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## Review

## Pulmonary arterial hypertension in systemic sclerosis

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## ABSTRACT

Pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc) is a complex clinical situation resulting from restricted flow through the pulmonary arterial circulation ending in increased pulmonary vascular resistance and right heart failure. PAH is a common and life-threatening complication in connective tissue diseases, specifically in SSc if not treated rapidly and adequately. Based on the emerging knowledge in SSc epidemiology by large scale patient cohorts such as EUSTAR, of PAH pathophysiology and advances in cardiopulmonary diagnostic techniques, several novel treatment approaches have been examined and have proceeded to licensing and daily use in the clinical practice. Amongst them are different endothelin receptor antagonists and PDE-5 inhibitors, but several other ideas are being currently pursued to improve the long-term outcome of the affected patients.

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## 1. Definition of pulmonary arterial hypertension (PAH) and prevalence of PAH in SSc

PAH is a syndrome resulting from restricted flow through the pulmonary arterial circulation, resulting in increased pulmonary vascular resistance and right heart failure [1]. Among rheumatic diseases, PAH is a common complication in systemic sclerosis (SSc), and in a smaller number of patients with other rheumatic diseases such as systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), rheumatoid arthritis (RA), dermatomyositis, polymyositis and Sjögren syndrome [2].

SSc is a heterogeneous connective tissue disorder characterised by dysfunction of the endothelium with generalised microangiopathy, dysregulation of fibroblasts with excessive production of collagen and abnormalities of the immune system with a prevalence of about 5 per 100 000 [3]. The prevalence of PAH in SSc is about 10–12% [4], varying in the different reports between 4.9% and 26.7% [5], especially as the individual diagnostic tool contributes to this difference. Isolated PAH, in the absence of lung fibrosis, was found to be more frequent in the limited form of SSc (45%) than in the diffuse form of the disease (26%) [3]. In a cohort of 3656 SSc patients, the prevalence of lung involvement was estimated as follows: pulmonary fibrosis was more common in diffuse SSc (53.4%) than in limited SSc (34.7%), whereas the frequency of PAH diagnosed by echocardiography was similar between the two subsets – in 22.3% of patients with diffuse SSc and in 20.5% of patients with limited SSc. Of note, histopathological changes consistent with PAH have also been found in a larger proportion of patients at autopsy (about 65% to 80%). These data suggest a substantial prevalence of mild and moderate forms of PAH in SSc [1,6].

### 1.1. Prevalence of PAH in other rheumatic diseases

The prevalence of PAH in other rheumatic disease appears to be lower and is not that well known as in the SSc patients. Clinically significant PAH, which is clinically and pathologically nearly indistinguishable from idiopathic PAH can be found in about 1% to 9% of patients with SLE, although the elevated resting pulmonary arterial pressure (PAP) levels can be observed in a larger proportion asymptomatic patients (9–14%). Raynaud's phenomenon (RP) and antiphospholipid antibodies are more frequent in SLE patients with PAH [2,7,8]. All patients with a new diagnosis of PAH of unclear etiology should therefore be evaluated for occult collagen vascular disease with SSc and SLE being the two most likely entities [7]. PAH in RA and in polymyositis/dermatomyositis can be manifested in association with interstitial lung disease or as an isolated PAH resulting from a primary vasculopathy as observed in SLE and SSc. PAH has been rarely described in RA as a complication of interstitial lung fibrosis, pulmonary vasculitis, thromboembolic or cardiac disease [7]. One prospective echocardiographic study shows a 6% frequency of PAH secondary to lung disease, and a 21% prevalence of mild arterial PAH in unselected RA patients [2,9]. The clinical significance of this finding is not known, since the prevalence of RA in severe PAH is extremely low. High prevalence of PAH is cited in the literature in patients with MCTD as being between 23 and 50%, but this finding is difficult to interpret, because many patients have been later diagnosed as SSc or other autoimmune rheumatic diseases [2,10]. PAH has also rarely been reported in Sjögren syndrome.

## 2. Results from the EULAR Scleroderma Trials And Research (EUSTAR) group

In order to better understand the pathogenesis of SSc and to guide its treatment, the EULAR Scleroderma Trials And Research (EUSTAR) group was formed in June 2004. Currently there are more than 150 centers worldwide and more than 9000 enrolled patients. EUSTAR collects data prospectively using a form – “Minimal Essential Data Set” (Fig. 1) [3]. As PAH has been identified to be one of the most

important factor, that contributes to the increased morbidity and mortality in SSc [11], it has also stimulated several research approaches. The high incidence and prevalence of PAH in SSc, its poor prognosis and new evidence-based treatment, that improve prognosis and survival, resulted in the recommendation of an obligatory screening of SSc patients for the development of this complication. Among 429 patients with PAH associated with connective tissue disease (CTD) in the UK National registry – 73% suffered from PAH in the context of SSc [4].

## 3. Subtypes of PAH in SSc

### 3.1. PAH associated with pulmonary fibrosis

Pulmonary fibrosis can be found in more than one third of SSc patients with either the diffuse or limited form of the disease. Post mortem examination has revealed alveolar, interstitial, peribronchial and pleural fibrosis. In the affected patients, a moderate degree of PAH with relatively slow progression usually follows the widespread pulmonary fibrosis as a consequence of the gradually increasing resistance of the of pulmonary vasculature [12].

### 3.2. PAH without pulmonary fibrosis

PAH in SSc patients with minimal or no pulmonary fibrosis is a severe complication due to narrowing or occlusion of small pulmonary arteries caused by smooth muscle hypertrophy, intimal hyperplasia, inflammation, thrombosis in situ. The rate of progression of dyspnea from normal exercise tolerance to oxygen dependency is about 6–12 months with a subsequent mean duration of survival of 2 years. In contrast, SSc patients with PAH in the context of interstitial lung disease develop a similar degree of disability, but progress more slowly for a period of over 2, up to 10 years [1,12–14].

## 4. Genetics in PAH

A heterozygous germ line mutation in bone morphogenetic protein receptor 2, a member of the transforming growth factor family, has been identified in 60% of familial cases of idiopathic PAH and 25% of sporadic cases, but not in patients with PAH associated with autoimmune diseases or in the other secondary causes of PAH [2]. A study addressing candidate genes in SSc-related PAH in limited number of patients has also been conducted. Expression profiling in peripheral blood mononuclear cells from patients with idiopathic PAH and SSc-related PAH have been compared using PCR. In this approach, an increased expression of genes that encode key molecules of inflammation and angiogenesis, e.g. IL-8, vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 when compared with healthy controls, have been identified without observing a difference in patients with mild and severe PAH. Future studies about gene expression in SSc-related PAH may reveal new targets for early detection, prevention and treatment of this devastating complication [15].

