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Spruijt, O.A.

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CHAPTER 11

Summary and Future Perspective

OA Spruijt¹

¹Department of Pulmonary Medicine, VU University Medical Center, Amsterdam

Summary

Pulmonary arterial hypertension is characterized by remodeling of the small pulmonary arteries leading to an increase in resistance of the pulmonary vascular bed and an increase in pulmonary artery pressures. The vascular remodeling comprises several features. The lumen of the vessels is narrowed because of vasoconstriction, hyperproliferation of smooth muscle cells and endothelial cells, inflammation and several other aspects. The increase in resistance increases the load on the right ventricle.

Initially, the right ventricle will try to adapt to the increase in pressures and subsequent rise in wall stress through a complex interplay of ventricular remodeling, neuro-hormonal activation and changes in myocardial metabolism. Simplified, the first step in the process of remodeling is right ventricular hypertrophy and an increase in contractility. If, despite these adaptive changes, cardiac output cannot be maintained, the right ventricle will dilate further increasing wall stress. Finally, right ventricular failure will occur, which is the main cause of death in pulmonary arterial hypertension. In this thesis, a number of techniques and methods were evaluated that may contribute to earlier recognition of PAH and improved monitoring and prognostication.

Early recognition and prognostication in pulmonary hypertension

Due to the non-specific nature of symptoms at presentation, most patients with pulmonary arterial hypertension are diagnosed by the time their disease is in an advanced stage. It has been shown that early detection of PH and a timely initiation of treatment can significantly improve the clinical outcome. Computed tomography pulmonary angiography (CTPA) is a diagnostic tool often used in the diagnostic process of patients that present with unexplained dyspnea, for example to exclude pulmonary emboli. Such scans can already reveal clues for the presence of pulmonary hypertension. A well-known clue for the presence of pulmonary hypertension is an increased ratio between the diameter of the pulmonary artery and the diameter of the ascending aorta. In **chapter 2**, we investigated whether the predictive value of CTPA for the presence of pulmonary hypertension could be improved by combining this measurement with the diameter ratio of the right ventricle and left ventricle. We found that the predictive value of CTPA for precapillary pulmonary hypertension improved when ventricular and pulmonary artery measurements were combined.

The prognostic value of right ventricular parameters in pulmonary hypertension is well-established. Whether a combination of parameters of the right heart merged into a risk score predict outcome in

precapillary pulmonary hypertension was investigated in **chapter 3**. We found a good prognostic value of a simple right heart score and this score showed a good correlation with more established complex risk scores (REVEAL score and NIH score).

Treatment response in pulmonary hypertension

Since the prognosis of patients with pulmonary hypertension is determined by right ventricular function, monitoring of right ventricular function is of utmost importance. In **chapter 4** we summarized available methods for measuring the right ventricular response to therapy. Cardiac magnetic resonance imaging (CMRI) is the gold standard for monitoring right ventricular function. Since CMRI scans are expensive, not widely available and analyses are time-consuming, monitoring right ventricular function using simple echocardiographic measurements would be ideal in daily practice. Therefore, in **chapter 5**, we investigated the usage of simple echocardiographic parameters for the serial assessment of right ventricular function by comparing four different echo-derived parameters with CMRI-derived right ventricular ejection fraction. The strongest relationship was found between CMRI-derived right ventricular ejection fraction and echo-derived right ventricular fractional area change. However, the sensitivity of echocardiography to predict a deterioration in CMRI-derived right ventricular ejection fraction was poor for all four echo-derived parameters (ranging from 33-56%). Echo-derived parameters of right ventricular systolic function, in particular right ventricular area change, can reasonably distinguish between a decreased or preserved CMRI-derived right ventricular ejection fraction. However, echo-derived parameters are not suitable for the serial assessment of right ventricular systolic function.

Patients with idiopathic pulmonary arterial hypertension and a reduced diffusion capacity of the lung for carbon monoxide (DLCO) have a worse survival compared to idiopathic pulmonary arterial hypertension patients with a preserved DLCO. Whether this poor survival can be explained by unresponsiveness to pulmonary hypertension specific vasodilatory therapy is unknown. Therefore, in **chapter 6** we investigated the hemodynamic and cardiac response to PH specific vasodilatory therapy in patients with IPAH and a reduced DLCO. Baseline hemodynamics and cardiac function were not different in the two groups and hemodynamics and cardiac function improved in both groups after PH specific vasodilatory therapy without a worsening of oxygenation at rest or during exercise. Therefore, we concluded that patients with idiopathic pulmonary arterial hypertension and a severely reduced DLCO show a similar response to pulmonary hypertension - specific vasodilatory

therapy in terms of hemodynamics, cardiac function and exercise capacity as patients with idiopathic pulmonary arterial hypertension and a preserved DLCO.

Emerging modalities in pulmonary hypertension

Chapter 7 summarizes emerging imaging techniques in the setting of pulmonary hypertension. A well-known technique to characterize the myocardium with CMRI is the assessment of late gadolinium enhancement.

