The effects of pulmonary hypertension on cardiac function

Christiaan Tji-Joong Gan
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The effects of pulmonary hypertension on cardiac function

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'…research is like live itself: never quite clear in advance where it is going to lead, but always surprising during its evolution…'

Dr. B.S. Gan
Contents

Chapter one
Introduction, Pulmonary arterial hypertension: Insights, Classification and Treatment........ 11

Chapter two
NT-proBNP reflects right ventricular structure and function in pulmonary hypertension........ 33

Chapter three
Right ventricular diastolic dysfunction and the acute effects of sildenafil in pulmonary hypertension patients................................................................. 47

Chapter four
Impaired left ventricular filling due to right to left ventricular interaction in patients with pulmonary arterial hypertension ................................................................. 61

Chapter five
Interventricular mechanical asynchrony in pulmonary arterial hypertension:
Left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling ................................................................. 75

Chapter six
The right atrium compensates for impaired right ventricular function in pulmonary hypertension.................................................................................................................. 93

Chapter seven
Non-invasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension.................................................................................................................. 107

Chapter eight
Pathophysiology and management of right ventricular failure in chronic pulmonary hypertension.................................................................................................................. 123

Summary and future perspective................................................................. 139

Nederlandse samenvatting.................................................................................. 147

Dankwoord..................................................................................................... 155
Chapter 1

Pulmonary arterial hypertension
Insights, Classification and Treatment


Adapted from the reviews published in
The Netherlands Heart Journal 2004:12; 287-94 and 337-42
**General introduction: The heart and the circulation**

The human circulation constitutes the systemic and pulmonary vascular bed (Figure 1). These two vascular beds are coupled with the heart in series. The heart functions as a pump and consists of four chambers in series. The right atrium receives venous blood from the venae cavae and coronary artery systems. The venous blood passes to the right ventricle, which pumps the blood into the pulmonary circulation. In the lungs the blood becomes oxygenated and flows into the left atrium and the left ventricle, subsequently. The left ventricle is coupled to the systemic circulation and provides the organ tissues with the oxygenated blood. The systemic circulation is characterized by a high vascular resistance and it takes a lot of effort for the left ventricle to pump the blood in the systemic circulation. Therefore the left ventricle is regarded as a pressure pump, and has a conical shape with a thick myocardial wall. This anatomical characteristic of the left ventricle is in favour of myocardial metabolism. According to Laplace law a thick myocardium reduces myocardial stress and results in less oxygen demand. In contrast, the pulmonary circulation is a highly distensible, low resistance system and therefore less demanding for the right ventricle. The thin walled right ventricle encompasses the left ventricle. Because of the low-resistance and low-pressure system, the right ventricle is regarded as a volume pump. Under the circumstances where functional and morphological alterations of the pulmonary vessels result in increased pulmonary vascular resistance and elevated pulmonary artery pressure, the right ventricle is urged to compensate to maintain its function.

![Figure 1. Schematic presentation of the human circulation. The systemic and pulmonary vascular bed are coupled in series. The left ventricle (red) pumps the oxygenated blood into the systemic circulation. Venous blood returns to the right ventricle (blue), which pumps the blood into the pulmonary circulation.](image-url)
Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a rare and fatal disease characterised by distinct changes in the small pulmonary vessels, which lead to a rise in pulmonary vascular resistance and pulmonary artery pressure. This type of pulmonary hypertension (PH) is defined by the US National Institute of Health registry as a mean pulmonary artery pressure $\geq 25$ mmHg in rest or $\geq 30$ mmHg during exercise in the absence of another cause (1), and is named idiopathic PAH. In a French registry the estimated prevalence of PAH was 15.0 cases/ million and 5.9 cases/million adult inhabitants for idiopathic PAH. The incidence was estimated at 2.4 cases/ million adult inhabitants/year (2). The disease is progressive and leads to right heart failure and death within 2,8 years from diagnosis without treatment (3). The following overview summarizes the insights on the pathobiology, pathogenesis, and genes involved in PAH. In addition, the classification, diagnostic work-up and treatment of PAH are viewed.

Pathobiology, pathogenesis and genes

Pathobiology

PAH may occur in many diseases. The disease is characterised by obstruction of small pulmonary arteries in association with plexiform lesions, (i.e. arterial lumen occlusion, aneurismal dilatation, proliferation of interconnected vascular channels and endothelial and smooth muscle cell proliferation), medial hypertrophy, concentric laminar intima fibrosis, fibrinoid degeneration, and thrombotic lesions. Pathologic classification of patients having either plexiform or thrombotic arteriopathy seems to be arbitrary, because both are not distinct entities but rather polymorphic manifestations of a similar disease seen in different forms of PAH (4). The speculations about the pathogenic substrate for the origin of plexiform lesions have led to several theories. According to some investigators proliferation of smooth muscle cells and transformation into myofibroblast are the two mechanisms leading to formation of plexiform lesions. Other investigators proposed a theory where the beginning of phenotypic disease is induced by endothelial cells responding to cytokines, growth factors or vascular stress (5;6). In general pulmonary vascular proliferation and remodeling plays a key role in the pathogenesis of PAH, rather than vasoconstriction.

Pathogenesis

In PAH a variety of factors influences the subtle vasoactive equilibrium and smooth muscle cell proliferation.

Vasoactive factors

An imbalance of vasoactive factors, i.e. substances that result in vasodilation or vasoconstriction, may cause vasoconstriction and proliferation of smooth muscle cells. Several different studies conclude the following in accordance to vasoactive factors and PAH.

In PAH thromboxane and endothelin-1, both vasoconstrictors are increased. The latter is also a mitogen for smooth muscle cells. Prostacyclin, a vasodilator, is decreased in PAH (7). Nitric oxide (NO) produced by the endothelium and initiated by NO synthase, stimulates vasodilation and...
inhibits smooth muscle cell proliferation. The endothelium of the pulmonary arteries in PAH patients has negligible immuno-histochemical staining for NO synthase compared to healthy individuals, suggesting impediment of NO and its vasoactive effect (8).

The role of *vascular endothelial growth factor* (VEGF) in the pathogenesis of PAH remains controversial, because of contradicting study results (9).

*Angiopoietin-1* (Ang-1) a ligand of the endothelial-specific tyrosine kinase receptor Tie-2 promotes cell survival, vascular maturation, and stabilization. In the monocroteline (MCT) rat model gene transfer of Ang-1 to the pulmonary microvasculature prevents PAH development by inhibiting endothelial cell apoptosis, and down regulation of the Tie-2 receptor. These study results suggests an important role of the Ang-1/Tie-2 system in the protection of the pulmonary system (10;11).

**Serotonin signalling pathway: role of the Serotonin transporter**

Plasma concentration of serotonin, stored in platelets, is increased in PAH patients (12). In animal studies induced hypoxia-increased expression of serotonin transporters, which lead to an increased intracellular calcium concentration with resulting vasoconstriction and smooth muscle cell proliferation (13).

**Extra cellular matrix remodeling: the role of tenascin and matrix metalloproteinases**

The walls of small pulmonary vessels of patients with PAH show distinct changes with increased extra cellular matrix deposition of collagen. The increased deposition is due to an imbalance of matrix degradation and excessive production. Degradation of the extra cellular matrix, by vascular serine elastase and matrix metalloproteinase, release tenascin-C and matrix-bound mitogens, which induce smooth muscle cell proliferation (14). NO is able to reduce the serine elastase activity and thus prevents vascular remodeling (15). Rabinovitch et al have shown reversal of PH in the MCT rat model by a serine elastase inhibitor (16).

**Role of Ion channels**

Normally the voltage gated potassium channels control the electric equilibrium of the cell membrane and the intracellular calcium status. Hypoxia disturbs the equilibrium and the intracellular calcium status by inhibiting the potassium current, which is followed by depolarisation and calcium influx (17). Intracellular calcium functions as a trigger for vasoconstriction and smooth muscle cell hypertrophy. Yuan et al have shown that smooth muscle cells in PAH have a low mRNA status coding for voltage-gated potassium channels. Meaning a disturbance of the electric equilibrium of the cell membrane and an increase of the intracellular calcium concentration, leading to vasoconstriction (18).

**Coagulation (Plasminogen activator inhibitor type 1 and impaired fibrinolysy)**

Thrombosis leading to occlusion of the small pulmonary arteries is believed to have a role in PAH. Reports about pleomorphism in the plasminogen activator inhibitor type 1 with increased transcription resulting in decreased fibrinolytic activity support this hypothesis (19).

**Genes**

Studies by Deng and Lane in 2000 led to identification of the bone morphogenic protein receptor II (BMPR2) gene on chromosome 2q33, primarily associated with the idiopathic and familiar forms
of PAH. In 50% of the familial PAH and 26% of the idiopathic PAH, the heterogeneous germ line mutation on the BMPR2 gene is evident (20;21). The BMPR2 belongs to the TGFβ-receptor superfamily, which binds cytokines, bone morphogenic protein (BMP), activin, inhibin, and growth differentiation factor (22). Discovered in association with bone growth, the BMPR's bind ligands that are also important in cell proliferation and differentiation, and apoptosis. A mutation on the BMPR2 locus could lead to a decrease in bone-morphogenic-protein signalling and loss of antiproliferative and apoptotic function in the pulmonary vascular cell (23). However only 0-20% of the individuals with detectable mutations on BMPR2 have phenotypic disease (24) and of the patients with familial PAH only 60% have detectable BMPR2 mutations (25). This suggests genetic heterogeneity, i.e. the role of modifier genes, environmental triggers such HVV8 (26), and mutations in other parts of the gene or other genes that can alter function or expression of the BMPR2 gene or may lead to clinical PAH. Based on the latter it is hypothesized that individuals with BMPR2 mutations will present with phenotypic manifestations of disease if additional factors as mentioned are present (27) (Figure 2).