## 5. Pathomorphology of PAH in SSc

The process of pulmonary vascular remodeling involves all layers of the vessel wall. The histological analysis of PAH reveals a variety of arterial abnormalities e. g. intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis in situ, combined with varying degrees of inflammation and a plexiform arteriopathy [1,13,14].

## 6. Pathogenesis of PAH in SSc

Multiple pathogenic pathways have been implicated in the development of PAH. It is recognised that pulmonary arterial obstruction and vascular remodeling are the hallmarks of PAH pathogenesis.

# EUSTAR - MINIMAL ESSENTIAL DATA SET

1

Unique center N° .....

Unique patient N° .....

Date of birth (day/month/year) .....

Sex .....  male  female

Onset of Raynaud ..... month   year

Onset of first non-Raynaud feature of disease ..... month   year

ACR Criteria fulfilled (yes / no) ..... yes  no

Subset ..... diff. cut. SSc  lim. cut. SSc  other

ANA positive	yes <input type="checkbox"/>	no <input type="checkbox"/>	Elevated acute phase reactants	yes <input type="checkbox"/>	no <input type="checkbox"/>
ACA positive	<input type="checkbox"/>	<input type="checkbox"/>	Proteinuria (+ or more)	<input type="checkbox"/>	<input type="checkbox"/>
Scl 70 positive	<input type="checkbox"/>	<input type="checkbox"/>	Active disease *	<input type="checkbox"/>	<input type="checkbox"/>

\* Cross "yes" if activity score ≥ 3 according to attachment "EULAR Systemic Sclerosis Activity Score"

Date of filling out this form .....

Complete only in case of death: ..... Date of death

Death due to SSc   Death due to treatment   Death due to other

Version Aug 2004 – return to: EUSTAR, c/o Prof Matucci-Cerinic, Rheumatology, Villa Mbnna Tessa, Viale Pieraccini 18, 50139 Florence, ITALY. Fax: 003905579492

# EUSTAR - MINIMAL ESSENTIAL DATA SET

2

Unique center N°    Unique patient N°     Date of birth

WEIGHT	.....	<input type="text"/>	kg		
SKIN	Mod. Rodnan (max. 51).....	<input type="text"/>		yes	no
VASCULAR	Raynaud's.....	<input type="checkbox"/>		<input type="checkbox"/>	
	digital ulcers.....	<input type="checkbox"/>		<input type="checkbox"/>	
JOINTS	synovitis.....	<input type="checkbox"/>		<input type="checkbox"/>	
	joint contractures.....	<input type="checkbox"/>		<input type="checkbox"/>	
TENDONS	friction rubs.....	<input type="checkbox"/>		<input type="checkbox"/>	
MUSCLES	C.K. elevation.....	<input type="checkbox"/>		<input type="checkbox"/>	
	Weakness.....	<input type="checkbox"/>		<input type="checkbox"/>	
	atrophy.....	<input type="checkbox"/>		<input type="checkbox"/>	
G.I.T.	esophageal (dysphagia, reflux).....	<input type="checkbox"/>		<input type="checkbox"/>	
	stomach (early satiety, vomiting).....	<input type="checkbox"/>		<input type="checkbox"/>	
	intestinal (diarrhea, bloating, constip.).....	<input type="checkbox"/>		<input type="checkbox"/>	
RENAL	hypertension.....	<input type="checkbox"/>		<input type="checkbox"/>	
	Renal crisis.....	<input type="checkbox"/>		<input type="checkbox"/>	
Cardio-	dyspnoea (significant).....	<input type="checkbox"/>		<input type="checkbox"/>	
Pulmonary	palpitations.....	<input type="checkbox"/>		<input type="checkbox"/>	
	conduction blocks.....	<input type="checkbox"/>		<input type="checkbox"/>	
	diastolic function abnormal.....	<input type="checkbox"/>		<input type="checkbox"/>	
	reduced ventricular ejection fraction.....	<input type="checkbox"/>		<input type="checkbox"/>	
	fibrosis - plain X-ray.....	<input type="checkbox"/>		<input type="checkbox"/>	
	restrictive defect (lung function test).....	<input type="checkbox"/>		<input type="checkbox"/>	
	pulmonary hypertension (ECHO).....	<input type="checkbox"/>		<input type="checkbox"/>	
	DLCO.....	<input type="text"/>	% predicted		

COMMENTS

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Fig. 1. EUSTAR – minimal essential data set – an online form.



### 6.1. Prostanoids

The prostanoids prostacyclin and thromboxane  $A_2$  are key arachidonic acid metabolites. Prostacyclin is a potent vasodilator, which inhibits platelet activation and possesses antiproliferative properties. In contrast, thromboxane  $A_2$  acts as a vasoconstrictor and platelet activator. In PAH, prostacyclin synthase is decreased and an imbalance between the level of prostacyclin and thromboxane  $A_2$  can be found with prostacyclin deficiency. These alterations contribute to vasoconstriction, thrombosis and proliferation [1,16].

### 6.2. Nitric oxide (NO)

NO is also a potent vasodilator. Decreased synthesis of NO is implicated to play a role in the pathogenesis of PAH. The enzyme, that stimulates production of NO – NO-synthase, has been found to be decreased in patients with PAH [17]. The effects of NO are mediated by cyclic guanosine monophosphate (cGMP), which is rapidly inactivated by the enzyme – phosphodiesterase (PDE), especially the isoform 5. PDE-5 is present in large amounts in the lung, providing the rationale for the therapeutic use of PDE-5 inhibitors in PAH [1].

### 6.3. Endothelin (ET)

ET is a peptide, which inherits a number of deleterious effects. It promotes vasoconstriction, fibrosis, inflammation, stimulates the proliferation of pulmonary artery smooth muscle cells and vascular hypertrophy. ET-1 is the main isoform in humans. Plasma levels of ET-1 are found to be increased in SSc [18], and in most of the studies, a correlation with the severity of PAH has been found [1,19]. The distinct role of ET-1 in the pathogenesis of PAH is supported by its increased expression together with mRNA in samples of lung tissue in patients with primary PAH as compared with healthy controls [20]. There are two classes of receptors for this mediator –  $ET_A$  and  $ET_B$ .  $ET_A$  receptors are mainly expressed on vascular smooth muscle cells and cardiac myocytes, while  $ET_B$  are found primarily on endothelial cells and to a lesser extent on vascular smooth muscle cells and fibroblasts. Activation of  $ET_A$  receptors ( $ET_B$  on vascular smooth muscle cells) results in vasoconstriction and proliferation of smooth muscle cells.  $ET_B$  on endothelial cells receptors have clearance function and may facilitate vasodilation via release of smooth muscle relaxants such as NO and prostacyclin [21–26].

