Pulmonary Arterial Hypertension in systemic sclerosis

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For the third time recently, experts in Pulmonary Arterial Hypertension (PAH) from Croatia, Italy and Austria gathered at the "Alpe Adria Meeting on Pulmonary Hypertension". This time, the focus was on systemic sclerosis.

"In the field of systemic sclerosis science is moving quickly", said Prof. Dr. Horst Olschewski (Clinical Department for Pulmonology, Medical University Graz, Austria) in his introductory remarks. "Unfortunately, one has to admit that our therapeutic results lag behind the scientific findings. So we have a lot left to do".

SSc: definition, prognosis, epidemiology

Systemic Sclerosis (SSc) has to be differentiated from localized scleroderma which only affects the skin. In contrast, SSc almost always shows organ involvement which displays different patterns according to the subtype. The most common subtypes of SSc are limited cutaneous (lcSSc) and diffuse cutaneous SSc (dcSSc), the latter being the most severe form.

"The most severe forms of pulmonary involvement in SSc are interstitial lung disease, appearing in 70% of patients with dcSSc and 35% with lcSSc, and PAH, which appears in 5% of patients with dcSSc, but in 25% of patients with lcSSc", explained Dr. Ginevra De Marchi (Clinic of Rheumatology, University Hospital Udine, Italy).
We have to be aware that SSc patients with PAH have an especially bad prognosis", De Marchi added (1).
The prognosis is even worse if an SSc patient has PAH in association with interstitial lung disease (ILD) (2).
The estimated incidence of SSc is 19-23/million inhabitations/year, but these figures depend on the diagnostic criteria used. The prevalence is given as 233-277/mil inhabitants. There are geographic variations: incidence is higher in the USA and Australia, lower in Japan and Europa, and within Europe there is a slope from South to North. The ratio female:male is 7: 1. The causes of death have

shifted in the past decades: renal crises have strongly decreased, whereas lung fibrosis and PAH have massively increased (3).

PAH and "Non-PAH-PH"

"Don't expect new definitions of PAH or PH from me", stated Olschewski at the beginning of his talk. "Something like that has to be decided at a world conference, as it was done in the past. I would like to point out to you that what we are dealing with here is a clinical problem reaching far beyond names and definitions".
If one talks about PAH, it refers to group 1 of the current classification which contains, among others, idiopathic PAH (iPAH), PAH in SSc and a number of other subtypes. "Non-PAH-PH" is a collective term for the other groups (2-5) of the classification. These include PH in diseases of the left heart, the lung, chronic thromboembolic PH and other, rare causes. "Patients with Non-PAH-PH comprise the vast majority of all PH patients", Olschewski stressed.
"First of all we have to realise that – especially among elderly and old people – there are not only fully manifest diseases, but also latent and mild ones", Olschewski continued. "If, for instance, a patient has mild COPD, latent sleep apnoea and slight diastolic dysfunction, this combination can cause very significant elevations of pulmonary arterial pressure".
British registry data published in 2011 show that three year survival in PH because of left heart disease (73%) and because of chronic thromboembolic disease (71%) is best, whereas it is worst in PH because of lung diseases (44%) (4). Within the group of pulmonary diseases, patients with sleep disorders/alveolar hypoventilation have the best prognosis (3 year survival 90%), patients with ILD the worst prognosis (16%).
"We also have to ask ourselves what happens at the other end of the spectrum, i.e. with those patients who only have a slightly elevated pulmonary arterial pressure", Olschewski continued. A Japanese study showed that patients with idiopathic lung fibrosis who have a mean pulmonary arterial pressure (mPAP) ≥ 17mmHg have a significantly higher five year mortality than patients with an mPAP <17mmHg (5). Another study showed that the risk for acute exacerbations of COPD is significantly higher with an mPAP >18mmHg than with an mPAP ≤ 18mmHg (6).
"Both those cut-off values are within the normal range, since according to the current definition, PH is only present if the resting mPAP is ≥ 25mmHg", Olschewski said.

"So, we can draw the conclusion that the current definition of PH does not consider slightly elevated mPAP levels".

"Furthermore one has to admit that even the mPAP range between 25 and 39mmHg is scarcely studied. An elevation of mPAP above 25mmHg can be a variant of normal, but it can also be caused by comorbidities. Therefore we need a better definition of PH", concluded Olschewski.

