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Potential role of exercise echocardiography and right heart catheterization in the detection of early pulmonary vascular disease in patients with systemic sclerosis

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Abstract

Pulmonary vascular disease represents one of the most frequent complications in systemic sclerosis leading to increased mortality. The recognition and appropriate clinical management of early pulmonary vascular disease could significantly improve the prognosis of affected patients. Early pulmonary vascular disease is characterized by the histological signs of pulmonary vascular remodeling, mildly increased mean pulmonary arterial pressure (21–24 mmHg) at rest, abnormal pulmonary hemodynamics during exercise, decreased exercise capacity, and a high risk for development of pulmonary arterial hypertension. Pulmonary hemodynamics can be investigated during exercise by echocardiography or by right heart catheterization both representing important clinical tools for the screening and confirmation of early pulmonary vascular disease. Further studies are needed to better understand the clinical course of systemic sclerosis patients with early pulmonary vascular disease and to define the characteristics of patients that will or will not profit from pulmonary arterial hypertension treatment.

Keywords

Pulmonary vascular disease, exercise, systemic sclerosis, detection, echocardiography, right heart catheterization

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Pulmonary complications currently represent the major cause of death in patients with systemic sclerosis (SSc) and involve most frequently either the lung parenchyma in form of an interstitial lung disease, the pulmonary vessels leading to pulmonary arterial hypertension (PAH)[1], or both. The estimated incidence of PAH among patients with SSc lies between 0.61 and 2.0 cases per 100 patient years.[2–7] Unfortunately, PAH is typically recognized in a late stage, when patients already present with severe symptoms, hemodynamic deterioration, and poor prognosis.[8] Early recognition and therapy of PAH associated to SSc has been aimed for in recent screening programs resulting in an increased awareness in the community and the promise of improved prognosis of patients.[9] An even further step would be the recognition of a population among SSc patients with early pulmonary vascular disease (PVD), who do not yet fulfill the strict hemodynamic criteria of PAH in order to prevent them from developing the disease in the future. The assessment of demographics, certain laboratory parameters (e.g. N-terminal pro brain natriuretic peptide), lung diffusion capacity, and pulmonary hemodynamics may help to identify patients at increased risk for the development of PVD.[10,11]

How to define early PVD?

PAH is hemodynamically defined as mean pulmonary arterial pressure (mean PAP) $\geq$ 25 mmHg with a pulmonary arterial wedge pressure (PAWP) $\leq$ 15 mmHg and a pulmonary vascular resistance (PVR) $>$ 3 Wood Units as assessed

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by right heart catheter (RHC) at rest.[12] However, under physiologic conditions, mean PAP is only 14.0 ± 3.3 mmHg and the upper limit of normal is 20 mmHg.[13] A mild elevation of mean PAP above 20 mmHg may represent early PVD. A recent study showed that the elevation of mean PAP into the range between 20 and 25 mmHg—independent of age and comorbidities—is associated with increased mortality.[14] In the context of SSc, these considerations are supported by case reports describing extensive remodeling of the pulmonary arteries in SSc patients with a baseline mean PAP in the range of 20–25 mmHg[15] and follow-up data from the DETECT study showing the frequent development of pulmonary hypertension (PH) in this population.[16] The possible clinical relevance of mildly elevated mean PAP has been recognized at the 6th World Symposium on Pulmonary Hypertension in Nice, 2018, and the mean PAP threshold in the definition for PH has been lowered from 25 to 21 mmHg. The proceedings of the symposium suggested to define precapillary PH as mean PAP > 20 mmHg, PAWP ⩽ 15 mmHg, and a PVR > 3 Wood Units.[17]

In the context of comorbidities, left heart diseases should be emphasized which may often explain a mild PAP increase. In these cases, however, we expect PVR values below 3 Wood Units.

According to an alternative concept, pathologic pulmonary hemodynamics during exercise may define patients with early PVD and at risk for the development of PAH. This is based on the assumption that early signs of pulmonary vascular remodeling may be unmasked by an excessive increase of PAP during exercise. Historically, mean PAP values above 30 mmHg during exercise were considered as pathologic[18,19] (exercise PH). Due to the fact, however, that mean PAP increase during exercise is dependent on pulmonary blood flow, in recent years, the mean PAP/cardiac output relationship has been increasingly used to distinguish between a physiologic and pathologic response of pulmonary hemodynamics to exercise.[20] A recent study assessed pulmonary hemodynamics during exercise in patients with early PVD (defined as patients without PH who either developed PAH later or had chronic pulmonary thromboembolic disease) or left heart disease and compared them with healthy controls.[21] The investigators found that patients with early PVD and left heart disease surpassed both mean PAP values > 30 mmHg and a total pulmonary resistance (TPR) > 3 Wood Units during maximal exercise, whereas this was not the case in healthy subjects. As TPR is calculated as mean PAP/cardiac output, both criteria are only fulfilled, if high PAP values are reached at relatively low cardiac output and therefore at low exercise levels. An expert statement of the European Respiratory Society adopted these criteria for the suggested definition of exercise PH.[22] A subsequent small pilot study showed that those SSc patients who fulfill the suggested criteria of exercise PH have significantly worse survival as compared to SSc patients with normal pulmonary hemodynamics during exercise.[23] In fact, SSc patients with exercise PH had similar survival as those with manifest PAH. In addition, some studies confirmed that an excessive increase in PAP during exercise is associated with decreased exercise capacity[24] and may be a risk factor for the development of PH in SSc.[4,25] Interestingly, the assessment of exercise hemodynamics also increased the sensitivity for recognizing the presence of increased resting mean PAP values in SSc patients.[26,27] The main features of early PVD in patients with SSc are summarized in Table 1.