A mutation in another TGFβ-receptor gene, activin-receptor-like kinase 1 (ALK-1), was identified in families with hereditary haemorrhagic telangiectasia (associated with ALK-) and severe PAH (28). The latter provides evidence for genetic heterogeneity. ALK-1 mutation may lead to PAH, hereditary haemorrhagic telangiectasia or both. The observation of mutations on two different genes but with a common outcome, i.e. clinical PAH, points out the importance of TGFβ-receptors as a molecular pathway at the base of vascular remodelling.

The ‘Venice’ classification of 2003 World Health Organisation consensus meeting

Although the old classification of PAH has worn well for both clinical practice and research, i.e. drug evaluation and basic science, the World Health Organisation (WHO) conducts a consensus meeting to revise the classification of PAH every 5 years. This so-called ‘Venice Task Force on PAH’ proposed an adapted clinical classification in June 2003. The disagreement of the old classification with today’s insights on the treatment of PAH, and the evolving knowledge on the pathogenesis of PAH forms the base for a new classification.

The most distinct change in nomenclature is the abandoning of the term primary pulmonary hypertension (PPH). Although the titles and the content of some of the categories have changed, the subdivision of PH in five main categories remains unaltered.

The definition PAH covers a group of patients with identical obstructive pathological changes of the pulmonary vascular system, and benefit from long-term infusion of prostacyclin (29-31) according to the 1998 WHO classification. In this category the PPH class is replaced by the idiopathic and familiar PAH class. (Table 1, Box 1). Based on clinical interpretation and etiological insights, PAH with significant venous and/ or capillary involvement; veno-occlusive disease and pulmonary capillary haemangiomatoses, are added to the PAH category. Both diseases are regularly associated with PAH and have the same clinical presentation, though in both the clinical deterioration is much more progressive and the disease rapidly fatal.
Chapter 1

The second category, Box 2, is preserved for PH with left-sided heart disease, which requires a specific treatment of its own. Category 3; PH associated with lung disease and/or hypoxemia, and category 4; PH due to chronic thrombotic and/or embolic disease, remains unchanged. Except the Neonatal Lung Disease and Alveolar-Capillary Dysplasia classes are abandoned from the classification of PH. The fifth category is named Miscellaneous and Compression of Pulmonary Vessels from category 2, is added (32).

**Pulmonary arterial hypertension diagnostic work-up**

Similarity in clinical presentation of PH with other diseases is a cause of delayed diagnosis, but it remains the starting point of the path leading to the diagnosis (33). PH may be diagnosed as an
incidental finding. For example chest-X-ray, ECG and/or echocardiography performed for other clinical purposes may yield PH associated characteristics. As mentioned clinical presentation, history, physical examination, and a suspicion of PAH may lead to the first step in the diagnostic work-up, as follows from Figure 3.

The diagnostic work-up is emanated from the classification system. To diagnose PAH other causes of PH have to be excluded and distinguished from PAH. Pulmonary function testing and high-

Table 1. The 'Venice classification'

<table>
<thead>
<tr>
<th>Pulmonary Arterial Hypertension</th>
<th>Box 1</th>
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<tbody>
<tr>
<td>– Idiopathic/sporadic</td>
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<tr>
<td>– Familial</td>
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<tr>
<td>– Related to:</td>
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<tr>
<td>Collagen Vascular Disease (CVD)</td>
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<tr>
<td>Congenital Heart Disease (CHD)</td>
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<td>Portal Hypertension (PoH)</td>
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<tr>
<td>HIV</td>
<td></td>
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<tr>
<td>Drugs and toxins</td>
<td></td>
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<tr>
<td>Other PAH with significant venous and/or capillary involvement</td>
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<tr>
<td>– Pulmonary veno-occlusive disease</td>
<td></td>
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<tr>
<td>– Pulmonary capillary haemangiomatosis</td>
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<tr>
<td>– Persistent Pulmonary Hypertension of the New-born (PHN)</td>
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<table>
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<tr>
<th>PH with left heart disease</th>
<th>Box 2</th>
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<tbody>
<tr>
<td>– Atrial or ventricular heart disease</td>
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<tr>
<td>– Valvular heart disease</td>
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<table>
<thead>
<tr>
<th>PH with lung disease and/or hypoxemia</th>
<th>Box 3</th>
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<tr>
<td>– Chronic obstructive pulmonary disease</td>
<td></td>
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<tr>
<td>– Interstitial lung disease</td>
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<td>– Sleep disorders</td>
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<td>– Alveolar hypoventilation</td>
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<tr>
<td>– Chronic exposure to high altitude</td>
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<tr>
<td>– Developmental abnormalities</td>
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<tr>
<th>PH due to chronic thrombotic and/or embolic disease</th>
<th>Box 4</th>
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<tbody>
<tr>
<td>– Thromboembolic obstruction of proximal pulmonary arteries</td>
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<tr>
<td>– Thromboembolic obstruction of distal pulmonary arteries</td>
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<tr>
<td>– Pulmonary embolism (tumor, parasites, foreign material)</td>
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<tr>
<th>Miscellaneous</th>
<th>Box 5</th>
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<tr>
<td>– Sarcoidosis,</td>
<td></td>
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<tr>
<td>– Histiocytosis X,</td>
<td></td>
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<tr>
<td>– Lymphangiomatosis</td>
<td></td>
</tr>
<tr>
<td>– Compression of pulmonary vessels (adenopathies and tumor, fibrosing mediastinitis)</td>
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Proposal for an adapted clinical classification, The 'Venice' classification

(see text, The 'Venice' classification of 2003 World Health Organisation consensus meeting) On the basis of novel insights into pathobiology and pathogenesis, PH with significant venous and/or capillary involvement has been added to box 1. The term ‘primary pulmonary hypertension’ (PPH) has been abandoned and idiopathic and familial PAH are distinct diagnostic classes. Compression of pulmonary vessels (adenopathies and tumor, fibrosing mediastinitis) has been added to box 5. Boxes 2 to 4 remain unaltered. Adapted from the 3rd World Symposium on Pulmonary Arterial Hypertension, Venice, 23 to 25 June 2003.
resolution computer tomography (HRCT) is helpful in excluding parenchymal lung disorders. In the majority of PAH cases the function test is normal but slightly reduced in lung volumes and mildly reduced diffusing capacity for carbon monoxide (34). The 6-minute walk test is a standard method to assess exercise performance, response to therapy and predict prognosis (35;36). A sleep study may be performed to exclude the obstructive sleep apnoea syndrome (OSAS).
Typical findings on chest X-ray are, enlarged pulmonary arteries, right atrial and ventricular dilatation and clear lung fields (37). When parenchymal lung disease or fibrosis of the mediastinum is thought to be the underlying cause of PH, HRCT might discriminate (38). Next step in the diagnostic work-up is echocardiography. This imaging modality is a practical clinical tool and accessible in every modern hospital. In addition to estimations of pulmonary artery pressures, insights on right ventricular structure and function can be obtained by echocardiography (39). Furthermore, congenital heart disease or left-sided heart disease, such as mitral-valve disease or left-ventricular dysfunction can be excluded (40). Echo-Doppler is useful in the diagnosis and follow-up of patients with pulmonary hypertension to monitor progression of the disease and the response to therapy (41-43). Clinical-chemical testing is non-specific but a liver function test may be helpful in excluding porto-pulmonary hypertension (44). Haematological and immunological testing may identify PAH associated with HIV or systemic sclerosis (45). Consultation of a rheumatologist must be considered interpreting laboratory results. Brain natriuretic peptide and N-terminal pro brain natriuretic peptide (NT-proBNP) has shown their value in monitoring disease, therapy, and is able to predict prognosis in PAH. Imaging techniques, ventilation-perfusion scintigraphy and pulmonary angiography discriminate PH due to chronic thrombo-embolic disease from other forms of PH (46). In the VU University Medical Center Amsterdam a Magnetic resonance imaging (MRI) protocol was developed to evaluate the structure and function of the right atrium, ventricle, the interventricular septum and pulmonary artery in a short period of time (47;48). In addition to the diagnostic information, this MRI protocol can also be used for non-invasive monitoring of drug therapy (49). Of all diagnostic tools right heart catheterisation with selective pulmonary vasodilator testing remains the gold standard to confirm or exclude the definitive diagnosis of PH (50). Standard right-heart catheterisation measurements are summarized in Table 2.

According to the National Institutes of Health registry PH patients have a mean pulmonary artery pressure greater than or equal to 25 mmHg, a pulmonary capillary wedge pressure less than 5 mmHg and a pulmonary vascular resistance more than 240 dyn·s·cm⁻⁵ (51). Of note is that even in patients with veno-occlusive disease, pulmonary capillary wedge pressure is normal, and thus an elevated pulmonary capillary wedge pressure excludes diagnosis of Box 1, Table 1 (52). Thus, a normal wedge pressure is critical for the choice of therapy. In case there is doubt about the accuracy of the wedge measurement, which is often the case, left ventricular pressures should be measured. Acute vasoreactivity testing is mandatory in all forms of PAH (Box 1). The rationale to perform vasoreactivity testing is to identify the small group of PAH patients who may benefit from calcium channel blocker therapy, and show improved long-term survival if treated with this medication (53). Initial baseline hemodynamic evaluation is performed while patients are breathing room air.

