy.

Composite noninvasive indices

Whether combinations of noninvasive indices, covering the multiple vasculopathic domains listed in the previous section, may enhance prognostic evaluation is ripe for further investigation. Studies are ongoing to determine optimal weighting of composite indices, defined by multivariable evaluation against key clinical outcomes and by the presence of PH at RHC. In this way, the utility of noninvasive composite indices in the selection of patients for RHC and their inclusion as end-points in pivotal trials can be established.

Harnessing of technological advances

Recent advances in PH and in ILD have included deep phenotyping data (CT vascular morphometry, SPECT/CT, PET metabolomics, four-dimensional MRI, machine learning) and in ILD, automated quantification of pulmonary vascular volume using CALIPER, with major added value in prognostic evaluation. In particular, it appears increasing likely that machine learning, applied both to individual modalities and to combinations of techniques, will enhance prognostic evaluation. This is likely to be particularly relevant to powering trials by selecting patients more likely to have adverse outcomes.

Table 11.4: Noninvasive PH markers

Cardiac functional impairment
Echocardiography
Cardiac magnetic resonance
PH severity evaluation
Echocardiography
Cardiac stress
BNP
Morphologic consequences
PA dilatation on CT
Global functional consequences
6MWD
Oxygen desaturation during 6MWD
Heart rate recovery
Pulmonary function vasculopathy profiles
Severe reduction in D_{LCO}
D_{LCO} reduction that is disproportionate to reductions in lung volumes – K_{CO}, the D_{LCO}/FVC ratio

PH = pulmonary hypertension; BNP = B-type natriuretic peptide; PA = pulmonary artery; CT = computed tomography; 6MWD = 6-min walk distance; D_{LCO} = diffusing capacity of the lung for carbon monoxide; K_{CO} = transfer coefficient of the lung for carbon monoxide; FVC = forced vital capacity.

Summary and conclusion

SAPH is a significant cause of morbidity and mortality in advanced pulmonary disease. An approach to detection of SAPH was developed by the committee. This approach relies on information from patient history, physical examination, pulmonary function testing, chest imaging and serum biomarkers. The echocardiogram remains the most commonly used next step in the patient with risk factors for SAPH. However, RHC is needed to confirm the diagnosis and properly categorise the type of PH. Potential treatments for SAPH are available. The committee felt that the interpretation of the RHC and the use of specific treatments should be made by a multidisciplinary team including both a specialist in sarcoidosis and PH.

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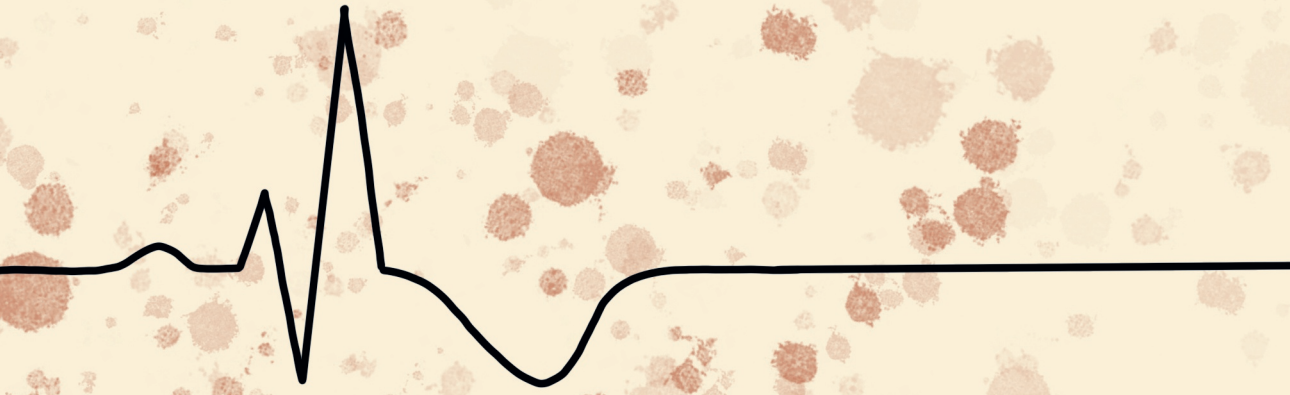
PART V

SUMMARY AND DISCUSSION



CHAPTER 12

Summary and general discussion

Summary

This thesis focuses on the prevalence, aetiology and diagnosis of sarcoidosis associated pulmonary hypertension (SAPH), which is outlined in Figure 12.1.

PART I: Prevalence and aetiology

Chapter 2 reports on the prevalence of PH in sarcoidosis patients based on data of the PULSAR study. Patients with intermediate and high PH probability on echocardiography were referred for right heart catheterisation (RHC). The study revealed an estimated PH prevalence of 2.9%, which is fairly lower compared to previous studies which investigated a more severely diseased population or used other definitions to define PH. Risk factors for PH were a longer history of the diagnosis sarcoidosis, worse NYHA functional class and Scadding stage IV on chest X-ray.

Chapter 3 retrospectively studied 40 sarcoidosis patients with PH and classified them into different phenotypes based on WHO classification and suspected PH mechanisms in sarcoidosis. The majority (n=29) had a 'parenchymal phenotype', of whom 20 also showed elevated pulmonary vascular resistance which was associated with lower DLCO. Three patients had a post capillary component of PH of whom one had isolated post capillary PH. Six patients showed a 'compression of pulmonary vasculature phenotype', one patient 'suspected vasculopathy phenotype' and one the 'chronic pulmonary emboli phenotype'. The 'parenchymal phenotype' showed the lowest mean pulmonary artery pressure (PAP) of all subgroups. This research learned that the presence of fibrosis is not essential to develop PH in sarcoidosis, and different clinical phenotypes have varying haemodynamic profiles.

In **chapter 4**, measurements on wall thickness and vascular properties by intravascular ultrasound was used to visualise early vascular disease in more distal pulmonary arteries. In total 31 intravascular ultrasound and concomitant RHC procedures were performed. It showed an upper lobe predominance of increased wall thickness and decreased distensibility and compliance in sarcoidosis patients with PH, and significant correlations with mean PAP. These findings suggest the presence of sarcoidosis related vasculopathy as a contributor to the development of PH.

PART II: Diagnosis

Chapter 5 evaluates the value of echocardiographic PH probability for diagnosing PH in pulmonary sarcoidosis, and included 479 patients of the PULSAR study combined with outpatient clinic sarcoidosis patients visiting for check-up who were referred for

PH screening. Low, intermediate and high PH probability was present in 437, 29 and 13 patients respectively. Thirty-six patients underwent RHC, PH was confirmed in 17 patients. Maximal tricuspid regurgitation velocity (TRV max) was measureable in only 46% of the patients. TRV max <2.9m/s successfully ruled out PH whereas TRV max >3.4 confirmed PH in all patients. Half of the patients with a TRV max between 2.9 and 3.4m/s had PH. Secondary echocardiographic signs were less discriminative for PH in sarcoidosis.