Table 1. Features of early pulmonary vascular disease in systemic sclerosis.

Significant pulmonary vascular remodeling in the lung tissue
Mildly increased mean pulmonary arterial pressure (21–24 mmHg) at rest
Abnormal pulmonary hemodynamics during exercise
Decreased exercise capacity
High risk for development of pulmonary arterial hypertension
Increased mortality

The question, if patients with mildly elevated mean PAP at rest also have abnormal pulmonary hemodynamics during exercise, has been investigated as well. In fact, 86% of patients with resting mean PAP values between 20 and 25 mmHg also fulfilled the above suggested criteria of exercise PH.[28] One important caveat is, however, that not only patients with early PVD may present with such hemodynamic characteristics at rest and during exercise. Patients with mild left heart disease may have slightly elevated PAWP at rest and strongly elevated PAWP during exercise, which may lead to an increase of mean PAP above 20 mmHg at rest and above 30 mmHg at low exercise levels. Besides the assessment of exercise hemodynamics, fluid challenge has been suggested as alternative method to unmask mild left heart disease. Patients with chronic airway diseases may also present with mildly elevated resting mean PAP[29,30] and develop dynamic hyperinflation during exercise, leading to an increase of all intrathoracic pressures and fulfilling the criteria of exercise PH. This implies that a mild elevation of resting mean PAP and the proposed definition of exercise PH may be suitable for differentiating between normal and abnormal pulmonary hemodynamics, but are not specific for early PVD.[31–33]

In addition, the mean PAP response to exercise is significantly dependent on age, even elderly subjects without clinical and echocardiographic signs of left heart disease having higher PAP values at given levels of cardiac output during exercise than younger ones.[34] The main reason for that is probably an increased filling resistance of the left ventricle at rest and particularly during exercise, which may be part of a physiologic aging process. As a consequence, the consideration of age and comorbidities makes the interpretation of exercise data highly complex.

Clinical assessment of early PVD

Echocardiography and RHC are the most frequently used methods to assess pulmonary hemodynamics. Both of them may be used for resting and exercise measurements, and both may play a role in the recognition of patients with early PVD. If exercise is performed, some methodical issues must be kept in mind. Independent of the modality, how changes in pulmonary hemodynamics during exercise are assessed, incremental exercise tests (step or ramp protocol) with repeated hemodynamic measurements may provide most valuable clinical information on the pulmonary circulation. In clinical practice, cycle ergometry and treadmill are the most widely used exercise methods. In contrast, isometric exercise has little or no effect on cardiac output, and may considerably change pleural pressure and systemic vascular pressure and resistance. Therefore, it is not suitable to challenge the pulmonary circulation. The risk/benefit ratio of the assessment of pulmonary hemodynamics during exercise is unfavorable in patients without thorough resting hemodynamic examinations, patients with unstable disease, or patients with decompensated right heart failure.[22]

Besides the recognition of early PVD, the assessment of pulmonary hemodynamics at rest and especially during exercise may contribute to the assessment of right ventricular function. In patients with severe PAH, a diminished increase of PAP during exercise suggests a reduced contractile reserve of the heart and is an independent marker of a poor prognosis.[35] Some hemodynamic variables assessed during exercise (e.g. cardiac index) outperformed the prognostic relevance of resting hemodynamics.[36,37]

Right heart catheterization at rest and during exercise

RHC is the gold standard to assess pulmonary hemodynamics. It must be performed in order to correctly diagnose and classify PH.[12] There are important advantages of RHC in the assessment of early PVD as compared to echocardiography or any other method. First, RHC allows the accurate and precise measurement of mean PAP, PAWP, and cardiac output, as well as the exact calculation of PVR and TPR. This makes the recognition of mildly elevated mean PAP values and exercise PH possible. Second, the specific pattern of hemodynamic changes is suggestive, of airway diseases, left heart dysfunction, early PVD, or a combination of these. The major drawback of RHC lies in its invasive nature, although in experienced centers the rate of complications is very low.[38]