<table>
<thead>
<tr>
<th>Table 2. Standard right heart catheterisation measurements</th>
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<tr>
<td>Right atrial pressure</td>
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<tr>
<td>Right ventricle pressure</td>
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<tr>
<td>Pulmonary artery pressure</td>
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<tr>
<td>Pulmonary capillary wedge pressure</td>
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<tr>
<td>Pulmonary arterial vasoreactivity</td>
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air. Subsequently patients are tested with $O_2$ and inhalation of nitric oxide (54). Both gasses are administered through a facemask each over 5 minutes and with a minimum pause of 5 minutes in between the two tests. The vasoreactivity test is continued with a prostacyclin, epoprostenol, administered intravenously. Every 5 minutes the dosage is increased. The test is ceased when patients experience adverse effects or show a vasoreactive response. Calcium channel blockers are not indicated for vasoreactivity testing, because of possible live threatening adverse effect (55). Several definitions of vasoreactive response are being handled. In the VU University medical center the definition of Galié is being used (56). Patients with no response must be treated with specific pulmonary vasodilators/anti-vascular remodeling. A positive vasoreactivity test is, when pulmonary vascular resistance decreases $\geq 20\%$ and this decrease is associated with a reduction of mean pulmonary artery pressure $\geq 20\%$ and no change or increase in cardiac index. The performance of vasoreactivity testing is of diagnostic and prognostic value. It has been shown that pulmonary vasoreactivity correlates well with survival in patients with PAH of the familiar and idiopathic kind (57).

**Treatment of pulmonary arterial hypertension**

The conceptual shift in the pathogenesis of PAH makes it clear that effective treatment of PAH patients must target vascular remodeling, i.e. proliferation of pulmonary vascular smooth muscle cells. Treatment strategies focus on interference of known pathobiological pathways leading to clinical PAH. Besides conventional treatment - oxygen, anticoagulant therapy, diuretics and cardiac glycosides (58)- the following drugs are available or approval is in sight for treatment of PAH (Figure 4).

**Calcium channel blockers (CCBs)**

The treatment of PAH with CCBs is reserved for patients with a positive vasoreactive response to an acute challenge with vasoactive substances during right heart catheterisation. A minority (<10%) of the group who respond to vasoreactive testing may benefit from long-term administration of CCBs (59). Therefore true responders have to be monitored carefully to see whether there is a sustained response. For patients whom might not benefit from long-term administration with CCBs and clinical deterioration is evident, medication can be replaced or added.

**Prostacyclin and analogues**

Epoprostenol (Flolan®) has a vasodilatory and platelet antiaggregatory effect. Epoprostenol interferes with pulmonary vascular remodelling and affects the anti-inflammatory process (60). Continuous infusion of epoprostenol has been shown effective, also in the long term, for PAH of the familiar and idiopathic types and PAH associated with connective tissue disease. Improvement in exercise capacity, hemodynamics and survival in long-term randomised controlled trials has been shown for epoprostenol (61-65). One of the disadvantages of continuous infusion is increased risk of septic complication (66). This complication might also arise with iloprost given intravenously. Iloprost is a more stable prostacyclin with a half-life of 20 to 30 minutes compared with 1 to 2
minutes for epoprostenol (67). This may offer theoretical advantages, although no large trial can confirm the advantages yet. Because of the known complications with intravenous administration, prostacyclin analogues with a different route of administration are of great interest in treating PAH. Beraprost (oral), iloprost (inhaled) and treprostinil (Remodulin® subcutaneous) are examples of potential ‘alternatives’. Significant improvement in exercise tolerance and hemodynamics has been shown in several studies (68-70). Trials that compare these prostacyclin analogues with epoprostenol on endpoint criteria have to be designed. The prostacyclin analogues should be reserved for NYHA class II or early but stable class III. In some cases the prostacyclin analogues treprostinil (Remodulin*) and iloprost can be administered in NYHA class IV patients (Figure 4).

**Endothelin-receptor antagonist (ERA)**

The endothelin-receptors A (ET$_A$) and B (ET$_B$) are situated on the smooth muscle cell membrane. Stimulation induces vasoconstriction and smooth muscle cell proliferation (71). The ET$_B$ receptor
, also positioned on the endothelial cell, works as a physiological negative feedback mechanism by clearance of ET-1 and induction of NO and prostacyclin production. Blockage of the receptors by an endothelin receptor antagonist may have an anti-inflammatory effect, it prevents permeability of the pulmonary vasculature and animal studies have shown the prevention of fibrosis after pulmonary vascular inflammation, and decrease of pulmonary arterial pressure, pulmonary vascular hypertrophy and right ventricular hypertrophy (72). Randomised controlled studies with the dual receptor antagonist bosentan and selective endothelin-A-receptor antagonist sitaxsentan showed both an increased exercise capacity, improvement in hemodynamics and WHO functional class, and increased time to clinical deterioration (73-75). Bosentan (Tracleer®) and sitaxsentan (Thelin®) are indicated as treatment for NYHA class III patients with PAH.

Substances interfering with the NO/cGMP pathway
Inhaled nitric oxide (NO) improves exercise capacity (76). The limitation of treatment with NO is the requirement of continuous inhalation to maintain its positive effect. NO is synthesised from L-arginine, a precursor amino acid, by NO-synthase. Administration of L-arginine to patients with pulmonary hypertension has shown beneficial effects on exercise capacity (77). A controlled clinical trial is underway.

Phosphodiesterases (PDEs) are a group of several isoenzymes. Isoenzymes 3 and 4 hydrolyse cAMP and cGMP. cAMP is primarily involved in the vasodilatory effect of prostacyclin and cGMP mediates this effect for NO (78). Sildenafil®, a PDE-5/6 inhibitor, increases the concentration of cGMP and cAMP (79). PDE-5 is expressed in lung tissue. Although the distribution of PDE in tissue is heterogeneous, with a high deposition in the skeletal muscle, heart and vascular smooth muscle (80), the mechanism explains the pulmonary vasodilatory effect.

The SUPER trial showed the efficacy of Sildenafil (Revatio®) in the treatment of PAH (81). In addition, studies show that in PAH patients addition of sildenafil to other oral therapy such as bosentan (82,83) improved six-minute walk distance.

Combination of drug therapies
Present-day treatment focuses on interference of known pathobiological pathways leading to clinical PH. Vascular remodeling and proliferation of pulmonary vascular smooth muscle cells are the targets of interest. From Figure 2 it is evident that the different pathways leading to clinical PAH can be present concomitantly.

The administration of one drug may interfere with several different pathways. Future treatment strategies should focus on combination of drugs that theoretically target either different or similar pathobiological pathways. The net effect should result in a reduction of vascular remodeling and cessation of proliferation of pulmonary vascular smooth muscle cells. This should lead to an increase in exercise capacity and improvement in cardiac hemodynamics and NYHA functional class. Studies on epoprostenol and other prostacyclin analogues have demonstrated efficacy and should be considered as today’s standard. Newer drugs should either be compared with this standard or added to a prostacyclin. Possible combination treatments would be epoprostenol-bosentan,
epoprostenol-sildenafil, iloprost (inh)-bosentan (84) or sildenafil, beraprost (or)-bosentan (85). Novel insights in the molecular deformities revealed by the genetic causes of PAH changed the classification of PAH. In addition, based on the novel insights on the complex molecular pathways in PAH, combination treatment will be the standard therapy in the near future.

Surgical treatments
Surgical intervention in PH patients has its limitations due to cardiopulmonary hemodynamic instability. Patients with chronic thromboembolic PH (CTEPH) show improvement in exercise capacity and immediate improvement in ventilatory efficiency after pulmonary endarterectomy (PEA) (86). Atrial septostomy can be beneficial in patients with severe PAH (87). The results of several studies demonstrate significant hemodynamic and clinical improvement and increase in exercise capacity (88,89). Despite the positive effect of atrial septostomy in selected patients with severe PAH, the intervention has a palliative character and has to be interpreted as a bridge to lung transplantation (90).

Lung transplantation is the only curative therapy for PAH (91) and it still plays a pivotal role, as long-term results of current drug therapy are still unsatisfactory. The main issue is when a patient should be listed for transplantation. According to the ‘Task force consensus on position of transplantation’ the option for transplantation should be discussed early in the treatment plan according to the regional waiting list time. However, the time of listing remains a point of discussion. Consensus guidelines for referral are described in Table 3 (92).

Rationale of the thesis
The majority of PAH research focuses on the diseased pulmonary vessels. This research gives novel insights on the pathobiology, pathogenesis and genes involved in this disease. These insights form the rationale for drug therapies, which specifically target molecular pathways. New treatment strategies as described has improved the survival of PAH patients considerably in the last years (93;94). However, prognosis is still grim, which is inevitably associated to right heart failure; i.e. end-stage disease where the right ventricle is unable to pump the blood against the high pulmonary vascular resistance. Despite the recognition that both morbidity and mortality of PAH patients

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Table 3. Consensus guidelines for referral for lung transplantation

<table>
<thead>
<tr>
<th>Criterion</th>
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<tr>
<td>6 min walk distance &lt; 300 m</td>
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<tr>
<td>Significant right ventricle dysfunction</td>
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<tr>
<td>(measured by MRI, Echocardiography or chemical markers; neuroendocrine markers, troponin)</td>
</tr>
<tr>
<td>VO&lt;sub&gt;2&lt;/sub&gt; &lt; 10 ml/min/kg</td>
</tr>
<tr>
<td>Hemoptysis</td>
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<td>Rapid pulmonary artery dilatation</td>
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Guidelines for referral for lung transplantation are: exercise capacity measured by 6 minute walk distance less than 300 meters; right ventricle dysfunction measured by Magnetic Resonance Imaging, echocardiography, chemical markers (neuroendocrine markers or troponin are under study); lung function, measured by O<sub>2</sub> consumption less than 10 ml/min/kg; hemoptysis; rapid pulmonary artery dilatation quantified by imaging techniques. Adapted from the 3rd World Symposium on Pulmonary Arterial Hypertension, Venice June 23<sup>rd</sup>-25<sup>th</sup> 2003.
are largely driven by the function of the right ventricle (95). There is an impressive relative lack of studies of the right ventricle in both animals and humans. Insight in the pathophysiological mechanisms, which precede end-stage disease, is a requisite to be able to support the patient in times of failure. In addition, the rationale to study the effect of PH on the physiology of the heart is that cardiac function in PH patients remains an important determinant of outcome and suggests an important role of the right ventricle in this disease. To be able to study the pathophysiology of the heart accurately, merely omitting geometrical assumptions, magnetic resonance imaging (MRI) was used. The aim of this thesis is to provide a better understanding of the mechanisms involved in cardiac failure in PAH.