Remodelling of the pulmonary arteries is, among other things, influenced by myeloid cells from the bone marrow and some yet undescribed factors stemming from the lung. "We urgently need new drugs for patients with Non-PAH-PH", Olschewski demanded. Currently, imatinib and riociguat are investigated in Phase II/III.

SSc-PAH: diagnostics

"About 12% of all SSc patients develop PAH", explained Prof. Dr. Asja Stipić-Marković (Department for Clinical Immunology, Pulmonology, Rheumatology, University Hospital "Sveti Duh", Zagreb).

"It's essential to diagnose PAH as early as possible, especially in SSc patients, because progression of PAH can be very rapid in these patients", said Stipić-Marković.

SSc-PAH is still underrecognized and undertreated, and collaboration of pulmonologists, cardiologists and rheumatologists is essential for an early diagnosis.

"The diagnosis of SSc-PAH is a clinical challenge, because the unspecific symptoms of PAH are often hard to differentiate from the symptoms of various SSc comorbidities. These symptoms are shortness of breath, syncopes, chest pain, dyspnoea after exertion, ascites, oedema of the lower extremities and anorexia. Comorbidities that can cause some of these symptoms are left heart disease with diastolic dysfunction, pericardial effusion, congestive heart failure, myocardial fibrosis, ILD, pleuritis, pleural effusion, aspiration pneumonia, chronic kidney disease and musculoskeletal disorders.

"Risk factor for PAH in SSc are late onset of the disease, isolated reduction of DLCO, a FVC/DLCO ratio >1.6, high serum levels of NT-proBNP and a heavy loss of pulmonary capillary density", Stipić-Marković explained. "However, high NT-proBNP levels can also appear in various heart diseases", she added.

Further factors pointing to an elevated risk of PAH are the CREST syndrome and anticentromere antibodies. "The sensitivity of those antibodies, however, is only 30%. And unfortunately, early diagnosis of SSc-PAH is especially difficult, whereas in later stages of the disease it becomes easier to make the correct diagnosis because of increasing symptoms", said Stipić-Marković. Evaluation begins with the history, physical examination, chest x-ray and ECG. Pulmonary function tests are abnormal in 80% of patients. A reduction of FVC (forced vital capacity) reflects fibrotic infiltration. The DLCO (CO diffusion capacity) is a sensitive parameter which can be helpful in determining lung involvement at an early stage. "The ration FVC/DLCO is also extremely helpful", Stipić-Marković added.

High-resolution CT (hrCT) has a high sensitivity to uncover pulmonary involvement. Some added information is gained from CT angiography by means of adding a contrast agent.

Echocardiography is an important screening tool for SSc patients and should be performed annually.

Figure 1 shows a screening algorithm on the basis of echocardiography.
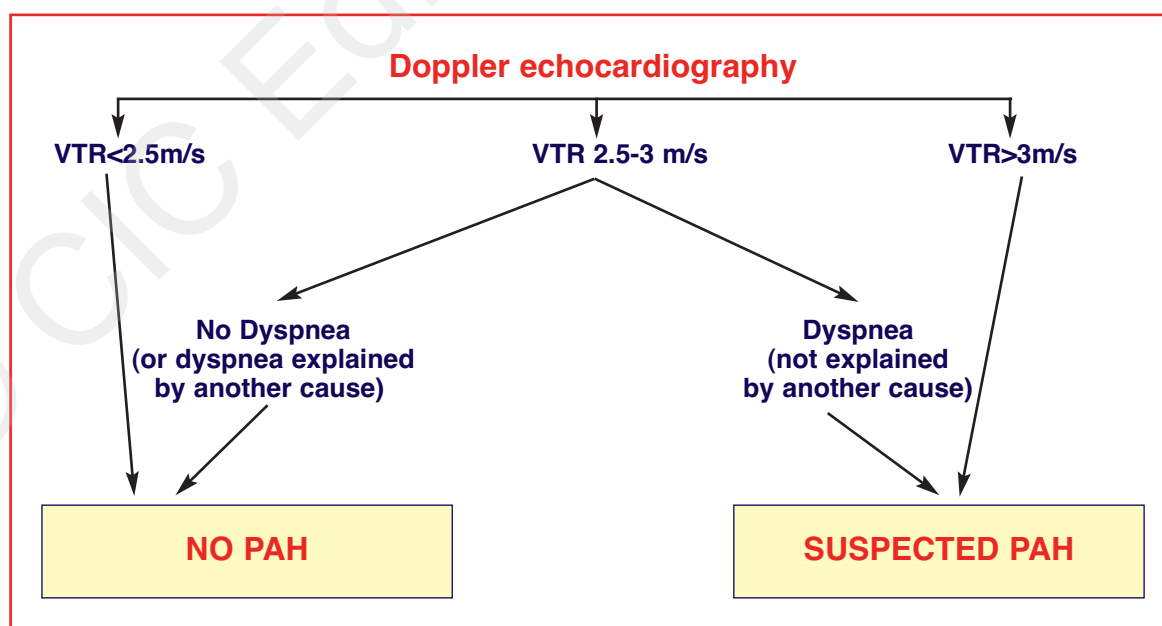