### 6.4. Platelet derived growth factors (PDGFs)

PDGFs are primary mitogens for the mesenchymal and neuroectodermal cell types. They were first described as a serum factor that stimulates proliferation of smooth muscle cells. The PDGF family consists of four different polypeptide chains – PDGF – A and B and more recently described C and D. They form homodimers PDGF – AA, BB, CC, DD and one heterodimer – AB. PDGF A and B are secreted in active forms, while C and D are secreted in latent forms and require proteolytic activation [27,28]. PDGFs exerts their biological activities by activating two structurally related tyrosine kinase receptors –  $\alpha$  and  $\beta$ . PDGF  $\alpha$  and  $\beta$  receptors are structurally similar, their activation induces homo- and heterodimerisation and leads to autophosphorylation of specific tyrosine residues. Phosphatidylinositol 3 kinase, ras-MAPK, src family kinase and phosphorylase C $\gamma$  are the subsequently activated pathways as a result of the activation of PDGF receptors. This results in induction of several pathways, which include cellular proliferation, chemotaxis and actin reorganization [28]. PDGF A and B are almost undetectable in normal vessels, but are highly expressed in vasculature of different diseases such as atherosclerosis, organ fibrosis, tumorigenesis and PAH [28,29].

### 6.5. Vascular endothelial growth factor

VEGF is an endothelial cell-specific mitogen and a potent angiogenic peptide, whose expression is induced by hypoxia-inducible factor that is formed in hypoxic conditions. VEGF has been shown to be implicated in several physiological and pathological processes that require proliferation of endothelial cells. In SSc, serum levels of VEGF have been found to be elevated [30]. Its role for the formation of plexiform-like lesions in medium-sized pulmonary arteries as a result of endothelial proliferation is also known [31]. In addition, a correlation between the VEGF levels and the presence of PAH in SSc, the dyspnea score and the reduction of DL<sub>CO</sub> exists [30].

### 6.6. Natriuretic peptides

Natriuretic peptides have been initially examined for the diagnosis of acute heart failure. Brain natriuretic peptide (BNP) and its more stable analogue N-terminal pro-BNP (NT-proBNP) are currently discussed as marker for a variety of abnormal cardiovascular conditions. They are released by myocytes in response to pressure or volume overload. Both atrial natriuretic peptide and BNP correlated with survival in idiopathic PAH. Recent studies have demonstrated that BNP and NT-proBNP are highly attractive for the diagnosis and the prediction of PAH in SSc. NT-proBNP allows the detection of both PAH and reduced left and right ventricular contractility [32]. Pro-BNP and NT-proBNP are increased in the early stages of the disease and correlate with hemodynamic parameters and patients survival [33,34]. Pro-BNP levels are increasingly being used and appear to correlate with right ventricular enlargement and dysfunction. The predictive value of high NT pro-BNP levels for the development of PAH revealed a 90% sensitivity and specificity and a negative predictive value of 90% in SSc patients. [1].

### 6.7. CD40L

The soluble form of CD40L is released by activated T-cells and is involved in B-cell activation, fibrosis and expression of adhesion molecules on endothelial cells. Its level has been found to be increased in SSc patients. Higher values have been detected in patients with limited SSc than in those with the diffuse form of the disease. A positive correlation with PAH and digital ulcers has also been reported [34–36].

### 6.8. Calcitonin gene related peptide (CGRP)

CGRP is a potent endogenous vasodilator, which is widely distributed in perivascular nerves. Bunker and coworkers described a significant reduction of CGRP immunoreactive neurons in the papillary dermis and around capillaries in deeper dermis in the skin of patients with primary RP and in RP secondary to SSc [37]. CGRP-like immunoreactivity is also localised in the lung and in nerve fibres of the airways from trachea to the level of alveoli. Tjen-A-Looi et al. previously showed that exogenous CGRP is able to reduce PAP in hypobaric hypoxic rats [38]. Bartosic et al. examined plasma levels of CGRP in 29 SSc patients and found higher levels in patients with SSc and PAH than in those with normal PAP. In addition, a correlation between the plasma levels of CGRP and the pulmonary systolic pressure as well as with the erythrocyte sedimentation rate has been observed. Possible explanations of the finding are that either CGRP is reflecting disease activity in isolated PAH or a CGRP release is secondary to pulmonary vasoconstriction [39]. Many patients in this study had a short disease duration, which might explain the difference in the results of this group as compared of those of Matucci-Cerinic et al., who found decreased level. In addition, CGRP is supposed to be associated with the process of inflammation. CGRP is reported to have a proliferative effect on human endothelial cells. Intradermal injection

of CGRP in humans leads to a prolonged erythema, accompanied by an infiltration with polymorphonuclear leucocytes [39,40].

#### 6.9. Serotonin (5-hydroxytryptamine – 5HT)

Serotonin is a vasoconstrictor and promotes proliferation of pulmonary artery smooth muscle cells, pulmonary arterial vasoconstriction and local microthrombosis. Transgenic mice, overexpressing the serotonin transporter, develop PAH [41]. The inhibition of serotonin transporter and 5-HT receptor – 1B are both effective approaches in preventing and reversing experimental PAH and serotonin-induced proliferation of pulmonary artery smooth muscle cells derived from patients with idiopathic PAH. Therefore, targeting both the serotonin transporter and 5-HT receptor – 1B may be a novel therapeutic approach to PAH [42]. The administration of selective serotonin reuptake inhibitors has been reported to be associated with decreased development of PAH as well as with decreased mortality in patients with established syndrome. These observations suggest a rationale for clinical trials of these drugs in PAH [43].

#### 6.10. Vasoactive intestinal peptide (VIP)

VIP is a member of the glucagon-growth hormone-releasing superfamily. Serum and lung tissue VIP levels are decreased in PAH patients, and exogenous VIP may decrease PAP, inhibit platelet activation and smooth muscle cell proliferation [1,2,44].