Outline of this thesis
This thesis is concerned with the effects of PH on the physiology of the heart. A brief outline of each chapter follows.

In PAH the cardiac hormone N-terminal pro brain natriuretic peptide (NT-proBNP) plasma level is increased and parallels alterations in hemodynamics and functional status during treatment. Insight in to changes in right ventricular structure and systolic function in relation to NT-proBNP are lacking. The temporal relationships of NT-proBNP with right ventricular structure and systolic function are studied in Chapter 2. Although it is well known that right ventricular systolic function is impaired in PAH, little is known about right ventricular diastolic function. In Chapter 3 we investigated whether right ventricular diastolic function is impaired in PH patients, and whether this impairment is related to right ventricular mass and afterload. Sildenafil was used to investigate whether an acute reduction of right ventricular afterload improves right ventricular diastolic function. Finally, we assessed the relation between right ventricular diastolic function and cardiac parameters that reflect disease severity in PH.

A hallmark in patients with pulmonary hypertension is the paradoxal septum movement, i.e. leftward ventricular septal bowing. We hypothesized that in PAH patients the presence of leftward ventricular septal bowing impairs left ventricular filling, as a consequence left ventricular end-diastolic volume is reduced and according to Frank-Starling's law, a decreased stroke volume results. The hypothesis is tested in Chapter 4. Left-to-right delay in myocardial shortening might be the cause of leftward ventricular septal bowing. The study presented in Chapter 5 explores whether the cause of the Left-to-right delay lies in the onset of shortening, in the duration of shortening, or in both. In addition, the functional impact of the Left-to-right mechanical asynchrony is determined by assessing its association with leftward ventricular septal bowing, left ventricular filling and stroke volume.

Changes in right ventricular structure and function as a result of chronic pressure overload demands adaptation of the right atrium which might as a consequence also alter right ventricular filling and function. This is studied in Chapter 6. Total compliance of the pulmonary vascular bed, defined as the ratio of stroke volume and pulse pressure, predicts mortality in pulmonary arterial hypertension. A large part of total vascular bed compliance is located in the proximal arterial branches. Chapter 7 describes the predictive value of non-invasively assessed proximal pulmonary
artery stiffness. Finally *Chapter 8* places the pathophysiological mechanisms of right heart failure described in this thesis in a more clinical perspective.
References


Chapter 1


89. Sandoval, J., Gaspar, J., Pulido, T., Bautista, E., Martinez-Guerra, M.L., Zeballos, M., Palomar, A., and...


Chapter 2

NT-proBNP reflects right ventricular structure and function in pulmonary hypertension


European Respiratory Journal 2006;28(6):1190-4
Abstract

Aim: To investigate whether alterations in N-terminal pro brain natriuretic peptide (NT-proBNP) reflect changes in right ventricular structure and function in pulmonary hypertension patients during treatment.

Methods and Results: Thirty pulmonary hypertension patients were studied, 15 newly diagnosed and 15 on long-term treatment. NT-proBNP, right heart catheterization and cardiac MRI measurements were performed, at baseline and follow-up. There were no significant differences between newly diagnosed and on treatment patients at baseline and follow-up with respect to NT-proBNP, hemodynamics and right ventricular parameters. Relative changes in NT-proBNP during treatment were correlated to the relative changes in right ventricular end-diastolic volume index ($r = 0.59$, $p < 0.001$), right ventricular mass index ($r = 0.62$, $p < 0.001$) and right ventricular ejection fraction ($r = -0.81$, $p < 0.001$)

Conclusion: NT-proBNP measurements reflect changes in MRI measured right ventricular structure and function in pulmonary hypertension patients. An increased NT-proBNP over time reflects right ventricular dilatation concomitant to hypertrophy and deterioration of systolic function.
**Introduction**

Pulmonary hypertension (PH) is a disease characterized by increased pulmonary vascular resistance leading to chronic right ventricular (RV) pressure overload. Without treatment patients have a poor prognosis and die of right heart failure. Right atrial pressure, measured by right heart catheterization, has been shown an important prognostic parameter in pulmonary arterial hypertension (PAH)\(^{(1)}\). Recently, the search for a less invasive prognostic marker was successful with the detection of the cardiac hormone brain natriuretic peptide (BNP) and its biologically inactive alternative N-terminal pro brain natriuretic peptide (NT-proBNP). Research performed in patients with a diseased left ventricle, i.e. ischemia, pressure or volume overload, showed the clinical and prognostic value of this hormone \(^{(2-5)}\). Nagaya et al. showed in idiopathic PAH patients that a high BNP level at baseline and a further increase in BNP at follow-up was associated with a poor prognosis \(^{(6)}\). In patients with increased RV load it has been shown that BNP is related to functional status; initial hemodynamics; RV systolic function and structure \(^{(7-9)}\). In PAH patients BNP parallels alterations in hemodynamics and functional status during treatment \(^{(10)}\). Although these findings emphasize the clinical significance of the change in BNP after long-term therapy in PAH patients, insight in to changes in RV structure and systolic function in relation to BNP are lacking. Furthermore, in previous reports BNP was measured, while it is unclear whether measurements of NT-proBNP show similar relations. Therefore the aim of this study was, to assess the temporal relationships of NT-proBNP with RV structure and systolic function in PH patients.

**Methods**

**Study design**

A total of 30 PH patients with an average age of 48 [21; 80] years and a male to female ratio of 8/22 were studied. Fifteen patients were newly diagnosed and 15 patients were on long-term treatment (27 ± 16 months) at the start of the study and were being reevaluated for treatment effect and/or add on therapy. All patients had a mean pulmonary artery pressure > 25 mmHg, pulmonary capillary wedge pressure < 15 mmHg at right heart catheterization and normal systemic blood pressure and renal function (serum creatinine < 20 µmol/l). PH due to left sided heart diseases, interstitial lung disease or hypoxemia, was excluded by further diagnostic work-up (echocardiography, high resolution CT-scan and lung function test) following the 2003 Venice consensus guidelines on the diagnosis and treatment of PAH \(^{(11)}\). The different etiologies of PH were distributed as follows, idiopathic PAH (n = 19), PAH related to the limited type of systemic sclerosis (n = 7), PAH related to HIV (n = 1), PAH related to porto-pulmonary shunts (n = 1) and PH due to chronic thrombo-embolic disease (n = 2). Measurements were repeated after an average follow-up period of 10.5 months (range 3.7 to 15.6). Patients were treated with; bosentan \(^{(11)}\), nifidipine \(^{(1)}\), epoprostenol \(^{(6)}\), sitaxentan \(^{(2)}\), and combination therapy consisting of; epoprostenol-sildenafil \(^{(5)}\) or bosentan-sildenafil \(^{(5)}\). The study was part of the project that evaluates and monitors cardiac function in PAH by MRI, which was approved by the Committee on Research Involving Human Subjects of the VU University Medical Center. Written informed consent was obtained from all patients.
Chapter 2

Cardiac catheterization
Diagnostic right heart catheterization was performed with a balloon tipped, flow directed 7F Swan-Ganz catheter (3HF7; Baxter Healthcare Corp; Irvine, CA). The patient was in a stable condition lying supine breathing room air. Right atrial, right ventricular, pulmonary artery and pulmonary capillary wedge pressures were measured. Blood was sampled, with the catheter positioned in the main pulmonary artery to assess mixed venous oxygen saturation. Left ventricular pressure measurements and coronary angiogram were performed in two patients with PAH associated with systemic sclerosis and old age (> 70 years) to exclude coronary artery disease. Arterial oxygen saturation was measured from blood sampled from the radial or femoral artery. Cardiac output was assessed by the Fick method and pulmonary vascular resistance was calculated using the standard formula: (mPap-Pcwp)/cardiac output, where mPap is the mean pulmonary artery pressure and Pcwp is the pulmonary capillary wedge pressure.

MRI measurements
Magnetic resonance imaging was performed on a Siemens 1.5T Sonata scanner (Siemens Medical Solutions, Erlangen, Germany), using a four-element phased array cardiac receiver coil, according to the MRI protocol described previously (12). Perpendicular to the four chamber end-diastolic image, a stack of consecutive short-axis breath hold cine images were made with temporal resolution of 34 ms, and slice distance of 10 mm. From the stack of parallel short-axis cine images, quantitative analysis of volumes and geometry was performed by manual detection of endocardial and epicardial borders on each slice, using the MR Analytical Software System (Medis, Leiden, The Netherlands). The MRI data was analyzed by C.T.G., whom was unaware of the NT-proBNP levels at the time of analysis. The interventricular septum was considered part of the left ventricle. Right ventricular end-diastolic volume (RVEDV) and myocardial mass (RVM) were calculated an indexed (indicated with suffix I). Stroke volume was measured using MR phase-contrast flow quantification (velocity sensitivity was 150 cm/s, and temporal resolution 22 ms), ejection fraction was calculated as follows: right (RVEF = 100 * stroke volume/RV end-diastolic volume) and left ventricular ejection fraction (LVEF = 100*stroke volume/LV end-diastolic volume).

Plasma NT-proBNP levels
Blood was sampled from a peripheral vein with the patient at rest, within 24 hours of MRI measurements and right heart catheterization. N-terminal pro brain natriuretic peptide (NT-proBNP) plasma levels were analyzed on an ELECSYS 1010 bench top analyzer (Roche Diagnostics Netherlands). Temporal changes were expressed as percentage of the baseline values.