Additionally, **chapter 6** describes a real world multinational cohort study on the correlation between echocardiographic right ventricular systolic pressure (RVSP) compared to invasive systolic PAP, including database data of 124 SAPH patients (PULSAR study, ReSAPH registry) and 49 sarcoidosis patients without PH (Cincinnati Sarcoidosis Clinic). RVSP showed a moderate correlation with systolic PAP ($r=0.640$, $p<0.001$), and this correlation remained significant independent of sex, ethnicity and in an FVC>60% of predicted. In patients with an FVC <50% of predicted the correlation was less robust. Echocardiographic over- and underestimation of the systolic PAP with a 10mmHg variance limit occurred in 24% and 27% respectively. Overestimation tended to occur mostly in lower systolic PAP, whereas underestimation mainly occurred in higher systolic PAP.

In **chapter 7** we investigated an echocardiographic technique named "knowledge based reconstruction" (combination of echocardiographic images with three-dimensional coordinates) to obtain right ventricular volumes in 281 patients of the PULSAR study, who underwent echocardiography and the gold standard cardio magnetic resonance imaging (CMR) within 90 days interval. Right ventricular end diastolic volume and end systolic volume correlated strongly with CMR ($r=0.73$ and $r=0.76$ respectively), while there was only a weak correlation for right ventricular stroke volume and ejection fraction. Only end diastolic volume also had a good agreement in Bland Altman analyses, while it tends to overestimate the right ventricular end systolic volume and thereby underestimates stroke volume and ejection fraction. There were no signs of interference by learning curve or time between CMR and echo.

A research letter in **chapter 8** describes the retrospectively evaluated measurements of the pulmonary artery on chest-CT as predictor for PH in 89 sarcoidosis patients with an estimated PH prevalence of 28.1%. The best diagnostic accuracy was found for the pulmonary artery diameter indexed for body surface area (AUC 0.88, $p<0.001$). With a cut-off value of 16.02mm·m^{-2}, it showed a positive and negative predictive value of 70.0% and 93.2% respectively. In a sub analysis of patients with intermediate PH probability ($n=18$) the diagnostic accuracy remained high.

PART III: Treatment and prognosis

In **chapter 9** the effects and safety of Macitentan in six SAPH patients with at least twelve months follow up were studied retrospectively in a case series (three men, median age 64 years, median mean PAP 49mmHg). One patient discontinued treatment after five days because of side effects (muscle aches and fatigue). In the other patients Macitentan was well tolerated. In three patients there was clinical improvement and in two patients echocardiographic improvement after one year. Two other patient were hospitalised several weeks after initiation but remained stable after adding sildenafil. In general Macitentan showed to be safe in sarcoidosis patients and might benefit a specific subgroup of patients with SAPH.

The survival of the PULSAR cohort is described in **chapter 10**. In total, 399 patients were followed for a mean period of 4.3±0.7 years, with a 1, 2-, 3- and 4 year survival rate of 100%, 99.0%, 98.2% and 94.6% respectively. Survival was better compared to previous studies which investigated more severely diseased sarcoidosis populations. Elevated RVSP and presence of PH on echocardiography were associated with mortality, as well as progressive fibrotic disease and decline in pulmonary function, also captured by scoring systems such as the CPI score or modified Walsh. Cause of death in all ten diseased patients was very heterogeneous including sarcoidosis related causes including respiratory failure, cardiac and neurological complications (n=8) and non-sarcoidosis related causes (n=2).

PART IV: Recommendations

A task force was established by the World Association of Sarcoidosis and Other Granulomatous disease (WASOG) to summarise the current level of knowledge and provide guidance for the management of SAPH. This is shown in **chapter 11**. It elaborates consensus statements regarding initial screening, referral for and interpretation of RHC and recommendations on treatment, with due regard for significant defects in current knowledge. The task force stated that SAPH is a significant cause of morbidity and mortality in advanced pulmonary disease. Based on history, physical examination, pulmonary function testing, chest imaging and serum biomarkers information should be gathered to evaluate symptoms and signs for PH. The first step in screening is an echocardiogram. Dependent on the result, RHC is needed to confirm the diagnosis and categorise into a type of PH. Potential treatments for SAPH are available. The interpretation of RHC and use of specific treatments should be made by a multidisciplinary team with expertise in both PH as sarcoidosis.

General discussion and future perspectives

Published in parts/based on: Sarcoidosis-Associated Pulmonary Hypertension. Seminars in Respiratory and Critical Care Medicine. 2020;41(5):659–672. M.P. Huitema · H. Mathijssen · J.J. Mager · R.J. Snijder · J.C. Grutters · M.C. Post

Sarcoidosis is a rare disease with a prevalence ranging from 1 to 161 per 100,000 inhabitants, dependent on the country and type of study. In approximately 50% of the patients the disease is self-limiting and in 20% it develops into a chronic progressive disease.[1] Pulmonary hypertension (PH) is an increasingly recognised complication of pulmonary sarcoidosis.

In current literature and this thesis, it is important to bear in mind the limitations of clinical studies. Because sarcoidosis and PH are both rare diseases, the number of patients are small with inherent methodological and/or statistical limitations. Furthermore, most studies are retrospective and were conducted in tertiary centers for sarcoidosis, resulting in populations with higher disease severity and higher rates of PH. Another complicating factor is the definition of PH. Due to the retrospective nature or ethical considerations, studies frequently use right ventricular systolic pressure (RVSP) on echocardiography to define PH, using a cutoff value of 40 or 50mmHg. The gold standard right heart catheterisation (RHC) is lacking, and false positives or negatives frequently occur.

The PULSAR study is one of the first prospective studies on prevalence and diagnosis of sarcoidosis associated pulmonary hypertension (SAPH). To collect better data in larger populations with this rare disease, a few years ago joint forces initiated the observational Registry for Sarcoidosis Associated Pulmonary Hypertension (ReSAPH), which aims to collect prospective data on patients to gain insight in initial presentation and the clinical course of SAPH all over the world.

Selecting patients for PH screening

Identifying patients at risk for PH is a major challenge, since symptoms and signs of PH and sarcoidosis overlap, and often present themselves in more advanced stages of PH. Most often the pulmonologist, as a "sarcoidologist", is a gatekeeper who needs a helicopter view taking into account multiple patients aspects to assess the likelihood of PH in each specific sarcoidosis patient.[2] First by taking into account the PH prevalence. As described in chapter 2, the prevalence of PH in non-selected sarcoidosis patients in tertiary centers varies between 3% to 20%.[3–6] In patients with persistent dyspnea

numbers rise up to 45%[7,8] and in patients awaiting lung transplant 79%.[9,10] Some patient characteristics are associated with a higher likelihood for PH. For example, various ethnicities show different phenotypes of sarcoidosis and PH. In Japanese sarcoidosis patients, PH prevalence is low, however they present more often with myocardial involvement putting patients at risk for post-capillary PH.[3] In black populations sarcoidosis often is more severe with higher prevalence and severity of PH,[5,11] whereas in Caucasian populations PH prevalence is generally lower and more in line with fibrotic lung disease.[12] Routine tests that are used to monitor sarcoidosis can be helpful to raise suspicion of PH. According to the ATS clinical guideline for sarcoidosis,[13] suspicion of PH is based on clinical manifestations such as disproportional dyspnea in relation to pulmonary function tests, exertional chest pain and/or syncope, prominent P2 of S4 during physical examination, reduced six minute walk distance, desaturation with exercise, reduced diffusing capacity for carbon monoxide (DLCO), increased pulmonary artery diameter (especially when indexed for body surface area) and elevated brain natriuretic peptide. Many of these symptoms or signs are not specific, and should be used as a trend rather than a single observation. Concluding, the presentation of PH in sarcoidosis is very heterogeneous and there is a lack of concrete indicators for the presence of PH. Large future registries should point out predictors to optimise screening in the sarcoidosis population. For now, echocardiographic screening for PH should be low-key if symptoms or signs of PH are present. Incorporating routine echocardiographic screening every several years in patients with a high risk profile based on ethnicity, stage of sarcoidosis and clinical course, might lead to early recognition of PH and might benefit the clinical course if patient tailored treatment can be deployed.