#### 6.11. Matrix metalloproteinases

The hypoxic injury to the pulmonary vascular wall, which induces matrix protein breakdown appears to be one of the important pathogenic mechanisms of vascular remodeling in PAH. The activity of collagenolytic metalloproteinases in the lung tissue is stimulated in hypoxic conditions. As a result, matrix fragments of the collagen cleavage are produced, which may be implied in the triggering of mesenchymal proliferation in peripheral pulmonary arteries. This concept is supported by the fact that a synthetic inhibitor of matrix metalloproteinases – batimastat – effectively prevents the development of PAH [45].

#### 6.12. Inflammation in PAH

Pulmonary arterial lesions in the lungs of patients suffering from CTD with isolated PAH are often similar to those observed in primary PAH including plexiform lesions, “onion-bulb” lesions and medial hypertrophy. This similar pathobiology suggests also a similar pathophysiology. In SSc-related PAH, inflammatory infiltrates around the involved vessels have been observed including T-, B-lymphocytes and macrophages, supporting the concept that inflammatory cells play a role in PAH [46].

### 7. Detection of PAH in SSc – steps to the diagnosis

The most common *presenting symptoms* of PAH include dyspnea on exertion, fatigue, chest pain, dizziness, palpitations, and edema at the lower extremities. Exercise capacity is classified by *World Health Organization (WHO) functional classes*: The criteria for description of the functional class of PAH have been modified by the New York Heart Association at the World Symposium on Primary Pulmonary Hypertension in France (1998) [47,48]. *Class I* PAH does not limit physical activity, and does not cause abnormal dyspnea or fatigue, chest pain, or syncope. *Class II* PAH results in a measurable limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity causes dyspnea or fatigue, chest pain, or pre-syncope symptoms. *Class III* PAH results in a marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary physical activity causes immediate dyspnea or fatigue, chest pain, or

pre-syncope symptoms. *Class IV* PAH results in an inability to perform any physical activity without symptoms. The patient has also signs of right heart failure. Dyspnea, fatigue, or both may be present even at rest. In all stages of cardiovascular physical examination signs range from subtle – accentuated pulmonary component of the second heart sound, gallop and pansystolic murmur of tricuspid regurgitation to severe features of right heart failure in the later stages [5].

The *chest X-ray* and *electrocardiogram* may also reveal symptoms suggestive of PAH (enlarged pulmonary artery, attenuation of peripheral pulmonary vascular markings in the later stages at the chest X-ray; peaked P wave  $\geq 2.5$  mm in leads II, III and aVF), that require further examination [1,5].

If PAH is suspected, a *transthoracic Doppler echocardiography* has to be performed [1,5]. According to echocardiographic findings, PAH is defined as mean PAP  $> 25$  mmHg at rest,  $> 30$  mmHg during exercise or systolic pulmonary pressure  $> 40$  mmHg. Echocardiographic finding suggestive of the complication are elevated tricuspid regurgitation velocity jet above 2.8 m/s, dilated right ventricle or dilated atrium [49]. Hemodynamic parameters are most often measured at rest, while a substantial part of the patients experience dyspnea with exercise. Exercise echocardiography may be used to detect exercise-induced PAH. It is challenging both to perform and interpret and is normally placed in a research setting. The consensus is that no treatment decisions can be made on the basis of exercise-induced PAH alone [1].

*Pulmonary functional testing*, particularly *carbon monoxide diffusing capacity (DLco)* values are of crucial value for prediction development of PAH. Abnormal DLco is a marker of pulmonary vascular disease and predicts the presence of PAH and poor prognosis in SSc. Dyspnea in SSc should prompt an immediate search for PAH, especially in those patients with a low single breath DLco or progressive declining of DLco over time [50]. A decreasing DLco is an excellent predictor of the subsequent development of isolated PAH in limited SSc. The DLco may be significantly decreased for many years prior to the diagnosis of PAH. In a group of 104 SSc patients, the individuals with PAH had a significantly lower mean DLco (52% of predicted) almost 5 years before the diagnosis of PAH [51].

There is a growing interest in *novel noninvasive imaging techniques* in the evaluation of patients with PAH. *Computed tomography* and *magnetic resonance* imaging techniques are being explored to assess right ventricular mass, volumes, and function. Promising magnetic resonance markers of PAH are the ratio of septal curvature, right ventricular ejection fraction, right ventricular volume etc. [1].

*Comparison of noninvasive methods for assessment of PAH with right heart catheterization (RHC)* in 49 SSc patients resulted in 58% sensitivity and 96% specificity for Doppler echocardiography and for magnetic resonance imaging a sensitivity – 68% and specificity – 71%. The ratio of forced vital capacity to diffusion capacity (%FVC/%DLCO)  $> 2.0$  by pulmonary function tests resulted in 71% sensitivity and 72% specificity. Echocardiography appeared to be the most useful among the noninvasive tests, mainly due to the high specificity and high positive predictive value [52].

Careful *invasive assessment* of pulmonary hemodynamics is of crucial importance in the evaluation of patients with suspected PAH. All patients that are suspected of having PAH after noninvasive evaluation should undergo RHC prior to initiation of therapy for measuring PAP, calculating pulmonary vascular resistance, and performing vasodilator testing. Due to the low sensitivity of noninvasive testing, however, RHC still remains the gold standard for the diagnosis of PAH [1,52]. Pulmonary hypertension commonly occurs with high transpulmonary flow in the setting of exercise, anemia, pregnancy, sepsis etc. In these conditions, the pulmonary vascular bed is anatomically normal and the pulmonary hypertension resolves when the cardiac output returns to normal levels. The transpulmonary gradient (PAP mean-wedge) is significantly elevated only in PAH patients, but not in patients whose pulmonary hypertension is due to increased cardiac output, left heart myocardial, or valvular disease. Pulmonary vascular resistance (PVR) is a more

reliable diagnostic criterion for PAH, because it reflects the influence of transpulmonary gradient and cardiac output and is only elevated if the vascular obstruction occurs within the precapillary pulmonary circulation. However, PVR can also be elevated in patients with valve disease or left ventricular heart disease [1]. Therefore, PAH remains a diagnosis of exclusion. After excluding lung disease, thromboembolic disease, left ventricular heart disease, or valve disease, the diagnostic criteria for PAH requires both a mean PAP greater than 25 mm Hg and a PVR greater than 3 Wood units with a pulmonary capillary wedge pressure <15 mmHg (to exclude left heart disease). As the mean PAP cannot be determined easily by echocardiography, an estimated systolic PAP >35 mmHg and/or an increased tricuspid velocity are used as indicators of probable PAH [1,52]. It is the opinion of the majority of experts, who concluded that over-reliance on noninvasive, echocardiographically derived estimates of PAP is not recommended and invasive hemodynamic studies are essential to establish a correct diagnosis. Exercise RHC is technically difficult to perform and interpret. It is not used routinely in most clinical settings and is an area of active investigation [1].