Statistical analyses
SPSS 11.0 software package was used for statistical analyses and p< 0.05 was considered statistically significant. Results are reported as median and interquartile range, unless otherwise indicated. Wilcoxon signed rank test was performed for comparison of baseline and follow-up values. Baseline NT-proBNP was correlated to hemodynamics and MRI measurements. Similar correlations
were assessed for the relative changes in NT-proBNP, hemodynamics and MRI measurements. Correlation analyses were performed with a Spearman rank correlation test.

Results
At the start of the study six-minute walk distance, hemodynamics and MRI measurements were not different between newly diagnosed and on treatment patients. Furthermore, there was no clinically relevant difference in functional class among the newly diagnosed and on treatment patients. The coronary angiogram performed in the two patients with PAH associated with systemic sclerosis did not reveal coronary artery disease. Furthermore, left ventricular ejection fraction measured by MRI was greater than 60% in all patients.

Hemodynamics and MRI measurements
The functional status, hemodynamics and MRI measurements at baseline and follow-up are summarized in Table 1. At baseline the most patients were in NYHA functional class III. Hemodynamic measurements showed that all patients had significant pulmonary hypertension, which is also reflected by the MRI measured RV parameters; i.e. RV dilatation, hypertrophy and impairment of systolic function. A small but significant hemodynamic improvement in pulmonary artery pressure and pulmonary vascular resistance index was observed during follow-up. However

Table 1. Functional status, hemodynamics and MRI measurements at baseline and follow-up

<table>
<thead>
<tr>
<th>Function status</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA (II : III : IV)</td>
<td>5:22:3</td>
<td>13:15:2</td>
</tr>
<tr>
<td>6 MWD (m)</td>
<td>425 [342; 509]</td>
<td>461 [370; 591]</td>
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<table>
<thead>
<tr>
<th>Hemodynamics:</th>
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<tbody>
<tr>
<td>Pra (mmHg)</td>
<td>6 [4; 10]</td>
<td>6 [3; 10]</td>
</tr>
<tr>
<td>sPrv (mmHg)</td>
<td>72 [56; 93]</td>
<td>65 [56; 82]*</td>
</tr>
<tr>
<td>dPrv (mmHg)</td>
<td>9 [5; 13]</td>
<td>9 [6; 13]</td>
</tr>
<tr>
<td>mPap (mmHg)</td>
<td>47 [38; 57]</td>
<td>43 [32; 52]*</td>
</tr>
<tr>
<td>SvO2 (%)</td>
<td>67 [58; 71]</td>
<td>66 [61; 74]</td>
</tr>
<tr>
<td>CI (l/min·m²)</td>
<td>2.8 [2.0; 3.6]</td>
<td>3.1 [2.6; 4.0]</td>
</tr>
<tr>
<td>PVRI (dyn·s·cm⁻³·m⁻²)</td>
<td>384 [236; 528]</td>
<td>324 [160; 430]*</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>6 [5; 9]</td>
<td>7 [5; 11]</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>MRI measurements:</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>RV EDVI (ml/m²)</td>
<td>92 [76; 111]</td>
<td>98 [76; 109]</td>
</tr>
<tr>
<td>RVMRI (g/m²)</td>
<td>38 [29; 51]</td>
<td>45 [31; 53]</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>34 [23; 50]</td>
<td>38 [31; 53]</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>333 [192; 1363]</td>
<td>541 [99; 1027]</td>
</tr>
</tbody>
</table>

NYHA = New York heart association class; 6 MWD = six-minute walk distance; Pra = right atrial pressure; sPrv = systolic right ventricular pressure; dPrv = diastolic right ventricular pressure; mPap = mean pulmonary artery pressure; SvO2 = mixed venous saturation; CI = cardiac index; PVRI = pulmonary vascular resistance index; PCWP = pulmonary capillary wedge pressure; RV EDVI = right ventricular end-diastolic volume index; RVMRI = right ventricular mass index; RVEF = right ventricular ejection fraction; NT-proBNP = N-terminal pro brain natriuretic peptide. Values are expressed as median and interquartile range. * p<0.05, between baseline and follow-up
this improvement was not reflected by RV parameters or a decrease of NT-proBNP (normal values between 68-112 pg/ml) (13).

Correlations of NT-proBNP with hemodynamics and MRI measurements at baseline
At baseline serum NT-proBNP was related to invasively measured hemodynamic variables such as right atrial pressure, mixed venous saturation and cardiac index but not to pulmonary artery pressure or pulmonary vascular resistance index. Furthermore, NT-proBNP was positively related to RV end-diastolic volume index, and inversely related to RVEF, but not related to RV mass index. (Table 2).

Correlation of the relative change in NT-proBNP with RV parameters during follow-up
Although for the whole group most of the variables did not change significantly during follow up, there was a considerable individual variation in the relative change of RV parameters, as is shown in Figure 1. The relative changes in NT-proBNP were closely related to the relative changes in RV end-diastolic volume index ($r = 0.59, p = 0.001$), mass index ($r = 0.62, p< 0.001$) and inversely to RVEF ($r = -0.81, p< 0.001$) (Figure 1). The patient with the significant increase of NT-proBNP at follow-up was a patient with an unsuccessful transition on bosentan after being stable on epoprostenol therapy for more than four years.

Discussion
This study showed that in PH patients, NT-proBNP parallels changes in RV structure and systolic function. BNP is a cardiac hormone synthesized and cleaved together with NT-proBNP from a pro-hormone in ventricular and atrial cardiomyocytes. The potential advantages of NT-proBNP measurements above BNP are a longer plasma half-life, biological inactivity and lower biological variability (4;5). However, head-to-head comparison of BNP and NT-proBNP in patients with left ventricular dysfunction could not confirm a clinical significant advantage of NT-proBNP over

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation Coefficient ($r$)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pra (mmHg)</td>
<td>0.49</td>
<td>0.008</td>
</tr>
<tr>
<td>mPap (mmHg)</td>
<td>0.28</td>
<td>0.143</td>
</tr>
<tr>
<td>SvO2 (%)</td>
<td>-0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI (l/min·m²)</td>
<td>-0.45</td>
<td>0.019</td>
</tr>
<tr>
<td>PVRI (dyn·s·cm⁻⁵·m⁻²)</td>
<td>0.30</td>
<td>0.122</td>
</tr>
<tr>
<td>RVEDVI (ml/m²)</td>
<td>0.53</td>
<td>0.004</td>
</tr>
<tr>
<td>RVMI (g/m²)</td>
<td>0.37</td>
<td>0.052</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>-0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>-0.51</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Correlation of NT-proBNP with hemodynamics, right ventricular parameters and six-minute walk distance at baseline. Abbreviations as mentioned earlier
NT-proBNP reflects right ventricular structure and function

BNP (16;17). Under normal physiological conditions the left side of the heart determines BNP and NT-proBNP levels (18). Elevated NT-proBNP in PH patients presumably results from augmented synthesis and release by the overloaded RV.

Figure 1 Correlation of the relative change in NT-proBNP with the relative change in right ventricular mass index (RVMI) (top); right ventricular end-diastolic volume index (RVEDVI) (middle); and right ventricular ejection fraction (RVEF) (bottom) in patients with pulmonary hypertension. Open circles represent newly diagnosed patients (n = 15) and black triangles represent on treatment patients (n = 15).
In this study, baseline NT-proBNP was elevated related to hemodynamics characterizing RV pressure overload. MRI measurements showed RV dilatation, hypertrophy and impaired function. Compared to earlier studies (19-21), this study showed similar, but modest, correlations of NT-proBNP and hemodynamics. In addition, NT-proBNP was related to RV end-diastolic volume index and showed a strong inversed relation with RV ejection fraction. The relation of NT-proBNP and RV mass index was not significant. In the study by Nagaya et al. BNP was correlated to RV mass and systolic function, but not to RV volume (22). The different findings between this study and the earlier studies might be explained by the small variation on the hemodynamic data at baseline in our study. Furthermore, RV hypertrophy is a compensatory physiological mechanism aimed at normalizing wall stress. In case of RV volume and/or pressure overload, an increase in RV mass decreases wall stress and as a consequence may reduce NT-proBNP. This may explain the absence of a significant correlation between NT-proBNP and RV mass index at baseline. In our study, long-term follow-up showed that changes in NT-proBNP paralleled changes in RV structure and function. The long-term follow-up study by Leuchte et al (23) has shown that in PH patients there are parallel changes in hemodynamics and BNP confirming the work of a three months follow-up study and studies performed in an acute setting (24-26). In addition our study shows that temporal changes in NT-proBNP are associated with alterations in RV structure and particularly systolic function.

Ventricular dilatation has been suggested to be a pathological state of cardiac remodeling. However data on RV dilatation and outcome in PH patients are lacking. Although an echocardiography study showed that absolute RV end-diastolic area measured as a singular parameter was not a significant predictor of outcome(27), our finding does not exclude the prognostic importance of a change in RV end-diastolic volume over time and should be investigated in future studies. The relative change in NT-proBNP showed a positive correlation with the change in RV myocardial mass. Since NT-proBNP is produced by the cardiomyocyte, this correlation suggests that hypertrophied RV cardiomyocytes are associated with increased transcription of the proBNP gene and NT-proBNP release. Impaired RV systolic function predisposes to right heart failure which is associated with an increased risk of death (28) in idiopathic PAH patients. Our data shows that NT-proBNP is valuable parameter marking alterations in RV systolic function. The correlations of the change in RV parameters and NT-proBNP were stronger than between baseline RV parameters and NT-proBNP. This supports the idea that serial measurements have higher sensitivity than baseline values. Taking the current results and previous research(29), one may hypothesize that the importance of an increasing NT-proBNP level, despite treatment, is directly related to failing RV systolic function.