Diagnosing PH in sarcoidosis

The gold standard to diagnose PH is RHC. The cutoff value to define PH (mean pulmonary artery pressure (PAP) of ≥25mmHg) is up to debate since in healthy adults mean PAP mostly does not exceed 15mmHg and almost never reach 20mmHg.[14] The recently published guideline revised the definition of pre-capillary PH into a mean PAP>20mmHg.[15] Changing the definition of PH would significantly increase the PH prevalence in sarcoidosis. As for the PULSAR study, PH prevalence would increase from 2.9% to 3.7%.[12]

Echocardiography currently is the main screening tool to select patients who should be referred for RHC.[13,16] Complications related to RHC are low,[17] however it remains invasive, expensive and resource limited. The optimal screening tool is yet to be discovered. In line with previous studies in interstitial lung disease, we showed in chapter 5 that RVSP was only measurable in 46% of the sarcoidosis patients.[18–20] If measurable, the correlation

with invasive pulmonary artery pressure (PAP) in patients with advanced lung disease is limited, with frequent underestimation of echocardiographic RVSP in higher systolic PAP and overestimation in lower systolic PAP.[21] Partly, this may be caused by incorrect measurement of the tricuspid regurgitation velocity (TRV) signal. Other factors may be quality of acoustic windows in interstitial lung disease, or malcoaptation of the tricuspid valve in severe right ventricular dilatation. Secondary signs on echocardiography are not able to discriminate for the presence of PH.[19,20,22] Our study showed that especially in patients with an intermediate PH probability based on the ESC/ERS PH guideline classification, e.g. with a TRV max of 2.9 to 3.4m/s without secondary signs or patients with no measurable TRV max with secondary PH signs, the presence of PH is difficult to predict and may be present in approximately half of the patients.[20]

Echocardiography is widely available, however not designed to assess the complex geometrical shape of the right ventricle. This calls for more advanced non-invasive imaging of the right heart. Cardiac magnetic resonance (CMR) is the gold standard for determining right ventricular dimensions and function, however costly and resource limited. Software and new echocardiographic techniques to assess the three-dimensional shape of the right ventricle are being developed. In chapter 7, we measured right ventricular dimensions and function by Knowledge-Based Reconstruction (KBR) using echocardiography combined with three dimensional coordinates assessed by a magnetic field, and compared outcomes with CMR.[23] We could only find good agreement with right ventricular end diastolic volume. Other studies showed better agreement,[24–26] however they mainly investigated patients with known PH and no history of lung disease, which might impact the image quality. Apart from KBR, there are other modalities using different techniques for 3D echocardiography focusing on right ventricular morphology and function, and is offered on most of the echocardiographic software modules. However, all of these modalities only detect increased right ventricular dimensions or decreased function, which are late markers of PH. Right ventricular strain measurements using speckle tracking echocardiography or CMR might be able to detect early right ventricular changes due to pressure overload.[27] Other promising features of CMR that might lead us to non-invasive early detection of changes in the pulmonary vasculature could be measurement of pulmonary arterial flow, compliance and vasoreactivity.

For now, RHC remains the gold standard for diagnosing PH. Besides diagnosis, RHC provides us with additional information such as the influence of left heart disease by measuring the wedge pressure, or identifying patients with a poor prognosis with high mean PAP, high pulmonary vascular resistance or low cardiac output. The question remains who to refer for RHC. Decision making should be made on case by

case basis and weighing potential risks and benefits, guided by an important principle as stated in the Hippocratic oath: '*primum non nocere*' (first, do no harm). For example, a patient with severe extinguished fibrotic pulmonary sarcoidosis with intermediate PH probability and slowly progressive symptoms is not likely to benefit from any form of currently available treatment. In this patient a working diagnosis PH would be sufficient. On the other hand, a patient with active sarcoidosis with low PH probability on echocardiography who demonstrates progressive dyspnea with stable FVC% predicted but decrease in DLCO% predicted might exhibit an early stage of PH, for which RHC should be considered. Indications to proceed with RHC might be evaluation for specific therapy, determination of prognosis, establishment of a diagnosis in case of clinically suspected pulmonary embolisms or disproportional PH, or as work up for surgical treatments including lung transplantation. By confirming the diagnosis and search for the aetiology of PH in order to initiate patient tailored treatment, the clinical course of this patient could be altered.

Aetiology and patient tailored treatment

To date, SAPH is classified as WHO group 5 PH and has shown multiple mechanisms and phenotypes. PH in sarcoidosis is often attributed to WHO class 3 'PH due to hypoxemia/vascular destruction capillary bed', and treatment with immunosuppressive therapy should be considered in patients with parenchymal enhancement on PET-CT.[18,28] Distinguishing other phenotypes of SAPH is important, since there might be feasible treatment options.

Indicators for other phenotypes of SAPH could be a rapid onset of symptoms or decline in DLCO% predicted with stable FVC and radiological imaging, or severe secondary signs of PH on echocardiography. Furthermore, a mean PAP above 35mmHg during RHC should raise suspicion for other causes, since in interstitial lung disease the mean PAP rarely exceeds this value.[29] There are several known phenotypes of SAPH apart from parenchymal disease. For example, left heart disease due to cardiac sarcoidosis in which case heart failure treatment, ICD and/or immunosuppressive therapy should be considered. Furthermore, sarcoidosis patients have a predisposition of venous thrombo-embolisms,[30,31] which puts patients at risk for chronic thrombo-embolic PH. In these patients PH targeted therapy, pulmonary endarterectomy or balloon angioplasty can be considered. Also, sleep apnea, which may cause PH, is more prevalent in sarcoidosis[32] and treatable with CPAP. Other phenotypes are less well defined. One of these phenotypes is compression of the pulmonary vasculature. If compression is caused by active lymphadenopathy, immunosuppressive therapy might be beneficial.[33] In addition, good results of pulmonary angioplasty and/or stenting have been