With regard to biomarkers for PAH, BNP and its more stable analogue NT-pro-BNP are promising screening parameters in SSc-related PAH. A correlation between disease severity and increased levels has been found. In addition, this biomarker appears also to predict survival [1,49]. In contrast, the presence of neutrophilia on bronchoalveolar lavage has not been found to be associated with time to decline in pulmonary function or with survival in SSc. Neither eosinophilia nor lymphocytosis on bronchoalveolar lavage was associated with mortality, rapidity of functional deterioration, or progression-free survival. These findings were unaltered when treatment status was taken into account [53]. Hofstee HM et al. suggested a hypothesis about a correlation between reduction of mean capillary density at capillaroscopic examination and presence of PAH in SSc [54], although not all authors support the idea about an association of capillaroscopic pattern and the form of the disease and visceral organ involvement in SSc [55].

## 8. Treatment of PAH in SSc

Acute vasodilator testing is usually performed during the same procedure as the diagnostic catheterization. Most commonly used agents are inhaled NO, intravenous epoprostenol or intravenous adenosine [1]. Although there is no evidence-based guideline for selection of vasodilators, according to ACC/American heart association 2009 consensus inhaled NO is the preferred vasodilator, while intravenous epoprostenol and intravenous adenosine are acceptable alternatives. It was demonstrated, that NO is a more sensitive predictor of response (79%), compared with inhaled oxygen (64%). Recent studies have demonstrated its efficacy as a screening vasodilative agent and as a predictor of a safe response to oral vasodilators. Inhaled NO is well-tolerated, and no systemic complications such as hypotension, bradycardia, chest pain or altered mental state were observed [56,57]. The rationale for vasodilator testing in evaluation of PAH patients is based on the following reasons: i) acute vasodilator responsiveness identifies patients with a better prognosis; and ii) responders are more likely to have a sustained beneficial response to oral calcium channel blockers than non-responders. At present, the current definition of a response is defined as a reduction in mean PAP of more than or equal to 10 mmHg, to a mean PAP less than or equal to 40 mmHg, together with an unchanged or even increased cardiac output [1]. Exercise capacity, measured by the 6-min walk test is also a widely used and validated method for evaluation the effect of treatment.

It has been accepted that the therapeutic approach in severe PAH in the context of autoimmune disease should follow the same treatment strategy as in primary PAH patients [2]. Low level aerobic exercise, such as walking when tolerated, is recommended for PAH patients. In 30 patients with stable therapy for PAH, the effect of intensive exercise training has been studied. After 15 weeks, an

improvement in 6-min walk test, quality of life, functional class, and peak oxygen consumption has been demonstrated. However, extensive physical or isometric exercise (straining against a fixed resistance) may evoke an exertional syncope and should be avoided. In addition, sodium consumption needs to be restricted to 2400 mg per day in patients with right ventricular failure. Of note, routine immunization against influenza and pneumococcal pneumonia are advised to prevent severe infections [1].

Although there are no data from clinical trials, the American College of Cardiology (ACC) guidelines 2009 recommend oxygen therapy in PAH patients with pulse oximetry saturation of less than 90% at rest or with exercise [1]. Abnormalities of the activated clotting system, impaired fibrinolysis, abnormal platelet function and histological evidence of microvascular thrombosis, that are evident in animal models and patients with idiopathic PAH, provide the rationale for anticoagulation therapy in these patients. The literature data support a beneficial effect of warfarin on survival in idiopathic PAH patients, although a large prospective randomized trial has not been performed. The results suggest that interruption of ongoing thrombosis with effective systemic anticoagulation therapy is associated with a better prognosis, especially for patients that were not responsive to vasodilators [1,58,59]. In the consensus of ACC/American heart association 2009 on PAH it is included the warfarin anticoagulation in patients with idiopathic PAH titrated to an international normalized ratio of 1.5 to 2.5. Regarding the CTD-associated forms of PAH, the recommendation is that anticoagulants should be considered in the more advanced stages, in cases with continuous intravenous therapy, and in the absence of contraindications [1]. Treatment of right heart failure with digoxin, diuretics and oxygen therapy is thought to offer little more than palliation [5]. As mentioned above, inflammation plays a significant role in the development and the progression of PAH [46]. Interestingly, occasional patients with severe PAH associated with some forms of CTD (e.g., SLE, primary Sjögren syndrome and MCTD) improved significantly with respect to their pulmonary vascular disease with corticosteroids and/or immunosuppressive therapy, emphasizing also the relevance of inflammation in these subsets of patients. However, this therapeutic response is not generally observed in patients with SSc-PAH, whose disease is usually quite refractory to immunosuppressive drugs [60].

Long acting nifedipine, diltiazem and amlodipine are the most commonly used calcium channel blockers. Verapamil should be avoided because of its potential negative inotropic effects. It has been observed that therapy with high doses of calcium-channel blockers in patients with primary PAH, who respond with reduction in PAP and pulmonary vascular resistance may improve survival [61].