The recent work by Fijalkowska(30) et al. has shown that NT-proBNP is related to RV structure and function, and serves as a prognostic parameter in PH patients. Our study shows that serial changes in NT-proBNP closely reflect alterations in RV end-diastolic volume and ejection fraction which are likely to be important prognostic markers in PH (31). Since impaired RV ejection fraction predisposes to right heart failure, serial measurements might be valuable in monitoring disease.
NT-proBNP reflects right ventricular structure and function

Although it has been shown that singular NT-proBNP measurements are of prognostic value in PH patients (32), longitudinal NT-proBNP measurements might potentially be superior with respect to prognosis, as was shown for BNP (33). In addition, serial NT-proBNP measurements may be valuable in clinical decisions when there is limited access to MRI or under the circumstance where the patient's condition does not allow invasive procedures.

We included newly diagnosed patients and patients being initially treated at the start of this study. Although there were no clinically relevant differences between the two patient groups, our study group was too small to draw any conclusion on the influence of treatment on NT-proBNP. The small study group and the limited changes in hemodynamic variables are important limitations of this study, which might explain the absence of significant correlations of several hemodynamic variables with NT-proBNP. An assumption in this study was that PAH treatment does not directly affect NT-proBNP production. However, there is some evidence from experimental animal research that, phosphodiesterase-5 inhibitor, sildenafil might act on the cardiac myocytes directly (34), therefore a direct effect on the myocardial production of NT-proBNP cannot be excluded.

**Conclusion**

The data from this study showed that the change in NT-proBNP over time provides indirect information on RV remodeling and the change in RV systolic function, measured by MRI. Elevated NT-proBNP levels over time reflect progressive RV dilatation and impaired systolic function, and thus should be interpreted as a sign of RV failure.
References


NT-proBNP reflects right ventricular structure and function


NT-proBNP reflects right ventricular structure and function
Chapter 3

Right ventricular diastolic dysfunction and the acute effects of sildenafil in pulmonary hypertension patients


Chest 2007 Jul;132(1):11-7
Abstract

Aims: This study investigated whether right ventricular (RV) diastolic function is impaired in pulmonary hypertension (PH) patients, and related to RV mass and afterload. In addition, the effects of an acute reduction of RV afterload by oral intake of sildenafil were studied. Finally, we assessed whether diastolic function is related to cardiac parameters of disease severity. Methods and Results: Twenty-five PH patients and 11 controls were studied. Right heart catheterization and NT-proBNP sampling were performed in patients. MRI measured RV ejection fraction, mass and diastolic function. Isovolumic relaxation time (IVRT), normalized early (E), atrium-induced (A) peak filling rate, and E/A, described diastolic function. Compared to controls, patients had prolonged IVRT (133.5±53.2 ms vs. 29.3±20.8 ms, p<0.001), decreased E (3.0±1.6 s⁻¹ vs. 6.4±2.5 s⁻¹, p<0.001) and E/A (1.1±0.7 vs. 5.3±4.9, p< 0.001), and increased A (3.0±1.4 s⁻¹ vs. 1.5±0.9 s⁻¹, p = 0.001). IVRT was related to RV mass (r = 0.56, p = 0.005) and pulmonary vascular resistance (r = 0.74, p< 0.0001). Sildenafil reduced RV afterload and improved RV diastolic and systolic function. IVRT was correlated to, NT-proBNP (r = 0.70, p< 0.001), and inversely related to cardiac index (r = -0.70, p< 0.001) and RV ejection fraction (r = -0.69, p< 0.001). Conclusion: In PH patients RV diastolic dysfunction is related to RV mass and afterload. RV diastolic function improves by reducing afterload. The correlations between diastolic function and prognostic parameters showed that diastolic function is most impaired in severely diseased patients.
Right ventricular diastolic dysfunction and the acute effects of sildenafil

Introduction
Pulmonary hypertension (PH) is a disease, which affects the right ventricle (RV) by an increased afterload. Eventually, patients die due to right heart failure. Although research mainly focused on the influence of PH on RV systolic function, and the prognostic significance of this parameter, insight on the role of diastolic function in PH is scarce. Research performed in the left ventricle has shown that diastolic dysfunction plays a significant role in patients with left ventricular pressure overload and heart failure(1), and is influenced by left ventricular afterload(2) and wall thickness(3). Thus, there are arguments that RV diastolic function may be impaired in PH patients. First, due to increased RV afterload myocardial relaxation and filling may be impaired. Second, RV compensatory hypertrophy to increased afterload reduces ventricular compliance and may impair diastolic function.

In this study we investigated whether RV diastolic function is impaired in PH patients, and whether this impairment is related to RV mass and afterload. Sildenafil was used to investigate whether an acute reduction of RV afterload improves RV diastolic function. Finally, we assessed the relation between RV diastolic function and cardiac parameters that reflect disease severity in PH.

Methods
Patients
Twenty-five PH patients, with normal renal function, and 11 non-smoking healthy controls were studied. Eighteen patients were referred to our center for the initial evaluation of PH and seven patients for evaluation of treatment effects (three patients were on epoprostenol and four received bosentan). The different etiologies of PH were distributed as follows, idiopathic PAH (n = 18), PAH related to the limited type of systemic sclerosis (n = 5) and PH due to chronic thrombotic disease (n = 2). PH due to left sided heart disease, interstitial lung disease or hypoxemia, were excluded by further diagnostic work-up according to the guidelines on diagnosis of PAH (4). The study was approved by the Institutional Review Board on Research Involving Human Subjects of the VU University Medical Center. Written informed consent was obtained from all subjects.

Study design
All patients underwent right heart catheterization and an MRI-scan one day prior to right heart catheterisation. There was no significant difference in heart rate during cardiac catheterization and MRI (catheterization = 80.3±12.0 bpm vs. MRI = 83.1±13.6 bpm, Paired t- test, t_{22} = 1.1, p = 0.27) and all patients were in sinus rhythm. Blood was sampled from a peripheral vein with the patient in rest, within 24 hours of MRI measurements. N-terminal pro brain natriuretic peptide (NT-proBNP) plasma levels were analyzed on an ELECSYS 1010 bench top analyzer (Roche Diagnostics Netherlands). The six-minute walk test was performed a day before right heart catheterization.

To study the effects of RV afterload reduction on diastolic function, ten patients; (idiopathic PAH (n = 7); PAH related to the limited type of systemic sclerosis (n = 1); and PH due to chronic thrombotic disease (n = 2), were admitted to the ICU for pulmonary vasoreactivity testing with inhaled NO.
(iNO), and oral sildenafil. ECG, arterial and pulmonary artery pressures were monitored continuously during the test. Each patient inhaled 20-30 ppm NO for 5 minutes. After hemodynamics returned to baseline values the patient took 50 mg sildenafil. Measurements were performed at baseline, after iNO and 50 minutes after sildenafil.

In these ten patients the effect of sildenafil on MRI measured RV function was studied one day prior to vasoreactivity testing on the ICU. For technical reasons iNO was not possible in the MRI. Baseline MRI measurements were performed at rest and repeated 50 minutes after sildenafil with a fasting period between the measurements. In this study we chose 50 mg of sildenafil. This dosage has been shown safe and pulmonary specific, and the maximum effect has been shown after 45 minutes (5;6).

Cardiac catheterization
Right heart catheterization was performed with a 7F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp; Irvine, CA). Right atrial, RV and pulmonary artery pressures were measured. Blood was sampled to assess mixed venous oxygen saturation. Arterial oxygen saturation was measured from blood sampled from the radial or femoral artery. Cardiac output was assessed by the Fick method and pulmonary vascular resistance was calculated using the standard formula: (mPap-Pcwp)/cardiac output, where mPap is the mean pulmonary artery pressure and Pcwp is the pulmonary capillary wedge pressure.

MRI measurements
MRI was performed on a Siemens 1.5T Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) according to the protocol described earlier(7). Four-chamber cine images were acquired by steady state free precession imaging, with 11 phase-encoding lines per heartbeat in a 14-heartbeat breathhold. With 30 reconstructed phases, the effective temporal resolution was in the range between 25 and 34 ms. Perpendicular to the four chamber end-diastolic image, a stack of consecutive short-axis breath hold cine images were acquired with the same sequence parameters as used for the 4-chamber cine, and with slice distance of 10 mm. From this stack of parallel short-axis cine images, quantitative analysis of RV volumes and mass was performed using the MR Analytical Software System (Medis, Leiden, The Netherlands). A RV 2-chamber cine series was localized as the image plane orthogonal to the most basal cardiac short-axis plane that intersected both the pulmonary and the tricuspid valve. This cine series displayed the onset of pulmonary valve closing and tricuspid valve opening.

Finally, stroke volume was measured using MR phase-contrast flow quantification in an image plane orthogonal to the main pulmonary artery, at 1 cm distance downstream from the pulmonary valves. Velocity sensitivity was 150 cm/s, and temporal resolution 22 ms. RV ejection fraction was obtained by the ratio of RV stroke volume and RV end-diastolic volume.

Quantification of RV diastolic function
Isovolumic relaxation time (IVRT) was the time interval between pulmonary valve closing and tricuspid valve opening(8) and was normalized for the RR-interval because of differences in heart
Right ventricular diastolic dysfunction and the acute effects of sildenafil

rate. RV filling was quantified from the RV volumetric filling curves as assessed from the stack of short-axis cine images (9). RV early (E), atrium-induced (A) peak filling rate (both measures were normalized for RV end-diastolic volume) and E/A quantified RV diastolic filling pattern.

Statistical analyses
SPSS 12.0 software package was used for statistical analyses and p< 0.05 was considered statistically significant. Results are reported as mean ± standard deviation for descriptive statistics. Results after iNO and sildenafil are reported as median and interquartile range. Mann-Whitney test was performed to compare RV parameters between PH patients and controls and Wilcoxon matched paired rank-test was performed to compare hemodynamics after iNO and sildenafil, and to compare RV diastolic and systolic function before and after sildenafil. Pearson correlation analyses were performed to investigate significant correlations. Because of multiple testing the threshold for significance was adjusted using the Bonferroni correction for families of tests, where 0.05 divided by the amount of tests assessed the adjusted significance level.