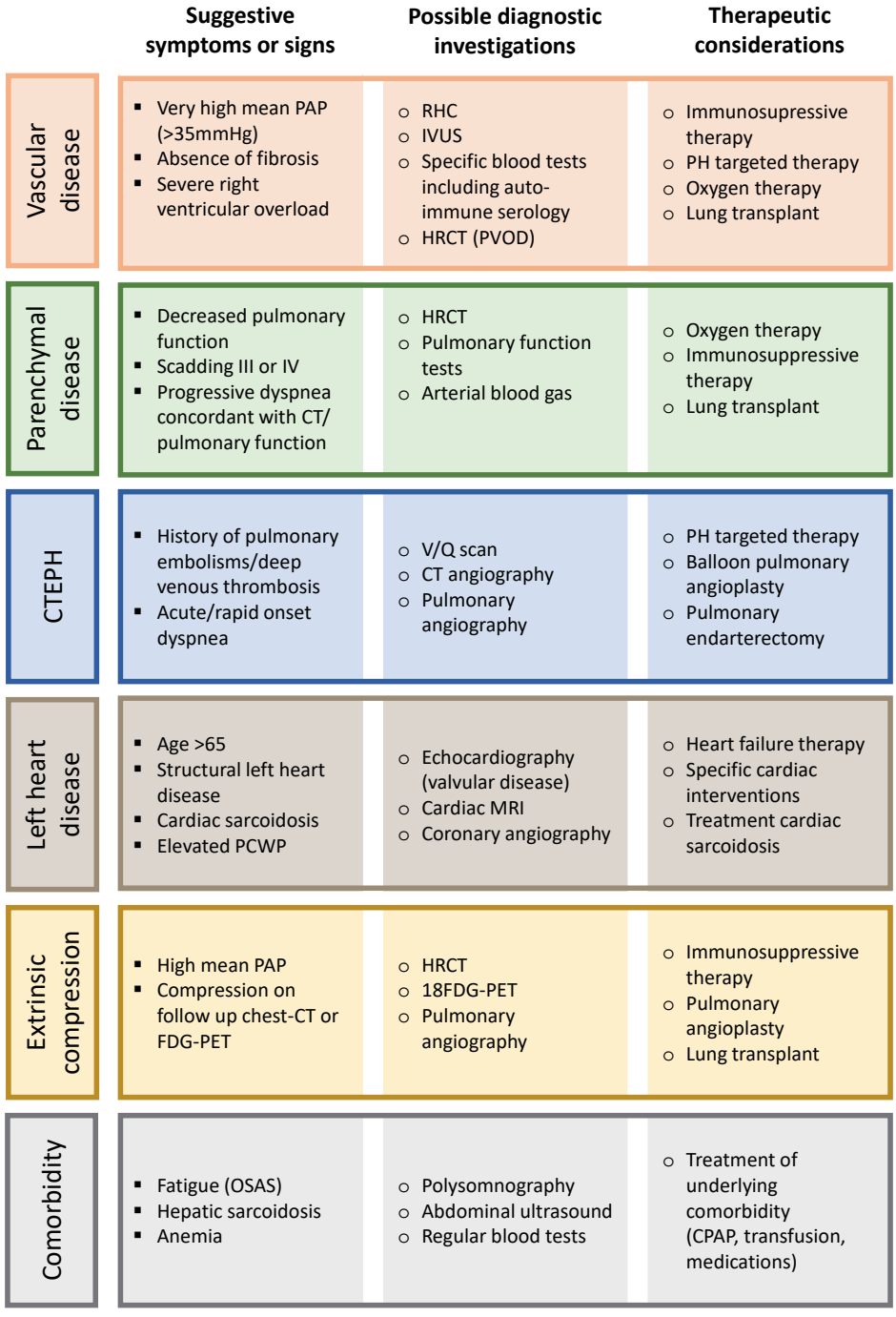


Figure 12.1: Outline of SAPH subtypes with diagnostic characteristics and therapeutic considerations.

described in case series.[34–36] However, research on optimising this procedure is needed since complications occurred such as in-stent thrombosis, and few is known about long term efficacy. There are some other less defined hypothesised mechanisms such as genetic disorders, granulomatous infiltration of pulmonary vasculature, vasculopathy, or the role of regulatory T-cells and other immune system modulators. Future research is needed to identify the role of these different mechanisms in sarcoidosis.

Considering the abovementioned, patients with SAPH should be analysed in a tertiary sarcoidosis and PH centre. Defining the phenotype is key for further diagnostic tests and treatment. In chapter 3 we gave it a start by distinguishing several phenotypes in SAPH.[23] In Figure 12.1 we related the different phenotypes with clinical investigations and treatment considerations. As for the vasculopathy phenotype much is to be discovered. In chapter 9 we found an upper lobe predominance of increased wall thickness and decreased distensibility and compliance in sarcoidosis patients with PH, suggesting a vascular component as contributor for development of PH. Autopsy studies in sarcoidosis showed granulomatous involvement throughout all layers of the arterial and venous pulmonary vascular walls in most patients,[18,37] often accompanied by intimal fibrosis, medial proliferation, inflammatory changes, necrosis, and destruction of the small-vessel architecture. It is hypothesised that granulomatous infiltration can cause endothelial damage, resulting in a rise of endothelin-1 levels that contribute to vasoconstriction and cell proliferation, which is associated with elevated pulmonary vascular resistance.[38] To date, this is an important target point for PH-targeted therapy. In sarcoidosis, raised endothelin-1 levels have been found in plasma and bronchoalveolar lavage specimens.[39–41] The pathogenesis of this possible mechanism in relation to SAPH remains unclear. A subset of patients with SAPH showed responsiveness to acute vasodilator challenge with inhaled nitrogen oxide or prostacyclin.[42,43] Nonetheless, this was not a predictor for a response to PH-specific therapy. Future research to further define phenotypes and evaluate treatment regimens is important to improve survival and quality of life in patients with SAPH. Also, research should acknowledge the different phenotypes in SAPH. It might explain differences in outcomes on treatment and prognosis, but also leads to improved patient tailored treatment in a very heterogeneous disease.

Changing the cut-off value for mean PAP to define PH into 20mmHg might significantly increase the PH prevalence mostly for the parenchymal phenotype, since these patients generally have lower mean PAP. It might lead to treatment with immunosuppressive drugs in earlier stages of pulmonary vascular remodeling. An interesting investigation would be to assess the capability of immunosuppressive therapy or oxygen therapy

to prevent hypoxic remodeling due to parenchymal destruction and thereby prevent development of (significant) PH. Earlier recognition of pulmonary vascular remodeling might prevent morbidity and mortality. Selection of patients can be based on PET enhanced parenchymal abnormalities, pulmonary function tests and future measurements, for example laboratory markers including endothelin-1 and/or measurements on pulmonary arterial compliance by either CMR, RHC or IVUS. Besides immunosuppressive therapy, PH targeted therapy can be considered in a subset of patients. Previous studies in patients with interstitial lung disease have reported complications after initiating PH targeted therapy.[44,45] Therefore PH targeted therapy should be avoided in patients with primarily the parenchymal phenotype, however it can be considered in patients with other phenotypes, especially those with a low wedge, high mean PAP (>35mmHg) and high pulmonary vascular resistance. Research is needed to identify sarcoidosis patients who benefit from PH targeted treatment including effects on prognosis and quality of life, but also on other tailored treatments to improve outcomes of SAPH in the near future.