Currently, there is no possibility to clinically assess the primary disease process in the pulmonary arteries of patients with pulmonary arterial hypertension. Therefore, in **chapter 8**, we investigated whether 3'-[18F]fluoro-3'-deoxythymidine ([18F]-FLT) positron emission tomography (PET/CT) could be used to quantitatively assess proliferation in the pulmonary vasculature of patients with idiopathic pulmonary arterial hypertension. Subsequently, we assessed whether [18F]-FLT could track the pulmonary vascular remodeling in a monocrotaline ratmodel (animal model of pulmonary hypertension) and the reverse remodeling after treating the animals with targeted therapies. We found that the uptake of [18F]-FLT in the lungs of patients with idiopathic pulmonary arterial hypertension was significantly increased compared to control subjects and was related to markers of disease severity. The uptake of [18F]-FLT was heterogeneous among IPAH patients. Furthermore, [18F]-FLT was able to track the pulmonary vascular remodeling in the monocrotaline ratmodel and the reverse remodeling after treating the animals with dichloroacetate and imatinib. Our results suggest that [18F]-FLT PET/CT can be developed as a tool to select IPAH patients with a hyperproliferative state that may benefit from anti-proliferative therapy. In addition, [18F]-FLT PET/CT might be used to assess treatment response.

An emerging technique to characterize the myocardium by CMRI is native T1-mapping. To quantify native T1-values, there is no need for a reference area of myocardium, making it possible to directly quantify the total myocardium. Furthermore, native T1-mapping has the advantage of not requiring the usage of contrast agents. In **chapter 9** we investigated this technique in precapillary pulmonary hypertension patients. Native T1-values were increased at the interventricular insertion regions compared to the RV free wall, LV free wall and interventricular septum. Native T1-values at the interventricular insertion regions were significantly related to markers of disease severity. No differences in native T1-values were found between patients with idiopathic pulmonary arterial hypertension, systemic sclerosis related pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Our results suggest that native T1-mapping can be

developed as an alternative technique for the characterization of the interventricular insertion regions with the advantage of not requiring the use of contrast agents.

Patients with pulmonary hypertension have a decreased exercise tolerance. This exercise intolerance is mainly determined by circulatory limitations. Whether this exercise intolerance coincided with an inability to increase right ventricular contractility was investigated in **chapter 10** using an invasive cardiopulmonary exercise test. We prospectively included patients with precapillary PH and control subjects. The rest-to-exercise change in load-independent measures of right ventricular contractility, the contractile reserve, as well as the rest-to-exercise change in the coupling between the right ventricle and its load (right ventricular arterial coupling) were assessed using single beat pressure-volume loop analysis. We found that, in contrast to controls, pulmonary hypertension patients have no contractile reserve. Failure to compensate for the rest-to-exercise increase in load on the right ventricle led to a deterioration in right ventricular arterial coupling during exercise. Furthermore, we found that the contractile reserve was not related to a recently proposed surrogate, the rest-to-exercise change in pulmonary artery pressure.

Future perspectives

Non-invasive quantification of pulmonary vascular remodeling

In chapter 2 we investigated the usage of 3'-[18F]fluoro-3'-deoxythymidine ([18F]-FLT) positron emission tomography (PET/CT) for quantitative assessment of proliferation in the pulmonary vasculature of patients with idiopathic pulmonary arterial hypertension (IPAH). In this study we found an increased uptake of [18F]-FLT in the lungs of patients with IPAH compared to control subjects. Furthermore, [18F]-FLT was able to track the pulmonary vascular remodeling in a monocrotaline ratmodel and the reverse remodeling after treating the animals with targeted therapies.

An important next study would be a test-retest study to assess repeatability of the uptake of [18F]-FLT in IPAH patients. Good repeatability is essential to be able to use [18F]-FLT PET/CT in the future to select patients with a hyperproliferative state that may benefit from anti-proliferative agents and to assess treatment responses. Current pulmonary hypertension therapies mainly have vasodilatory effects and thus may not influence proliferation rate. Therefore, application of [18F]-FLT should be assessed with future anti-proliferative compounds that directly target the pulmonary vascular remodeling.

In addition to the further development of [18F]-FLT, alternative tracers to quantify pulmonary vascular remodeling should be investigated. The increased expression of growth factor receptors may be reflected by enhanced uptake of radio-labeled tyrosine kinase inhibitors. It has been shown that there is an increased expression of the epidermal growth factor receptor (EGF-R) in the intima and media of pulmonary arteries of patients with pulmonary arterial hypertension [1]. In a pilot study we tested the tracer [11C]-Erlotinib (unpublished data), which binds to the EGF-R. We found that the uptake of [11C]-Erlotinib was not increased in patients with idiopathic pulmonary arterial hypertension compared to control subjects.