Results
There was no difference between the PH patients and controls with respect to age (PH = 49.1±15.3 years vs. controls = 46.5±11.4 years, t-test, t_{34} = 0.59, p = 0.56) and proportion of male to female (PH = 5/20 vs. controls = 3/8, Fisher's Exact test, p = 0.41). Patient characteristics and hemodynamics are summarized in Table 1. The majority of patients was female and in NYHA functional class III. Hemodynamics yielded characteristics of RV pressure overload. PH patients had a hypertrophied RV with impaired systolic function (Table 2).

Table 1. Characteristics and hemodynamic variables

<table>
<thead>
<tr>
<th>Functional status:</th>
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</thead>
<tbody>
<tr>
<td>NYHA (II: III: IV)</td>
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<tr>
<td>6 MWD (m)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemodynamics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pra (mmHg)</td>
</tr>
<tr>
<td>dPrv (mmHg)</td>
</tr>
<tr>
<td>sPrv (mmHg)</td>
</tr>
<tr>
<td>mPap (mmHg)</td>
</tr>
<tr>
<td>SvO(_2) (%)</td>
</tr>
<tr>
<td>CO (l/min)</td>
</tr>
<tr>
<td>PVR (dyn·s·cm(^{-5}))</td>
</tr>
<tr>
<td>Log NT-proBNP (pg/ml)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: NYHA = New York Heart Association functional class; 6 MWD = six minute walk distance; Pra = right atrial pressure; dPrv = diastolic right ventricular pressure; sPrv = systolic right ventricular pressure; mPap = mean pulmonary artery pressure; SvO\(_2\) = mixed venous oxygen saturation; CO = cardiac output; PVR = pulmonary vascular resistance; Log NT-proBNP = N-terminal pro brain natriuretic peptide. Values are expressed as mean ± SD.
Table 2. MRI measurements in controls and PH patients

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 11)</th>
<th>PH (n = 25)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVMI (g/m²)</td>
<td>19.5 ± 4.2</td>
<td>40.7 ± 16.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVEDVI (ml/m²)</td>
<td>79.6 ± 21.7</td>
<td>87.3 ± 30.4</td>
<td>0.542</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>51.4 ± 9.1</td>
<td>36.3 ± 12.8</td>
<td>0.002</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>29.3 ± 20.8</td>
<td>133.5 ± 53.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVRTn (ms)</td>
<td>0.04 ± 0.03</td>
<td>0.19 ± 0.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E (ml/s)</td>
<td>761.3 ± 230.9</td>
<td>443.9 ± 217.5</td>
<td>0.001</td>
</tr>
<tr>
<td>E/edv (s⁻¹)</td>
<td>6.4 ± 2.5</td>
<td>3.0 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A (ml/s)</td>
<td>247.5 ± 191.4</td>
<td>465.5 ± 239.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A/edv (s⁻¹)</td>
<td>1.5 ± 0.9</td>
<td>3.0 ± 1.4</td>
<td>0.001</td>
</tr>
<tr>
<td>E/A</td>
<td>5.3 ± 4.9</td>
<td>1.1 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Definitions of abbreviations: RVMI = right ventricular mass index; RVEDVI = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; IVRT = isovolumic relaxation time; IVRTn = isovolumic relaxation time normalized for the RR-interval; E = right ventricular peak filling rate; E/edv = right ventricular peak filling rate normalized for right ventricular end-diastolic volume; A = atrium-induced peak filling rate; A/edv = atrium-induced peak filling rate normalized for right ventricular end-diastolic volume; E/A = MRI derived ratio of right ventricular early and atrium-induced peak filling rate. Values are expressed as mean ± SD. Mann-Whitney test, Bonferroni adjusted significance level was p<0.005.

Figure 1 shows an MR RV two chamber cine images of a PH patient. The ECG below the images marks the time point within the cardiac cycle when the MR images were obtained. The first cine image marks the start of RV contraction. The onset of pulmonary valve closing and tricuspid valve opening was assessed from the middle and right cine images, respectively (Figure 1). IVRT was calculated accordingly. In PH patients IVRT was prolonged compared to controls, shown in Table 2.

Figure 2A illustrates the average change in RV volume over time in controls and PH patients obtained from MR short-axis cine images. In controls RV filling is characterised by an early fast filling (E), a plateau phase and atrial contraction (A). In contrast, E is absent in PH patient while A is more pronounced. The difference in RV filling is more explicitly shown in Figure 2B, which shows the average RV filling rate in controls and patients. In PH patients, E is reduced when compared to controls, and towards end-diastole A is higher and shows a significant atrial contribution, data shown in Table 2. The Bonferroni adjusted significance level was p< 0.005.

To assess the effects of RV hypertrophy and afterload on diastolic function, the different diastolic parameters were correlated to RV mass and pulmonary vascular resistance. Since we performed six Pearson correlation analyses, the Bonferroni adjusted significance level was p< 0.008. IVRT was related to RV mass and pulmonary vascular resistance, as illustrated in Figure 3A and B. Whereas E and E/A did not reach significance (p> 0.1).
**Acute effects of iNO and sildenafil**

Three patients were on mono therapy (epoprostenol or bosentan) at the time of pulmonary vasoreactivity testing. Compared to baseline (54.0 mmHg [44.5; 61.5]), iNO (43.0 mmHg [37.5; 53.0]) and sildenafil (44.0 mmHg [35.5; 54.0]), decreased mean pulmonary artery pressure
Wilcoxon signed matched ranks test, \( p = 0.004 \)). Changes in pulmonary vascular resistance and stroke volume during vasoreactivity testing are shown in Figure 4.

Compared to baseline (643.5 dyn·s·cm\(^{-5}\) [414.8; 1070.5]), iNO (500.0 dyn·s·cm\(^{-5}\) [309.5; 728.8]) and sildenafil (511.5 dyn·s·cm\(^{-5}\) [320.0; 789.8]) decreased pulmonary vascular resistance. The decrease after iNO was not different after sildenafil. Compared to baseline (60.5 ml [49.3; 76.3]), iNO (62.5 [57.8; 87.8]) did not change stroke volume, while sildenafil (69.5 ml [55.8; 85.3]) increased stroke volume (Figure 4B) (Wilcoxon signed matched ranks test, Bonferroni adjusted significance level was \( p < 0.006 \)).

Sildenafil was used to study the effect of afterload reduction on RV diastolic function in the MRI. The individual response in diastolic and systolic function to a reduction in RV afterload is shown.
Right ventricular diastolic dysfunction and the acute effects of sildenafil

In Figure 5, normalized IVRT decreased after sildenafil (0.12 [0.08; 0.22]) when compared to baseline (0.19 [0.14; 0.28]). RV ejection fraction improved with sildenafil (34.5% [28.3; 40.3]) when compared to baseline (4% [32.5; 46.3]). There was no significant change in RV peak filling or heart rate after sildenafil (Wilcoxon signed matched ranks test, Bonferroni adjusted significance level was $p < 0.01$).

**Correlations of RV diastolic function with cardiac parameters of disease severity**

IVRT was not significantly related to right atrial pressure ($r = 0.47$, $p = 0.018$), but was related to NT-proBNP ($r = 0.70$, $p < 0.001$), and inversely related to cardiac index ($r = -0.70$, $p < 0.001$) and RV ejection fraction ($r = -0.69$, $p < 0.001$). The Bonferroni adjusted significance level was $p < 0.01$.

**Discussion**

This study showed that: 1) In PH patients RV diastolic function, quantified by RV IVRT, peak filling rate and filling pattern, was significantly impaired compared to controls, 2) Diastolic function was related to RV mass and afterload, and improved by reducing RV afterload, 3) RV diastolic dysfunction was related to parameters of disease severity.

**Diastolic function in PH**

Diastole is characterised by ventricular relaxation and filling. Therefore not one single parameter can describe diastolic function (10). In this study we used time and volume. Earlier research focused on estimating pulmonary artery pressure by IVRT (11,12). Our findings of prolonged IVRT in chronic RV pressure-overload are in agreement with experimental and clinical studies (13-16). Stojnic showed that IVRT was prolonged in PH patients (15). This finding was confirmed by Tei (14) in primary PH patients. Although diastolic function was not the primary focus in these studies, the data revealed the presence of diastolic dysfunction in PH patients. Recently, it was
shown that chronic RV pressure overload increased IVRT (13;16). Our data showed that compared to controls there was a redistribution of RV filling in PH, characterised by a reduced E, increased A, and a decreased E/A ratio. From these data it might be concluded that in PH RV filling is largely dependent on atrial contraction.

**Mechanism of RV diastolic dysfunction in PH**
The mechanism of diastolic dysfunction can be intra- or extra myocardial. Chronic RV pressure-overload results in compensatory hypertrophy to decrease wall stress. However, ventricular compliance decreases concomitantly. Therefore ventricular hypertrophy has been suggested to cause diastolic dysfunction(3). Our data are in agreement with the latter, since IVRT was related to RV mass. Furthermore, IVRT was related to RV afterload, and an acute decrease in RV afterload improved diastolic function, which indicates that in PH patients the cause of diastolic dysfunction is in part extra myocardial. Since the reduction of pulmonary vascular resistance by iNO and sildenafil was not different, which is in agreement with earlier studies (7;8), improvement of stroke volume and RV systolic function with sildenafil might be attributed to the decreased afterload. However, stroke volume was greater with sildenafil when compared to iNO, while the decrease in pulmonary vascular resistance was not different. This suggests a direct effect of sildenafil on the cardiomyocyte, which has been shown in experimental research (19;20). In contrast to sildenafil, iNO solely affects the pulmonary vessels because of its short half-life. Thus improvement of RV diastolic function with sildenafil might be due to decreased afterload and a concomitant direct effect on the myocardium. There was no effect of afterload reduction on RV filling. This is in agreement with research on the left ventricle, which showed that the effect of myocardial relaxation on left ventricular filling pressures is heart-rate dependent (2). Since heart rate remained unchanged after sildenafil, this mechanism may also account for the RV.