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PART VI

APPENDICES

Nederlandse samenvatting/Dutch summary
List of scientific publications and presentations
Affiliations of the authors
Acknowledgements/Dankwoord
Curriculum Vitae/About the author

Nederlandse samenvatting/Dutch summary

Sarcoïdose en pulmonale hypertensie

In dit proefschrift worden diverse facetten van de relatie tussen sarcoïdose en pulmonale hypertensie (PH) onderzocht. Sarcoïdose is een zeldzame systeemziekte wat zich presenteert in 5–160 per 100.000 mensen, waarbij er granulomen (ophoping van witte bloedcellen en ander weefsel) in één of meerdere organen ontstaan. Deze granulomen kunnen waargenomen worden met microscopisch onderzoek, zoals weergegeven in Figuur A.1. In meer dan 90% van de patiënten bevinden de granulomen zich in de longen. Bij de ene patiënt verdwijnt de ziekte spontaan binnen enkele jaren, bij anderen ontwikkelt zich een chronische ziekte waarbij er orgaanschade kan ontstaan. Door de aanwezigheid van granulomen in de longen kan de longfunctie achteruitgaan. Tevens kunnen granulomen verlittekenen waardoor er permanente longfibrose ontstaat. Bij elke patiënt wordt een individuele keuze gemaakt of een behandeling met immunosuppressiva noodzakelijk is. Deze medicatie gaat ziekteactiviteit tegen waarbij men schade aan de betrokken organen probeert te voorkomen.

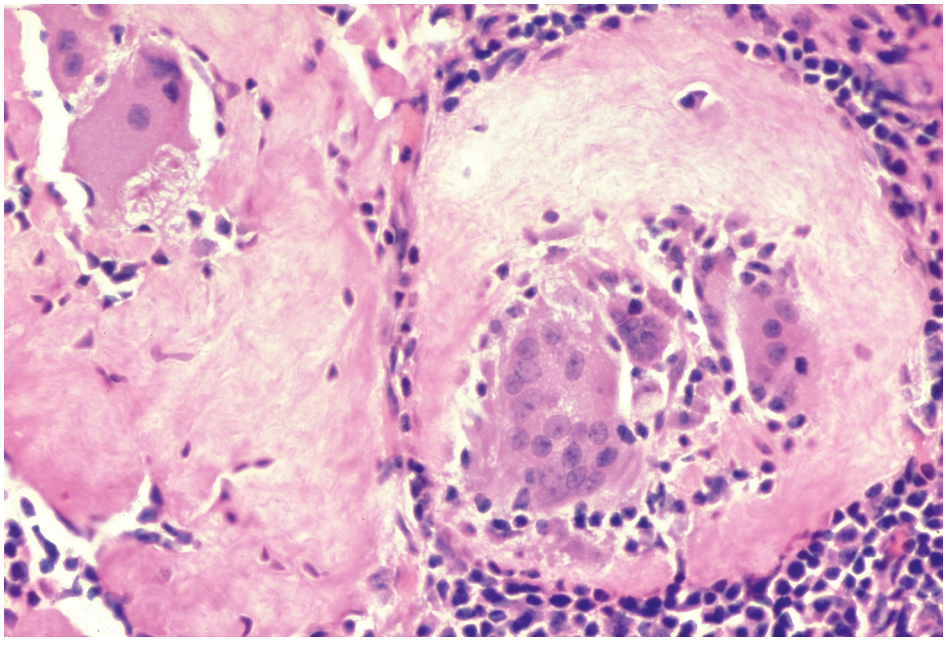

Figure A.1: Microscopisch onderzoek van een granuloom die deels gefibroseerd (verlittekend) is. Door Yale Rosen from USA - Sarcoidosis - Fibrosis of granulomas. Uploaded by CFCF, CC BY-SA 2.0, https://commons.wikimedia.org/w/index.php?curid=31127474.

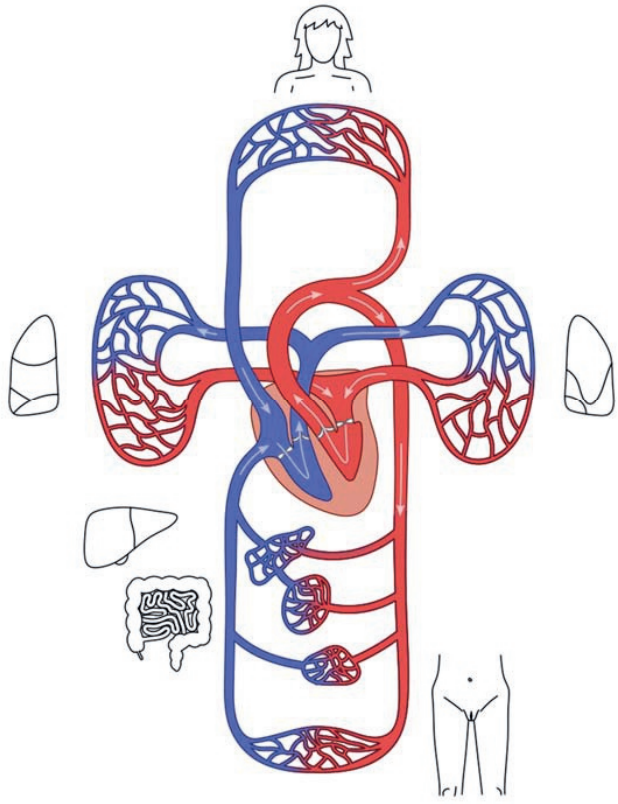

Figure A.2: De grote en de klein bloedsomloop, schematisch weergegeven.
Vanuit de rechter harthelft (op het plaatje links) stroomt het zuurstofarme bloed via de longslagader naar de longen. In de haartvaatjes die rondom de longblaasjes lopen wordt zuurstof afgegeven aan het bloed. Het zuurstofrijke bloed stroomt vervolgens via de longaders naar de linker boezem. Vanuit de linker boezem gaat het zuurstofrijke bloed naar de linker hartkamer die het vervolgens naar de grote bloedsomploop pompt. Figuur door Tomáš Kebert & umimeto.org - Own work, CC BY-SA 4.0, ttps://commons.wikimedia.org/w/index.php?curid=93084301.

PH is een zeldzame maar bekende complicatie, die vaker voorkomt bij sarcoïdose dan in de normale populatie. Hierbij is er sprake van een verhoogde bloeddruk in de longslagader, wat onderdeel uitmaakt van de kleine bloedsomloop. De kleine bloedsomloop is schematisch weergegeven in Figuur A.2. Bij verhoogde drukken in de longslagader moet de rechter hartkamer tegen hogere drukken in pompen. Dit kan leiden tot verdikking en later uitzetting van de hartspier, en uiteindelijk rechter hartfalen (Figuur A.3). PH wordt vastgesteld met rechter hartkatheterisatie, waarbij een zogenaamde *swan-ganz katheter* via een ader in het been of de hals in de longslagader wordt gelegd, waarbij met behulp van een sensor diverse drukmetingen worden gedaan. Vanaf een gemiddelde druk in de longslagader van 25mmHg spreken we van PH. In een recente richtlijn is deze grenswaarde verlaagd naar 20mmHg, echter wordt in dit proefschrift de oude grens-