Development of new effective treatments in the recent years has given impetus for early detection of this devastating complication [5]. As outlined above, prostacyclin synthase is reduced in PAH patients. There are currently three commercially available prostanoids: epoprostenol, treprostinil, and iloprost. Epoprostenol is a prostacyclin with a very short half-life of 6 min and the drug is unstable at pH values below 10.5. Therefore, it cannot be applied orally and requires intravenous application. The start dose is 1–2 ng/kg/min, which is increased up to 25–40 ng/kg/min. Intravenous epoprostenol improves functional class, hemodynamics, exercise capacity and survival in PAH. In randomized controlled study, that included 111 SSc patients in 17 PAH referral centers, it was demonstrated, that epoprostenol improve exercise capacity and survival in SSc-related PAH. Simultaneously it reduced the severity of RP and the frequency of digital ulcers. Epoprostenol must be delivered by continuous intravenous infusion. Patients have to be educated in the techniques of sterile preparation of the medication, operation with the ambulatory infusion pump, and care of the central venous catheter. The most common side effects are headache, jaw pain, flushing, nausea, diarrhea, skin rash, and musculoskeletal pain. Infections and infusion interruptions can be life-threatening [1,62]. Treprostinil is an epoprostenol analogue with a half-life of 4.5 hours and is stable at room temperature. It is usually given as a continuous subcutaneous infusion



at the dose of 10–20 ng/kg/min, but the drug can also be given intravenously. Intravenous and subcutaneous treprostinil produces similar haemodynamic effects compared to those of epoprostenol in patients with PAH. Long-term observations have suggested an improved survival, although controlled clinical trials have not been performed. The Food and Drug Administration (FDA) approved the subcutaneous treprostinil in 2002 for use in patients with PAH from functional class II, III and IV. In 2004, the intravenous treprostinil was approved by FDA for PAH patients, classified as functional class II, III, and IV, in whom subcutaneous infusion is not tolerated. The most common adverse effects in the course of treatment with treprostinil are pain or erythema at the site of the subcutaneous infusion, headache, diarrhea, rash, and nausea. Investigational trials with both inhaled and oral formulations of treprostinil are ongoing [1,63]. *Iloprost* is a chemically stable prostacyclin analogue with a longer half-life – 20–25 min and similar biological properties. The continuous intravenous infusion of iloprost seems to be as efficient as intravenous epoprostenol in PAH patients [64,65]. In addition it reduces frequency and severity of vasospastic episodes in severe RP secondary to SSc, relieves the pain and heals digital ulcers [66–68]. It causes vasodilation, inhibition of platelet aggregation, inhibition of leucocyte chemotaxis and adhesion to the endothelium. Iloprost downregulates expression of adhesion molecules on endothelial cells and phagocytes and enhances fibrinolytic activity [64]. Iloprost is given as venous infusion for 6–8 h at a dose of 0.5–3 ng/kg/min [64–68]. The observation of significant skin softening in SSc patients treated with iloprost, resulted in hypothesis, that this drug may inherit also disease-modifying activity [68]. Della Bella and colleagues reported that iloprost inhibits also lymphocyte adhesion to endothelial cells and significantly inhibits IL-1 $\beta$  induced endothelial expression of ICAM-1. Referring to the expression of VCAM-1 no significant effect has been detected [66]. After 5–7 days infusion of iloprost in SSc, Mittag and coworkers found reduced serum levels of sICAM-1, sVCAM-1, sE-selectin, ET-1 and VEGF. These authors suggested that iloprost, in addition to its vasodilative effect, may modulate inflammatory processes in SSc [67]. Side effects during infusion of iloprost are well known: headache, nausea, vomiting, diarrhea, myalgia, arthralgia, chill, fever, arrhythmia, hypotension, erythema and pain at the infusion site. In addition, iloprost can provoke chest pain especially in patients with coronary heart disease. The lack of pulmonary selectivity results in systemic side effects, tolerance and leads to progressive increases in the dose. Systemic side effects, the need for continuous infusion and potential recurrent infections of the intravenous catheter are main limiting factors for parenteral therapy with prostanoids [66–68].

*Prostaglandins for inhalation* are also used in therapeutic approach of PAH [65,66]. Iloprost is a stable analogue of prostacyclin that is associated with a longer duration of vasodilatation. When administered via inhalation its pulmonary vasodilative potency was similar to that of prostacyclin, but its effects lasted for 30 to 90 min, as compared with 15 min for prostacyclin. Inhaled iloprost have been found to be effective therapy for patients with severe PAH. Olschewski H et al. compared repeated daily inhalations of 2.5 or 5.0  $\mu$ g of iloprost (six or nine times per day; median inhaled dose, 30  $\mu$ g per day) with inhalation of placebo in patients with severe PAH (III and IV functional class). Clinical symptoms, hemodynamic parameters, functional class and the quality of life improved significantly [69]. Most patients tolerated the transition from intravenous to inhaled prostanoid therapy [70]. Observed side effect after administration of inhaled iloprost is syncope, which has not been associated with clinical deterioration or premature withdrawal from the study. It may occur late more than 2 h after the last inhalation [69]. Other common side effects are flushing, jaw pain, headache, cough and dizziness, which are usually transient and mild and generally improve within several days after initiation. Occasionally, it may induce bronchoconstriction; marked deterioration and deaths have also been reported. Some patients are transitioned to intravenous prostanoid therapy from

inhaled iloprost for clinical deterioration [70]. In 16 patients with PAH, who deteriorated while being treated with aerosolised iloprost, switching to continuous intravenous iloprost caused substantial improvement in exercise capacity in eight of them, but could not prevent progression of PAH in the remaining eight patients [65].

Beraprost is the first oral prostacyclin analogue with vasodilative and antiplatelet action and a half-life of approximately 1 h. The peak plasma level is reached within 2 h after oral administration. In the ALPHABET study, which included 130 patients with PAH, beraprost was used at an initial dose of 20  $\mu$ g 4 times daily. Thereafter, the dose was increased by 20  $\mu$ g to four times a day each week. The maximum allowed dose in the study was 120  $\mu$ g qid and the mean dose 80  $\mu$ g qid. The increase in dose was limited by side effects like flushing, diarrhea and headache. Beraprost is effective in primary and secondary PAH [71,72].

As mentioned above, ET is a peptide with a key role in the pathogenesis of PAH secondary to CTD. It has a number of deleterious effects and leads to vasoconstriction, fibrosis, inflammation and vascular hypertrophy [21–25].

*Bosentan* is a non-selective *endothelin receptor antagonist (ERA)* and is the first drug of this evolving family, which is approved for treatment of PAH associated with systemic rheumatic diseases in US, Canada, Switzerland and European Union. It is used at a dose of 62.5 mg twice daily for 4 weeks before titration up to 125–250 mg twice daily. Bosentan improves exercise capacity in patients with PAH (BREATHE-1 study), improves dyspnea index, WHO functional class and in long-term observations suggests a positive effect on outcome [1,73,74]. In 2008, Bosentan has also been approved in European Union for the treatment of mild PAH in SSc – WHO class II (EARLY study) [75], since in 2002 approved for advanced WHO functional classes – III and IV of patients with PAH in the context of CTD, and most recently also for prevention from new digital ulcers in SSc. Observed side effects are headache and elevation of liver enzymes, anemia and edema [73–76]. The FDA requires liver function tests to be checked monthly, and the hematocrit to be checked every 3 months. Hormonal contraceptives may be less effective with concurrent administration of bosentan, and barrier techniques of contraception are recommended. This is particularly important because bosentan is potentially teratogenic. There is also the concern that ERA as a class may be capable of causing testicular atrophy and male infertility. Younger males, who may consider conceiving, should be counseled regarding this prior to taking these drugs [1].