Figure 1 - Echocardiography-based screening algorithm for SSc-PAH.

The essential parameter here is the regurgitation velocity through the tricuspid valve (VTR). If VTR is >3m/s, there is suspicion of PAH. This is also the case if VTR is between 2,5 and 3m/s and there is dyspnoea not explained by another cause.

Nailfold capillary microscopy gives the possibility of differentiating into early, active and late stages of SSc. "Until today, however, right heart catheterization is necessary to confirm the diagnosis of PAH", the expert said finally.

Immunological mechanisms

"We see a marked activation of the immune system especially in the beginning of SSc", said Prof. Dr. Winfried Graninger (Clinical Department of Rheumatology, Medical University Graz, Austria). "Currently, scientific interest focusses on the fibroblast, more to the point: the activated fibroblast, also called myofibroblast".

The key role of the immune system in SSc can be illustrated by the large number of autoantibodies identified so far, some of which have already become part of routine diagnostic procedures.

"What we have learned so far, from animal models as well as genome-wide association studies, is that there are several mutations causing one or a few main aspects of SSc, like vasculopathy, fibrosis, inflammation or autoimmunity, but so far, no key mutation was found", Graninger continued (7, 8).

A potential molecular target in SSc is Interleukin 6 (IL-6) which is produced by and also targets fibroblasts. There are case reports of some response of skin changes in SSc to an IL-6 antagonist (9).

B-cells also play a role in SSc, for example by secreting IL-6 which has a profibrotic effect. "There are animal models and case reports about an amelioration of SSc symptoms through the CD-20 blocker rituximab", Graninger added.

"So we know that T- and B-lymphocytes produce a number of cytokines like IL-4, IL-6, IL-13 and TGF-β, which in turn stimulate fibroblasts and thus prompt fibrosis", Graninger concluded. "The future will show, if new therapeutic targets result from these findings".

Involvement of the heart …

"In terms of heart involvement in SSc there are three major areas to differentiate", referred Prof. Dr. Marco Matucci-Cerinic (Department of BioMedicine, Division of Rheumatology, University of Florence, Italy), "that is primary cardiac involvement, secondary cardiac involve-

ment through PAH and finally vascular involvement. Because of the complexity of the possible changes of the heart the diagnostic evaluation of heart involvement in SSc is extremely difficult – especially primary cardiac involvement is often overlooked".

The pathophysiological mechanisms of primary cardiac involvement in SSc comprise of characteristic vascular lesions and deposition of fibrotic material; they lead to an impairment of coronary microcirculation and of myocardial function (10, 11).

"Cardiac involvement in SSc is common and has high prognostic relevance, but it usually only develops symptoms in a late stage when extensive damage to the myocardium is already established and the available therapeutic options hardly work anymore", the rheumatologist explained (12, 13).

Diagnostic evaluation of cardiac involvement in SSc begins with history, ECG and chest x-ray. Echocardiography and natriuretic peptides are important, and so are cardiopulmonary exercise tests to reveal functional deficits.

"MRI has a special role here for several reasons", said Matucci-Cerinic. "First of all it is very sensitive for fibrosis and oedema – which are the primary myocardial changes in SSc, appearing fairly early in the course of cardiac involvement. MRI today is the gold standard for evaluation of right and left ventricular changes of the heart. The downside is that MRI is expensive and not available everywhere, and certain contrast agents are nephrotoxic", the rheumatologist concluded.

… and of the lung

"Lung involvement in SSc also poses complex problems", stressed Prof. Dr. Marco Confalonieri (Department of Pneumonology, University Hospital of Cattinara, Trieste, Italy).

First of all, the subtypes of SSc show different kinds of lung involvement – ILD is more common in dcSSc and often appears early in the course of the disease, whereas in lcSSc PAH (with or without ILD) is more common, but appears in later stages of the disease (14).