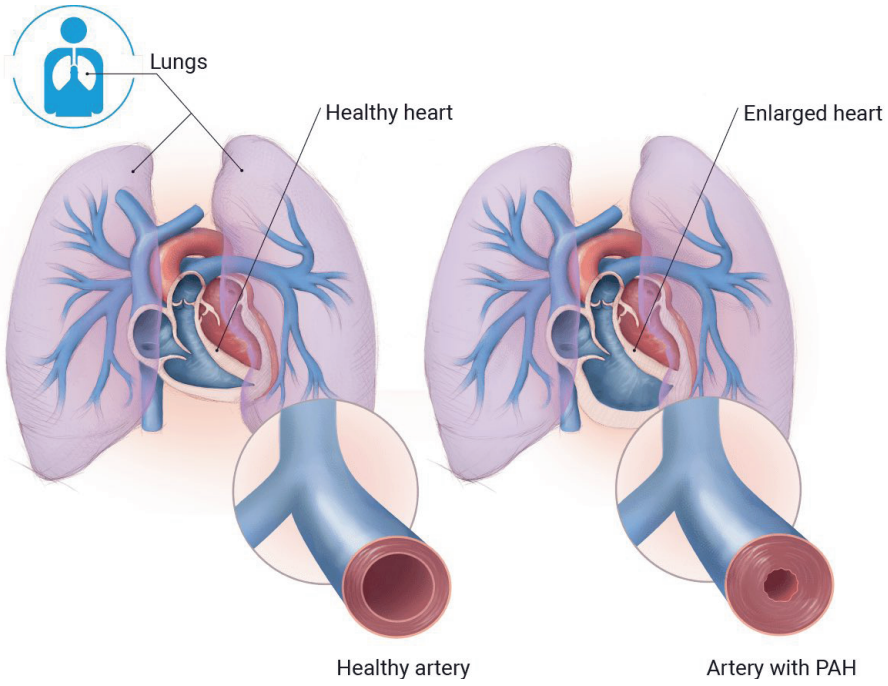

Figure A.3: Gevolgen van verhoogde drukken in de longslagader.
In het linker plaatje een gezond hart. Het rechter plaatje toont een verdikte rechter hartspier die ook uitgezet is. De longslagader zelf is ook verdikt, waardoor de rechter harthelft tegen een hogere druk in moet pompen. Dit is een voorbeeld van pre-capillaire pulmonale hypertensie. Afbeelding overgenomen van Stichting Pulmonale Hypertensie; https://stichtingpulmonalehypertensie.nl/.

waarde gebruikt. Naast de gemiddelde druk kunnen ook andere metingen en berekeningen worden uitgevoerd waardoor de weerstand in het longvaatbed kan worden ingeschat (afgekort PVR), alsmede de druk vanuit de linkerharthelft (afgekort PCWP). Deze metingen helpen om onderscheid te maken in de oorzaak van de PH. PH is in de meeste gevallen geen ziektebeeld op zichzelf, maar een uiting van een onderliggend ziektebeeld. Grofweg onderscheiden we twee typen: pre-capillaire en post-capillaire PH. Bij pre-capillaire PH ligt de oorzaak van de verhoogde druk in het longvaatbed of in de rechterharthelft (Figuur A.3). Hierbij is de PVR verhoogd. Bij post-capillaire PH ligt de oorzaak bij een verhoogde druk in de linkerharthelft, waarbij secundair de druk in de kleine bloedsomloop verhoogt. Bij langer bestaande post-capillaire PH kan de PVR ook verhoogd raken en een mengbeeld ontstaan.

Een rechter hartkatheterisatie is een informatief onderzoek, maar kent ook risico's en complicaties. Met behulp van screening wordt er een voorselectie gemaakt bij wie een rechter hartkatheterisatie zinvol is. Hierbij speelt echocardiografie een grote rol. Op basis van verschillende metingen worden patiënten ingedeeld in een lage, interme-

diaire of hoge waarschijnlijkheid op PH. De belangrijkste echocardiografische meting is de maximale stroomsnelheid over de lekkage van de tricuspidalis hartklep (RVSP), wat wordt gebruikt als surrogaat voor invasief gemeten pulmonaal drukken. Tevens kunnen secundaire kenmerken als uiting van een verhoogde druk met echocardiografie worden vastgelegd, waaronder bijvoorbeeld een verwijde rechterhartkamer of boezem, verandering in stroomsnelheden over de longslagader of een verwijde onderste holle ader. Bij patiënten met een intermediaire of hoge waarschijnlijkheid op PH kan een rechter hartkatheterisatie overwogen worden.

Dit proefschrift

Over PH in sarcoïdose is relatief weinig bekend, van prevalentie tot risicofactoren, mechanisme en behandeling. In dit proefschrift proberen we meer inzicht te krijgen in bovengenoemde zaken. In 2015 is een prospectief cohortonderzoek gestart, genaamd de PULSAR-studie, wat een hoeksteen vormt voor dit proefschrift. In deze studie zijn patiënten geïncludeerd die bekend zijn met (een voorgeschiedenis van) pulmonale sarcoïdose en nieuw verwezen zijn naar een tertiair sarcoïdose centrum, alsmede patiënten die onder controle zijn bij de longarts waarbij er een indicatie was voor PH-screening. Alle patiënten ondergingen PH-screening met behulp van echocardiografie, bloedonderzoek en een hartfilmpje (ECG). Op indicatie werden patiënten doorverwezen voor een rechterhartkatheterisatie.

Deel 1: Prevalentie en etiologie

In het eerste deel van dit proefschrift wordt de vóórkomen en de oorzaak van PH in sarcoïdose onderzocht. In de literatuur voorafgaand aan dit onderzoek wordt de prevalentie van PH in sarcoïdose in tertiaire ziekenhuizen geschat op 5–20%. De verschillende studies gebruiken echter verschillende en onofficiële definities voor PH. De prevalentie varieert per etniciteit, en ook bij ernstigere vormen van sarcoïdose komt PH vaker voor, bijvoorbeeld in ca 70% van de sarcoïdosepatiënten die wachten op longtransplantatie.

In **hoofdstuk 2** wordt de prevalentie van PH in sarcoïdose onderzocht vanuit de resultaten van de PULSAR-studie, in een groep van 399 met name Kaukasische patiënten die nieuw zijn verwezen naar het expertisecentrum. Het onderzoek toont een PH-prevalentie van circa 3%, waarbij de duur van het bestaan van sarcoïdose, de mate van benauwdheidsklachten en stadium 4 sarcoïdose op een röntgenfoto significante risicofactoren zijn voor het ontstaan van PH. De prevalentie is aanzienlijk lager dan in eerdere studies, waarbij eerdere studies een lagere representatie hadden van de Kaukasische etniciteit en patiënten vaker in een verder gevorderd stadium van sarcoïdose zaten.