*Sitaxsentan* is a new, oral, once-daily used, highly selective ERA, that has a long duration of action and high specificity for ET<sub>A</sub> receptors (ET<sub>A</sub>:ET<sub>B</sub> – 6500:1). It is used at the dose of 50–100 mg per day. Selective ET<sub>A</sub> receptor antagonism leads to blocking the vasoconstrictory effect of ET-1 and maintaining the vasodilative and clearance function of ET<sub>B</sub> receptors. The effectiveness of sitaxsentan in patients with PAH is proven in randomized, multicentre, placebo-controlled Studies (STRIDE). The observed side effects are similar to those during therapy with bosentan [77].

*Ambrisentan* is a potent and selective inhibitor of ET<sub>A</sub> receptors (ET<sub>A</sub>:ET<sub>B</sub> – 4000:1). The half-life of the medication is 9–15 h, which allows once-daily dosing (2.5–10 mg per day). Ambrisentan differs as compared to bosentan and sitaxsentan in its chemical structure. It is a propanoic acid class molecule rather than a sulfonamide class agent. Effectiveness of ambrisentan is evaluated in two phase-3 randomized, double-blind, placebo-controlled studies (ARIES-1,2) in patients with PAH. Ambrisentan improves exercise capacity with a dose dependent effect. It has an improved safety profile compared with sulfonamide class ERA, which can also cause liver abnormalities and require monthly liver function testing. In trials, ambrisentan has demonstrated a lower incidence of hepatotoxicity. Bosentan induces the cytochrome P-450 isoenzymes (CYP2C9 and CYP3A4) and may decrease the systemic exposure of other drugs that share this metabolic pathway. Sitaxsentan inhibits the activity of CYP2C9 and therefore increases the systemic exposure to drugs metabolized by this cytochrome P-450 isoenzyme (warfarin, sildenafil, oral



contraceptives, statins and cyclosporine A). The main metabolic pathway of ambrisentan is hepatic glucuronidation and to a lesser extent hydroxylation. It has little effect on the activity of cytochrome P-450. There are studies which prove that co-administration of ambrisentan and warfarin does not require correction the dose of the oral anticoagulants. Drug–drug interactions in co-administration of ambrisentan and sildenafil have also not been observed [78,79].

NO is a potent vasodilator and an inhibitor of platelet activation and vascular smooth muscle proliferation. The enzymes PDE degrade cGMP, which mediates the effect of NO. The isoform 5 of PDE is present in large amounts in the lung [17] and numerous studies have been performed to investigate the role of PDE-5 inhibitors in PAH [80]. Sildenafil is a specific inhibitor of the PDE-5 isoform. It has been utilized previously for treatment of erectile dysfunction. The SUPER-1 (Sildenafil Use in Pulmonary Arterial Hypertension) study was a randomized, double-blind, placebo controlled trial, that assigned 278 patients with PAH (either idiopathic and PAH associated with CTD) to placebo or sildenafil (20, 40, or 80 mg) orally 3 times daily for 12 weeks [81]. All sildenafil doses reduced the mean PAP and improved functional class. The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil versus placebo. Long-term data (available only at a dose of 80 mg 3 times daily) in 222 patients completing 1 year of treatment with sildenafil monotherapy showed sustained improvement from baseline at 1 year in the 6 minute walk test. The FDA approved dose of sildenafil for patients with PAH is 20 mg administered orally 3 times daily. The most common side effects, that are observed are headache, flushing, dyspepsia, and epistaxis. Whether or not higher doses might confer additional hemodynamic benefit is still a matter of discussion, but such doses continue to be “off-label” [82]. It causes vasodilation for less than 60 min after intake. In addition, Sildenafil (50 mg 3 or 4 times daily) has led to improved blood flow in patients with severe secondary RP in SSc [83–85].

Tadalafil is a new specific inhibitor of PDE-5 - with a longer half-life – 17.5 h versus 3.8 h for sildenafil, which produces maximum effect 75–90 min after intake. Similar to sildenafil, tadalafil is approved by the FDA for treatment of erectile dysfunction. Its effect in patients with PAH is under investigation [86].

Vardenafil is another new PDE-5 inhibitor, which has been approved for the treatment of erectile dysfunction. Its maximum vasodilative effect is induced after 40–45 min. Ghofrani et al. have performed a study with 60 patients with PAH and compared the hemodynamic and oxygenation responses to three PDE-5 inhibitors – sildenafil (50 mg daily dose), tadalafil (20, 40 and 60 mg daily dose) and vardenafil (10 and 20 mg daily dose). All three PDE-5 inhibitors caused a significant pulmonary vasorelaxation. Only sildenafil and tadalafil, but not vardenafil, caused also a significant reduction in the pulmonary to systemic vascular resistance ratio. Significant improvement in arterial oxygenation (equally to NO inhalation) was only noted with sildenafil. The authors concluded that the three PDE-5 inhibitors differ markedly in their kinetics of pulmonary vasorelaxation. Therefore, each new PDE-5 inhibitor needs careful evaluation for effectiveness in PAH [87].

Possible synergistic effects of the drugs available for PAH each targeting separate pathways of the pathogenesis of the disease provide a rationale for *combination therapy*. Several multicenter trials investigate the efficacy of various combinations of oral drugs as well as oral in combination with inhaled and intravenous drugs. The PACES trial demonstrated, that combination therapy of sildenafil (3 × 80 mg) with intravenous epoprostenol improves exercise capacity, time to clinical worsening, quality of life and hemodynamics in PAH patients. However, the efficacy of this combination in SSc-related PAH remains to be determined. A poorer response to combination of oral therapies has been observed in SSc-related PAH as compared with idiopathic PAH. Combination of sildenafil and bosentan improved 6-min walk distance and functional class in idiopathic PAH, while patients with

PAH in SSc did not experience significant improvement although clinical deterioration have been slowed [58].