In addition, there are some important methodical details for RHC that must be considered. First, the zero reference line must be chosen appropriately. This is usually not difficult in the supine position—in this case actual guidelines recommend the choice of the mid-thoracic line.[12,39] However, exercise studies are frequently performed in the semi-supine or upright position. In this case the determination of a zero reference point is suggested from the cross section of three planes: the frontal plane at the mid-thoracic level, the transverse plane at the level of the fourth anterior intercostal space, and the midsagittal plane.[40] A second important methodical detail is the consideration of respiratory swings. Normally, these cause no relevant hemodynamic changes at rest. During exercise, however, increased changes of intrathoracic pressure during the respiratory cycle lead to large variations of PAP and PAWP. In order to avoid over- or under-estimation of these values, it is suggested that pressures are averaged over several respiratory cycles. In addition, if we wish to compare exercise hemodynamics with resting parameters, it is advisable to perform measurements using the same standards both at rest and during exercise.[22,40] Third, the adequate determination of cardiac output is highly relevant. Gold standard is the direct Fick method, which necessitates the measurement of the oxygen saturation in the systemic and in the pulmonary arteries and the assessment of oxygen uptake. This is possible, with an indwelling RHC when cardio pulmonary exercise testing is performed. An acceptable alternative for the determination of cardiac output is thermodilution. Not recommended is the indirect Fick method which only uses estimated oxygen uptake values, leading to potential errors.[22]

Echocardiography and exercise (stress) echocardiography

Echocardiography is currently the most important noninvasive method in the diagnostics of PH. It is widely available and allows the estimation of PAP, cardiac output, and with some limitations also PAWP. The investigation may also be performed during exercise.[10,41] Although echocardiography and exercise echocardiography provide accurate estimates of the systolic pulmonary arterial pressure (no relevant bias at Bland–Altman analysis when compared with invasive measurements), they suffer from relatively low precision (wide limits of agreement at Bland–Altman analysis), which limits the value of these investigations for clinical decision-making in individual patients.[22,42] If we consider that the currently suggested hemodynamic criteria for exercise PH necessitate the determination of both mean PAP and cardiac output during maximal exercise, the combination of two estimated parameters may lead to even more inaccuracies. Therefore, exercise echocardiography is mainly considered as screening tool for early PVD in patients with increased risk for PAH (such as patients with SSc), but for the final assessment of early PVD, the hemodynamic results need to be confirmed by means of RHC.

From the methodological point of view, it must be considered that pulmonary hemodynamics change very quickly after exercise cessation. That is why it is of utmost importance that all echocardiographic hemodynamic measurements are performed during and not after exercise.

Table 2. Main advantages and limitations of right heart catheterization and echocardiography for the assessment of resting and exercise hemodynamics.

	Exercise right heart catheter	Exercise echocardiography
Assessment of hemodynamic variables	*Measurement* of PAP, PAWP, and CO	*Estimation* of PAP, limited accuracy for PAWP, and CO
Determination of underlying pathophysiology of exercise PH	Mostly possible	Less frequently possible
Complexity of examination	High	Very high
Potential complications	Invasive examination with potential exercise-associated and catheter-associated complications	Non-invasive examination with potential exercise-associated complications

PAP: pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CO: cardiac output; PH: pulmonary hypertension.

At exercise echocardiography, patients are frequently examined in the semi-supine position, slightly tilted to the left side, allowing optimal assessment of hemodynamic variables[22]; however, investigations in other positions have also been suggested.

The main advantages and limitations of right heart catheterization and echocardiography for the assessment of resting and exercise hemodynamics are listed in Table 2.

Unanswered questions

There are still several open questions regarding pulmonary hemodynamics during exercise in SSc patients. The most important one is whether patients fulfilling the suggested definition of exercise PH have a worse prognosis as compared to those with normal hemodynamics. A study suggesting such prognostic implications[23] was mentioned earlier; currently a multicenter, prospective study is being performed in order to adequately answer this question. The results of this study may contribute to the appropriate interpretation of the clinical relevance of pulmonary hemodynamics during exercise in future PH guidelines.

The insufficient precision of exercise echocardiography opens the field for further non-invasive tools to diagnose early PVD and the question arises which of them may be clinically most effective. Cardiac magnetic resonance imaging (MRI) may be a method which allows not only the assessment of right ventricular function but—with specific software—also the measurement of resting mean PAP.[43,44] Preliminary studies suggest that the method might effectively recognize patients even with mild mean PAP increase.[44] Recently also exercise cardiac MRI has been established.[45] Future studies may define the optimal role of this method in the diagnosis of early PVD.

Finally and most importantly, we need to answer the question, what is the appropriate treatment for SSc patients with early PVD. Small pilot studies suggested that PAH therapy may be safe and potentially effective[46–48]; however, current guidelines do not recommend such treatment. Currently, close clinical follow-up, regular hemodynamic re-evaluations, and optimized treatment of comorbidities are recommended. Multicenter, prospective randomized controlled trials are warranted to address the question if SSc patients with early PVD profit from PAH therapy.

Summary

In summary, early PVD represents a highly relevant clinical condition in patients with SSc. Exercise echocardiography and right heart catheterization will likely play an important role in the detection of this condition. Further studies are needed to better understand the clinical course of SSc patients with early PVD and to define the characteristics of patients that will or will not profit from PAH treatment.

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