Het mechanisme van PH in sarcoïdose is meervoudig. Derhalve wordt het volgens de WHO-classificatie (zie hoofdstuk 1 Tabel 1.3 op pagina 13) geschaard onder groep 5 PH (onbekend en/of multifactorieel mechanisme). In de praktijk kan PH in sarcoïdose karakteristieken hebben van WHO-groep 2, 3, 4 en mogelijk ook groep 1. Het merendeel van de patiënten valt in WHO-groep 3 (PH ten gevolge van longziekten/ hypoxemie). Echter komt PH ook voor bij sarcoïdose patiënten zonder significante parenchymziekte of fibrose, of zijn de pulmonaal drukmetingen significant hoger dan wat wordt verwacht bij WHO-groep 3. Dit suggereert dat er meerdere mechanismen zijn. Op basis van eerdere literatuur zijn mogelijke andere mechanismen het ontstaan van chronisch trombo-embolische PH bij een verhoogd trombo-embolisch risico in sarcoïdosepatiënten (WHO-groep 4), verminderde linkerkamerfunctie t.g.v. cardiale sarcoïdose (WHO-groep 2), en mogelijk een component vasculopathie (WHO-groep 1). Andere mogelijke oorzaken betreffen compressie van de pulmonale vaten, portale hypertensie en slaapapneu.

In **hoofdstuk 3** werden 40 sarcoïdose patiënten met PH retrospectief in verschillende fenotypes onderverdeeld aan de hand van de WHO-classificatie en vermoedelijke mechanismen van PH in sarcoïdose. Het merendeel (n=29) viel onder het parenchymale fenotype, waarvan 20 patiënten ook een verhoogde pulmonale vaatweerstand lieten zien. Drie patiënten hadden een post-capillair component, waarvan één geïsoleerde post-capillaire PH. Zes patiënten toonden een 'compressie van de pulmonaalvaten' fenotype. Eén patiënt werd verdacht van een vasculopathie fenotype, en één van het 'chronisch trombo-embolische' fenotype. Het parenchymale fenotype was geassocieerd met de laagste pulmonaaldrukken. Dit hoofdstuk laat zien dat de aanwezigheid van fibrose niet essentieel is voor het ontstaan van PH, en dat verschillende fenotypes ook variëren in hemodynamisch profiel.

In **hoofdstuk 4** worden afwijkingen in de pulmonaal vaten nader onderzocht met behulp van een intravasculaire echo (IVUS), waarbij in de distale pulmonaal arteriën de vaatwanddikte en vasculaire eigenschappen worden onderzocht. In de resultaten van 31 procedures werd gezien dat er met name in de bovenste longkwabben van sarcoïdosepatiënten met PH sprake is van een toegenomen vaatwanddikte en verminderde rekbaarheid van de vaten. Deze parameters correleren ook significant met de gemiddelde pulmonaal drukken, wat suggereert dat vasculopathie een bijdragende factor is in het ontwikkelen van PH in sarcoïdose.

Deel 2: Diagnostiek

Het tweede deel van dit proefschrift gaat dieper in op de diagnostiek van PH in sarcoïdose. Klachtenpatronen of tekenen van PH zijn aspecifiek en vaak een uiting van verder gevorderde PH. Bij routinematig onderzoek voor sarcoïdose kan er een verdenking ontstaan op PH, bijvoorbeeld bij afwijkende longfunctietest uitslagen, toename van de diameter van de pulmonaal arterie op de CT-scan, afwijkende bloedwaarden of tekenen van rechtsbelasting op het ECG. Bij een verdenking op PH wordt een echocardiografische screening ingezet. Afhankelijk van de screening en specifieke patiëntkarakteristieken wordt een patiënt eventueel doorverwezen voor rechterhartkatheterisatie. Uit eerdere onderzoeken bij patiënten met andere longaandoeningen blijkt de echo niet altijd goed bruikbaar als screeningstool. Deze studies zijn erg verschillend uitgevoerd met veel variatie in de onderzochte echocardiografische parameters en de definitie van PH.

Hoofdstuk 5 onderzoekt in het PULSAR-cohort de voorspellende waarde van trans thoracale echocardiografie op basis van het classificatiesysteem van de Europese richtlijn voor PH. Een lage, intermediaire en hoge PH-waarschijnlijkheid was aanwezig in respectievelijk 437, 29 en 13 patiënten. In navolging hierop ondergingen 36 patiënten rechter hartkatheterisatie, en werd de diagnose PH in 17 patiënten gesteld. Maximale tricuspidalisklep regurgitatie snelheid (TRV max) waaruit de RVSP berekend kan worden was slechts in 46% van de patiënten betrouwbaar te meten. Indien deze waarde laag (<2.9m/s) of hoog (>3.4m/s) was kon het goed gebruikt worden om de aanwezigheid van PH aan te tonen of uit te sluiten. Daartussen was onderscheid niet goed mogelijk. Secundaire echocardiografische tekenen voor PH hadden een laag onderscheidend vermogen.

In **hoofdstuk 6** wordt in een multinationaal studiecohort een vergelijking gemaakt tussen de pulmonaaldrukken o.b.v. inschatting op het echocardiogram (RVSP) en invasief gemeten tijdens rechterhartkatheterisatie. Deze studie liet zien dat metingen op echo matig-goed correleren met metingen tijdens rechterhartkatheterisatie ($r=0.640$, $p<0.001$) onafhankelijk van geslacht, etniciteit en een longfunctie van >60%. Bij patiënten met een FVC van <50% was er sprake van een minder robuuste correlatie. Overschatting en onderschatting met een variatielimiet van 10mmHg kwam frequent voor (respectievelijk 24% en 27%), waarbij overschatting met name voorkomt in lagere invasief gemeten pulmonaaldrukken, en onderschatting met name bij hogere invasief gemeten pulmonaaldrukken.

Hoofdstuk 7 onderzoekt of 'knowledge based reconstruction', een methode waarbij met driedimensionale coördinatoren rechterventrikelvolumes worden gemeten, een

betrouwbare methode is in vergelijking met de goudstandaard MRI. Uit de resultaten van 281 patiënten van de PULSAR-studie die zowel een echo als MRI binnen 90 dagen van elkaar hebben ondergaan, blijkt er een sterke correlatie tussen rechter ventriculaire diastolische en systolische volumes, echter een zwakke correlatie voor slagvolume en ejectiefractie. In een Bland Altman-analyse was er enkel een goede overeenkomst voor het gemeten diastolische volume en een overschatting van het systolische volume, met daardoor een onderschatting van slagvolume en ejectiefractie. Bij nadere analyse bleek dit niet te worden veroorzaakt door een leercurve of grotere tijdsinterval tussen beide onderzoeken.

Hoofdstuk 8 beschrijft een retrospectieve studie waarbij in 89 sarcoïdose patiënten metingen van de pulmonaal arterie werden verricht op de CT-scan. De geschatte prevalentie van PH in dit cohort was 28.1%. De meting met de beste diagnostische nauwkeurigheid was de pulmonaal arteriediameter geïndexeerd voor het lichaamsoppervlak (AUC 0.88, $p<0.001$). Een afkapwaarde van 16.02mm toonde een positief en negatief voorspellende waarde van respectievelijk 70.0% en 93.2%. In een sub analyse van patiënten met een intermediaire waarschijnlijkheid op PH bij echocardiografie (n=18) bleef de diagnostische nauwkeurigheid hoog.