Of the available *surgical options*, *atrial septostomy* creates a right to left inter-atrial shunt, decreasing right heart loading pressures and improving right heart function and left heart load in patients with worsened right heart function in severe PAH. The created shunt decreases systemic arterial oxygen saturation, and it is anticipated that the improved cardiac output will result in overall augmentation of systemic oxygen delivery. *Single and double lung transplantation and combined heart and lung transplantation* are ultimate therapeutic options in patients with end-stage disease [1].

The pathologically aberrant proliferation of endothelial and smooth muscle cells in PAH stimulated by the increased level of growth factors have drawn an analogy between PAH and a neoplastic process. As a result, antineoplastic drugs with anti-tyrosine kinase activity have been tested in experimental models and have been already reported in some occasional patient case reports. Two strategies are currently tested for treatment of PAH: disruption of PDGF- and of VEGF-signaling pathways. Imatinib is a small molecule tyrosine kinase inhibitor that binds competitively to the ATP-binding pocket of abelson-kinase (c-Abl) and thereby blocks efficiently its tyrosine kinase activity, which requires transition of ATP into ADP and phosphorylation of target proteins. C-Abl is an important downstream signaling molecule of TGF- $\beta$  and PDGF. In addition to its effect on c-Abl, imatinib mesylate interferes also with PDGF signalling by blocking the tyrosine kinase activity of PDGF receptors. Thus, imatinib targets simultaneously and selectively two major pro-fibrotic pathways activated in SSc [49,88]. Based on the evidence that PDGF signaling is an important process in the pathophysiology of PAH, imatinib has been tested and shown to be effective in experimental models of PAH. A Phase II multicenter trial, to evaluate the safety, tolerability and efficacy of this drug in patients with PAH, has been completed in the USA and Europe and the results are subject to publication [49,89]. The other target for tyrosine-kinase inhibition in SSc is VEGF receptor. Src-kinase mediates VEGF-induced angiogenesis. The uncontrolled overexpression of VEGF has deleterious rather than beneficial effects on angiogenesis that might further aggravate the vascular disease in SSc. This might suggest beneficial effects of inhibition of VEGF signalling in patients with SSc by novel tyrosine kinase inhibitors - such as semaxinib, vatalanib, and sorafenib. Imatinib and sorafenib are FDA-approved for other conditions (gastrointestinal malignancies, renal and hepatocellular carcinomas). It is suggested, that complete inhibition of VEGF signalling by tyrosine kinase inhibitors in patients with SSc might have more deleterious effects than over-stimulation of the VEGF. Thus, application of VEGF receptor tyrosine kinase inhibitors could even worsen vasculopathy in patients with SSc and could prevent angiogenesis, which is desperately needed for wound healing in SSc patients with ulcers. These drugs require careful evaluation in experimental models of SSc prior to clinical application [90]. Whether these new antineoplastic drugs with anti-tyrosine kinase activity will have a role in SSc and in idiopathic PAH remains to be determined [49].

*Inhibition of matrix metalloproteinases*, e.g. with the synthetic inhibitor *batimastat* effectively prevents the development of PAH and may be a potential future therapy [42,55]. It has been suggested, that statins may also influence pulmonary vasculature. For simvastatin a suppression of ET-1 induced matrix-metalloproteinase release through RhoA/ROCK (Rho-associated kinase) pathway has been demonstrated with subsequent influence of vascular remodeling [91]. Wang et al. (2007) performed an experiment with transplantation of *endothelial progenitor cells* in 15 patients with idiopathic PAH without autoimmune disorder. They found a significant improvement of the 6-min walk distance after 12 weeks of follow-up as compared with PAH patients, who received conventional therapy. Improved values for mean PAP, pulmonary vascular resistance and cardiac output have been detected in the absence of significant side effects [92].

Short-term *inhalation of NO* has substantial pulmonary specific vasodilator effects in humans [48]. Inhaled NO possesses pulmonary selectivity, but it is less potent than prostacyclin in the pulmonary

vasculature [69]. Long term inhaled NO therapy has also shown a benefit in small series and case reports, but it is unlikely to be given to a large number of patients as it is considered that its interruption can cause homodynamic deterioration [48]. Anecdotal reports suggest that treatment with *L-arginine*, the substrate of NO synthase, reduces PAP and increases exercise tolerance in patients with PAH. The administration of *VIP* in single patients with primary PAH have shown significant functional and hemodynamic improvement [48]. *Selective serotonin-reuptake inhibitors*, such as fluoxetine, may provide protection against PAH and their potential role in the therapeutic strategy of PAH remains to be determined [43,48].

## 9. Prognosis

SSc associated PAH historically had poor prognosis with a 1-year survival rate of 45% [4,93]. All three groups of advanced therapies – prostanoids, ERA, and PDE-5 inhibitors, used in idiopathic PAH, have been shown to improve pulmonary hemodynamics and functional status in patients with PAH in the context of CTD. Recent studies have concluded that survival in patients with SSc associated PAH is better in the modern treatment era than in historical cohorts. A recent 6-year follow up (2001–2006) of 315 patients with SSc-related PAH, who have been documented in the UK National registry has revealed 1-, 2- and 3-year survival rates of 78, 58 and 47%, respectively. Although the survival of SSc-related PAH has improved as compared with historical data, it still remains unacceptably poor and worse than in PAH associated with SLE (3-year survival rate – 75%) and with other forms of PAH [4,83,94]. This persisting medical problem requires continuous special attention for initial symptoms of PAH in SSc patients not only by the rheumatologists, but also at other levels of medical care. Screening with new laboratory markers, pulmonary functional testing, Doppler echocardiography and in cases of clinical symptoms invasive assessment have to be routinely used in the centers that offer rheumatologic care. Here, EUSTAR/EULAR activities and future clinical trial projects will facilitate improvements for the affected patients all over the world [95], as well as follow up the effect of the new drugs that are currently in the experimental phase in SSc-related PAH.

### Take-home messages

- Pulmonary arterial hypertension is a frequent complication in systemic sclerosis
- Pulmonary arterial hypertension in systemic sclerosis differs in various aspects from pulmonary hypertension in other diseases
- Pathophysiology of pulmonary arterial hypertension in systemic sclerosis is based on hypoxia, vascular alterations, fibrosis and aberrations of the immune system
- The diagnostic access to pulmonary arterial hypertension in systemic sclerosis includes a complex rheumatologic and cardiopulmonary set of diagnostic procedures
- Treatment of pulmonary arterial hypertension in systemic sclerosis includes predominantly vasodilative strategies aimed to improve oxygenation and overall clinical status, inhibit lung fibrosis and secondary cardiovascular failure

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