In so called SSc sine scleroderma (thus, without skin involvement) either ILD or PAH can appear (15).

"The problem becomes more complex still because a significant portion – between 14 and 45%, depending on the study cited – of all SSc patients have some kind of overlap syndrome and thus symptoms of a second autoimmune disease", Confalonieri said (16).

The most common pleuropulmonal manifestation in SSc is diffuse ILD (40-90%), followed by PAH (40%) and aspiration pneumonia (15%).

"As a clinician, one has to ask if ILD is present, and if so, if it is clinically significant, how to best diagnose it, if therapy is necessary, and if so, which therapy", Confalonieri continued.

Pulmonary function tests (FVC, FEV$_1$, DLCO) should be interpreted in the context of the clinical picture and other diagnostic results. In CT there are changes typical for ILD, like "ground glass" (100%), irregular, reticular lines (90%) and others (17).

"Lung biopsies should only performed if three conditions are fulfilled", said Confalonieri. "First there must be a clinically significant lung involvement, second the hrCT findings must be atypical for the particular connective tissue disease and third there must be a realistic possibility that the biopsy results might change patient management".

"For treatment, staging of ILD is important", concluded the pneumologist. "Standard therapy consists of a combination of prednisone with an immunosuppressant, usually cyclophosphamide".

Prevention and treatment of SSc-PAH

"As we heard already, SSC with PAH has a worse prognosis than SSc without PAH", explained Dr. Gabor Kovacs (Clinical Department for Pulmonology, Medical University Graz, Austria) (18, 19).
But SSc-PAH even has a worse prognosis than iPAH, as shown, among others, in the data of the REVEAL registry (20) and of the French registry (21).

"Therefore, we have to ask if we can predict the development of SSc-PAH", Kovacs remarked. Retrospective data from the French registry showed that patients with SSc-PAH more often display dyspnoea, fatigue, palpitations, syncopes or presyncopes on exertion, leg oedema, hepatojugular reflux and enlarged jugular veins (22). "Of course, all these are not very specific symptoms", Kovacs continued, "but the PAH group also show a lower DLCO". Another study, in which PAH was only diagnosed by echocardiography, also showed lower DLCO in PAH patients compared to patients without PAH (23).
The French group then showed in an observational trial that SSc patients who develop PAH had a significantly lower baseline DLCO than other patients (24).
Finally, another group develop a scoring system, the Cochin score, to predict the development of SSc-PAH. This score uses age, FVC and the ratio of DLCO and alveolar volume; with an appropriate cut-off value it was possible to reach a sensitivity of 89.5% and a specificity of 74.1% for the prediction of PAH (25). A further warning sign is the rising of mPAP on exertion, even if it still normal at rest and therefore – according to the current definition – PAH is not present. A study showed that in such patients there is high risk of developing – or even dying from – PAH within a few years (26).
"So, we can say that mainly DLCO and a disproportional rise of mPAP on exertion could be predictive factors for PAH", Kovacs summarised.
"In our group, in the VERY-EARLY-Study, we investigated the question if early therapy can delay the development of PAH in SSc", Kovacs reported. In this pilot study, ten patient with SSc and an mPAP at rest of <25mmHg, but an mPAP on exertion of >30mmHg, were first observed for one year, then treated with an endothelin antagonist for six months and underwent right heart catheterisation at baseline, after 12 and after 18 months (27).
"Our primary endpoint was the change of mPAP at 50W between the observation and the treatment phase", Kovacs explained. It turned out that this parameter significantly rose during the observation phase and then, compared to the observation phase, significantly fell during treatment.
"In terms of the treatment of SSc-PAH, basically the same recommendations as for iPAH apply", Kovacs reported (28). Those recommendations say that in the context of right heart catheterisation, vasoreagibility testing should be performed. If it turns out positive, therapy (in functional classes I-III) could begin with a calcium antagonist which in case of good response (FC I-II) could become a permanent therapy. Otherwise, in FC II endothelin antagonists (ambrisentan, bosentan) or PDE5 inhibitors (sildenafil, tadalafil) are recommended, and in FC III prostanoids (epoprostenol, iloprost, treprostinil) can also be used. In FC IV, prostanoids are first choice, but combination regimes are used more and more often (sequentially or up-front), even though the data for this kind of treatment are not yet sufficient.

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