Deel 3: Behandeling en prognose

Behandeling

De behandeling van PH in sarcoïdose kent weinig hard wetenschappelijk bewijs, en bestaat uit meerdere componenten waarbij er per patiënt een individuele keuze moet worden gemaakt welke toepasbaar zijn. Primair dient men de noodzaak tot algemene hartfalen en zuurstoftherapie te evalueren. Bij een selectie van patiënten met eindstadiumsarcoïdose of ernstige PH kan longtransplantatie een optie zijn. Daarnaast wordt er per patiënt gekeken naar specifieke behandelingen, waarbij het doel is om de hemodynamiek en kwaliteit van leven te verbeteren. Medicamenteuze behandeling wordt onderverdeeld in sarcoïdosegerichte behandeling en PH-gerichte behandeling. Sarcoïdosegerichte behandeling richt zich op bestrijden van inflammatie en daarmee voorkomen van eindorgaanschade met medicatie zoals prednison, of tweede en derdelijns immunosuppressiva. PH-gerichte behandeling in sarcoïdose is off-label en moet plaatsvinden onder strikte monitoring van een PH-team. Het kan op proef worden gestart bij patiënten met verdenking op vasculopathie of PH ten gevolge van chronische longembolieën. Bij patiënten met uitgebreide pulmonale fibrose is er een kleinere kans op aanslaan van de behandeling, en zelfs een kans op verslechterde oxygenatie. Er zijn verschillende PH-gerichte medicatiegroepen waar in sarcoïdose met

name in de vorm van case series onderzoek is gedaan, namelijk prostacycline analogen (epoprostenol, iloprost), endothelinereceptor antagonisten (bosentan, ambrisentan), en fosfodiesterase-5-remmers (sildenafil, tadalafil).

In **hoofdstuk 9** wordt in de eerste case serie van zes geselecteerde patiënten met PH en sarcoïdose (drie mannen, mediane leeftijd 64 jaar, gemiddelde pulmonaal druk 49mmHg) het effect en veiligheid van macitentan beschreven, met ten minste twaalf maanden opvolging. Eén patiënt is de behandeling na vijf dagen gestaakt i.v.m. bijwerkingen (spierpijn en vermoeidheid). De andere patiënten verdroegen macitentan goed. Drie patiënten toonden klinische verbetering, en bij twee hiervan was echocardiografische verbetering zichtbaar na 1 jaar. Twee andere patiënten werden enkele weken na de start opgenomen in het ziekenhuis, maar bleven stabiel nadat sildenafil werd toegevoegd aan de behandeling. Macitentan blijkt veilig in patiënten met sarcoïdose, en een specifieke subgroep van sarcoïdose patiënten met PH heeft mogelijk baat bij de behandeling.

Prognose

Het is bekend dat de mortaliteit in sarcoïdose significant stijgt wanneer er sprake is van PH, onafhankelijk van longfunctie. Een studie laat zien dat in patiënten met bewezen PH in sarcoïdose de 1, 2 en 5 jaar overlevingskans respectievelijk 84, 74 en 59% is, in vergelijking tot gematchte sarcoïdosepatiënten zónder PH waarbij de overlevingskans respectievelijk 100, 96 en 69% is.

De overlevingskans van het PULSAR-cohort wordt beschreven in **hoofdstuk 10**. De 399 patiënten werden voor een gemiddelde periode van 4.3 ±0.7 jaar gevolgd. De overleving op 1, 2, 3 en 4 jaar was 100%, 99%, 98.2% en 94.6% respectievelijk. Verhoogde rechtsdrukken en/of verdenking PH op het echocardiogram was geassocieerd met verhoogde mortaliteit. Andere associaties met overlijden werden gevonden voor progressieve fibrotische ziekte en verslechtering van de longfunctietest. De oorzaak van overlijden was heterogeen. Van de tien overleden patiënten overleden er acht aan respiratoire, cardiale of neurologische complicaties die gerelateerd waren aan sarcoïdose. Twee patiënten overleden aan oorzaken die niet gerelateerd waren aan sarcoïdose.

Deel 4: Aanbevelingen

In het vierde en daarmee afsluitende deel van het proefschrift worden aanbevelingen gedaan t.a.v. diagnostiek en behandeling van PH in sarcoïdose om de huidige kennis uiteen te zetten en richting te geven in de klinische praktijk. Er werd hiervoor een werkgroep gevormd vanuit de World Association of Sarcoidosis and Other Granul-

matous diseases (WASOG). In **hoofdstuk 11** worden uitvoerig consensus statements besproken omtrent initiële screening, verwijzingsindicaties voor rechterhartkatheterisaties en de interpretatie daarvan, en adviezen omtrent behandelingsstrategieën. Samengevat concludeert de werkgroep dat PH in sarcoïdose een belangrijke oorzaak is van ziekte en overlijden indien er sprake is van gevorderde ziekte. Op basis van anamnese, lichamelijk onderzoek, longfunctietesten, beeldvorming en laboratoriumonderzoek moet informatie worden verzameld die kan wijzen op PH. De eerste stap in diagnostiek is een echocardiogram. Afhankelijk van de uitslag is een rechter hartkatheterisatie nodig om de diagnose te bevestigen en het type PH te categoriseren. Mogelijke behandelingen voor PH in sarcoïdose zijn beschikbaar. De resultaten van de rechter hartkatheterisatie en de keuze tot specifieke behandeling dient te worden gemaakt door een multidisciplinair team met expertise in PH en sarcoïdose.

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Curriculum Vitae/About the author

Marloes Petra Huitema was born on the 23th of December 1989 in Alphen aan den Rijn, the Netherlands. She attended high school at "Het Groene Hart Lyceum" in Alphen aan den Rijn from which she graduated in 2008. She started her medical training at the end of summer in 2008 at Maastricht University. After her bachelor in 2011, she spent seven months traveling in South-America and India, where she started her clinical rotations at the dermatology department of Kasturba hospital, Manipal. During her clinical rotation Internal Medicine at the Viecuri hospital in Venlo she grew particularly fond of Cardiology, after which she did an elective rotation at the Cardiology department of the St. Antonius Hospital in Nieuwegein. During this time, she came in contact with prof. dr. Marco Post for research purposes and grew interested in pulmonary vascular disease and interstitial lung disease. She started a research internship in 2014, which was followed by a PhD trajectory on sarcoidosis associated pulmonary hypertension starting in 2015 under supervision of dr. J.J. Mager, prof. dr. J.C. Grutters and prof. dr. M.C. Post. The results of this PhD trajectory are presented in this thesis. During this trajectory she was an active board member of the 'Promovendi-Club", a committee providing training and support for fellow researchers, and attended several congresses both as a guest and speaker. Also, she was a member of the task force established by the World Association of Sarcoidosis and Other Granulomatous diseases (WASOG), participating in writing an expert statement on sarcoidosis associated pulmonary hypertension. In January 2020 she started her residency in Cardiology at the St. Antonius Hospital under supervision of dr. M.C.E.F. Wijffels. As part of her specialisation she worked at the department of Internal Medicine, St. Antonius Hospital under supervision of P.J. de Jong, and the department of Cardiology, Gelre Ziekenhuis Apeldoorn under supervision of dr. B.E. Groenemeijer. Recently, she returned to the St. Antonius hospital to finish the last part of her residency.