Other growth factors are upregulated as well in pulmonary arterial hypertension (platelet derived growth factor receptor (PDGF-R), vascular endothelial growth factor receptor (VEGF-R) and fibroblast growth factor receptor (FGF-R)) [2] and can potentially be used to quantify the pulmonary vascular remodeling using PET/CT. Nintedanib is a tyrosine kinase inhibitor targeting the PDGF-R, VEGF-R and FGF-R. Moreover, in preclinical studies Nintedanib showed potential to reverse pulmonary vascular remodeling [3]. Therefore, development of a Nintedanib tracer would be of interest to quantify pulmonary vascular remodeling in patients with pulmonary hypertension.

Characterization of myocardium using native T1-mapping

As described in chapter 7, native-T1 values of the right ventricular free wall could only be accurately assessed in small parts of the myocardium [4]. Presence of pericardial fat at the border of the frequently irregularly shaped right ventricular free wall can make it difficult to quantify native T1-values of the total right ventricular free wall. A voxel at the border of the right ventricular free wall can contain a partial volume of pericardial fat. Due to the fact that fat has a high signal intensity and very short T1-value, such a partial volume effect can already dominate the T1-value of the total voxel. This phenomenon can bias the quantification of native T1-values of the right ventricular free wall. By inserting a fat saturation pulse in the T1 mapping pulse sequence the effects of fat can be eliminated [5]. Future studies should test whether insertion of the fat saturation pulse can improve the quantification of the right ventricular free wall using T1-mapping.

Effect of exercise training on the right ventricle in patients with pulmonary hypertension

Several studies showed that exercise training programs can improve exercise capacity and quality of life in patients with pulmonary hypertension [6-11]. The mechanisms for the improvement in exercise capacity are yet incompletely understood. It has been shown that exercise training programs can increase capillarization of muscles [9] and can improve hemodynamics at rest and during exercise [6].

Handoko et al. evaluated the effects of exercise training on right ventricular function in a pulmonary hypertension rat model and showed that TAPSE decreased in rats with progressive pulmonary hypertension while an increased TAPSE was seen in rats with stable pulmonary hypertension [12]. In the same study exercise training did not affect right ventricular contractility at rest.

Currently, studies on the effects of exercise training on the right ventricle in patients with pulmonary hypertension are lacking. Randomized controlled trials are needed that investigate the effects of exercise training on the function of the right ventricle, not only at rest but also on the right ventricular contractile reserve. Ideally, assessment of right ventricular contractile reserve in such studies should combine pressure-volume loop analysis to assess the effects of exercise training on the load-independent contractile reserve (Chapter 10) and cardiac magnetic resonance imaging to assess the effects on the load-dependent contractile reserve [13-18], both measured during maximal incremental exercise protocols.

Contractile reserve of patients with scleroderma related pulmonary hypertension and patients with scleroderma and borderline pulmonary hypertension

In chapter 10 we compared the contractile reserve between control subjects and precapillary pulmonary hypertension patients. Whether differences exist between different precapillary pulmonary hypertension subtypes is unknown. In systemic scleroderma related pulmonary hypertension right ventricular contractility and right ventricular – arterial coupling at rest are more severely compromised compared to idiopathic pulmonary hypertension patients [19, 20]. Whether or not differences are even more pronounced during exercise is unknown. As such, it would be interesting to study the contractile reserve in systemic scleroderma patients with borderline pulmonary hypertension.

Effectiveness of inotropic drugs in patients with pulmonary hypertension

Contractility can increase due to β -adrenergic stimulation. Inotropic drugs increase catecholamine release which binds to β -adrenergic receptors subsequently activating sarcomeres, the contractile elements of cardiomyocytes.

The European pulmonary hypertension guideline recommends to treat patients with pulmonary arterial hypertension admitted to the hospital because of right ventricular failure with inotropes, with a preference for dobutamine [21]. However, this recommendation is mostly based on expert opinions rather than clear scientific evidence [22-24].

In the right ventricle of patients with pulmonary hypertension there is a downregulation and desensitization of β -adrenergic receptors [25, 26] and patients with pulmonary hypertension have an impaired exertional contractile reserve [13, 14, 16, 18]. Therefore, it can be questioned whether patients with pulmonary hypertension benefit from inotropic drugs. Decreased contractile reserve measured by TAPSE upon dobutamine infusion has been shown in patients with pulmonary hypertension compared to control subjects [27] as well as in a pulmonary hypertension piglet model [28].

Acosta et al. studied the effects of dobutamine in patients with liver cirrhosis and pulmonary hypertension and showed that load-independent right ventricular contractility could increase upon administration of dobutamine [29]. However, pulmonary hypertension in these patients was relatively mild and therefore we do not know whether these results can be extrapolated to pulmonary hypertension patients with more severely compromised hemodynamics.

Whether or not patients with pulmonary arterial hypertension admitted to the hospital because of right ventricular failure benefit from inotropic drugs is still unclear. Therefore, there is an urgent need for studies to unravel the effects of inotropics in patients with pulmonary arterial hypertension and right ventricular failure.

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