**Relation of diastolic function and disease severity**
Correlations of IVRT with cardiac parameters, reflecting disease severity in PH, were assessed; i.e. right atrial pressure, NT-proBNP, cardiac index and right ventricular ejection fraction (22-24). Right atrial pressure was not significantly related to IVRT, but there was a trend where elevated right atrial pressure was associated with prolonged IVRT. This relation is not surprising, since right atrial pressure is considered a reflection of RV diastolic function. IVRT was related to NT-proBNP and inversely related to cardiac index and RV systolic function, which emphasizes the importance of global RV dysfunction in PH patients. Based on the relations we speculate that diastolic dysfunction is not only a reflection of disease severity, but might also be an independent factor contributing to right heart failure and death in PH patients.

**Study limitations**
To characterize diastolic function RV pressure decline should be assessed next to IVRT and ventricular filling. However, pressure measurements were recorded with a fluid-filled catheter. It has been generally assumed that the frequency response of fluid-filled catheters is insufficient for
Right ventricular diastolic dysfunction and the acute effects of sildenafil

instantaneous pressure measurements, which is essential to measurements of pressure decline. Since one of our aims was to relate diastolic function to RV mass and ejection fraction, we choose MRI to measure RV diastolic function. The experience to measure diastolic function by MRI is limited, when compared to echocardiography. However, the feasibility has been recognized (9;25). Furthermore, our measurements of IVRT are comparable to the results obtained in echocardiographic studies (26;27). The study group was too small to draw any firm conclusions on the clinical value of diastolic dysfunction in PH patients. Larger studies and temporal assessment are warranted to assess the clinical value of RV diastolic function in PH.

**Conclusion**

RV diastolic function is impaired in PH patients, related to RV mass and the extent of RV afterload, and improves by reducing RV afterload. The found correlations between diastolic function and well-known prognostic parameters in PH showed that diastolic function is most impaired in severely diseased patients.
References

Right ventricular diastolic dysfunction and the acute effects of sildenafil


Chapter 4

Impaired left ventricular filling due to right to left ventricular interaction in patients with pulmonary arterial hypertension


The American Journal of Physiology Heart and Circulatory Physiology 2006 Apr;290(4):H1528-33
Abstract

Aims: To investigate the contribution of direct right to left ventricular interaction on left ventricular filling and stroke volume in pulmonary arterial hypertension (PAH) patients.

Methods and Results: Forty-six PAH patients and 8 control subjects were included. Magnetic resonance imaging measured stroke volume, right and left ventricular volumes, left ventricular filling rate and interventricular septum curvature. Transesophageal echocardiography measured left atrial filling. Compared to control subjects, PAH patients had decreased stroke volume (28±3 vs. 41±10 ml/m^2, p<0.001), left ventricular end-diastolic volume (46±14 vs. 61±14 ml/m^2, p<0.001) and left ventricular peak filling rate (216±90 vs. 541±248 ml/s, p<0.001). Among PAH patients stroke volume did not correlate to right ventricular end-diastolic volume or mean pulmonary artery pressure, but did correlate to left ventricular end-diastolic volume (r = 0.62, p< 0.001). Leftward interventricular septum curvature was correlated to left ventricular filling rate (r = 0.64, p< 0.001) and left ventricular end-diastolic volume (r = 0.65, p< 0.001). In contrast, left atrial filling was normal and not correlated to left ventricular end-diastolic volume.

Conclusion: In PAH patients ventricular interaction mediated by the interventricular septum impairs left ventricular filling contributing to decreased stroke volume.
Introduction

In severe pulmonary arterial hypertension (PAH), chronic pressure overload results in right ventricular (RV) hypertrophy and dilatation. Enlargement of the RV might affect the left ventricle (LV), which is intrinsically normal. Previous echocardiography studies have shown that in patients with chronic RV pressure overload LV filling dynamics are altered, i.e. early diastolic filling impairment and redistribution of LV filling towards late diastole (1-5). Research of our own group found similar results of impaired LV filling and showed that LV end-diastolic volume was reduced (6). The phenomenon, by which the RV directly influences LV diastolic filling, is known as direct ventricular interaction and is mediated by the interventricular septum (7-9). Direct ventricular interaction has been investigated extensively in animal models (7;10-14) and the presence in patients with chronic RV pressure overload has been associated with changes in LV filling dynamics (3;6;15;16).

However, the hemodynamic consequence of direct ventricular interaction in PAH patients has not been resolved. We hypothesized that in PAH patients the presence of direct ventricular interaction impairs LV filling, as a consequence LV end-diastolic volume is reduced and according to Frank-Starling’s law, a decreased stroke volume results. The aim of our study was to determine the effect of direct ventricular interaction on stroke volume, by using magnetic resonance imaging (MRI) and echocardiography in a large group of patients with severe PAH.

Methods

Study population.

All 46 PAH patients were referred to our center for evaluation and treatment of PAH. All investigations were part of the patients’ diagnostic work-up. The diagnosis PAH was based on cardiac catheterization data, i.e. mean pulmonary artery pressure greater than 25 mmHg at rest. Pulmonary hypertension due to lung disease and/or hypoxemia, chronic thrombotic and/or embolic disease or other possible causes, were excluded by further diagnostic work-up (ventilation perfusion scan, chest-X-ray, lung function test, high resolution CT-scan, pulmonary angiography) according to the flowchart of Barst et al (17). In 11 of the patients PAH was associated with systemic sclerosis (CREST-syndrome), based on clinical findings and serology. In 35 of the patients, idiopathic PAH was diagnosed. The study complies with the Declaration of Helsinki (18) and adheres to Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, and was approved by the Institutional Review Board on Research Involving Human Subjects of the VU University Medical Center. Written informed consent was obtained from all patients and 18 non-smoking control subjects (age 39 ± 17 years, 4 male vs. 14 female, BSA = 1.85 ± 0.23 m²) without a history of cardiopulmonary disease. None of the patients received PAH treatment at the time of examination, except for acenocoumarol.

Cardiac catheterization

Right heart catheterization was performed in all patients, not in controls, with a 7F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp; Irvine, CA), within two days of MRI and transesophageal
echocardiography (TEE) measurements. Cardiac output was calculated by the Fick method and pulmonary vascular resistance was calculated using the formula: \( \frac{\text{mPap - Pcwp}}{\text{cardiac output}} \), where mPap is the mean pulmonary artery pressure and Pcwp is the pulmonary capillary wedge pressure.

**MRI measurements**

MRI was performed on a Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) according to the protocol described earlier (19). Stroke volume (SV) was measured using MR phase-contrast flow quantification. End-diastole and end-systole were defined as the maximum and minimum volume. End-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction and myocardial mass were calculated using MR Analytical Software System (Medis, Leiden, The Netherlands). Direct ventricular interaction was quantified by the curvature of the interventricular septum and calculated according to a formula described by Roeleveld et al (20). A negative value of the curvature corresponds to a septum displacement towards the LV cavity. LV filling rate was defined as the change in volume over time.

The time onset of maximum curvature and LV peak filling rate were assessed and normalized to the ECG RR-interval for difference in heart rate among individuals. In a random group of 5 patients and 5 control subjects, LV filling was measured during all of diastole. Volumetric and geometric measurements were indexed (indicated with suffix I).

**Echocardiography**

TEE was performed in 20 patients with a 5 MHz; 64-element transducer (Hewlett-Packard Co., Andover, Mass) connected to a Hewlett-Packard Sonos 2500 or 5500 (Hewlett-Packard Co., Andover, Mass). The probe was positioned at the level of the left pulmonary vein and mitral valve and flow velocity patterns were obtained using pulsed Doppler. Mean peak systolic (PVF_syst), diastolic (PVF_dia) and atrial reversed (PVF_A) flow velocities were obtained in 5 consecutive beats with patients in sinus rhythm and mitral early (E) and atrial (A) peak flow was measured. Peak pressure gradients during early diastole (\( \Delta P_E \)) and atrial contraction (\( \Delta P_A \)) were calculated, using the modified Bernoulli equation: \( \Delta P_n = 4 \times V^2 \), where \( \Delta P_n \) = peak mitral valve pressure gradient and \( V \) = velocity in m/s.

**ECG analysis**

The ECG of all patients were analysed automatically for (in) complete right bundle branch block (RBBB). Complete RBBB was defined as a QRS complex equal or greater than 120 ms and an incomplete (RBBB) as a QRS complex greater or equal to 100 ms and smaller than 120ms.

**Data analysis**

SPSS 11.0 software package was used for statistical analyses and \( p < 0.05 \) was considered statistically significant. Results are reported as mean ± SD for descriptive statistics. Student \( t \)-test (paired) was performed to compare MRI measurements of the PAH group with the control group. Linear regression analyses were performed to assess the correlations between catheterization, MRI and TEE data.
Results

Patient characteristics and hemodynamic variables are shown in Table 1. With respect to cardiac catheterization and MRI measurements there were no statistical significant differences between patients diagnosed as idiopathic PAH and PAH related to systemic sclerosis. In 5 patients the ECG could not be analyzed. The PAH-group had a mean pulmonary artery pressure (mPap) of 55 ± 16 mmHg, a normal pulmonary capillary wedge pressure (7 ± 5 mmHg), and elevated right atrial pressure (10 ± 5 mmHg), as shown in Table 1.

There was no significant difference in heart rate during cardiac catheterization, MRI acquisition and TEE (catheterization: 81 ± 16 beats/minute; MRI acquisition: 82 ± 15 beats/minute: TEE: 88 ± 16 beats/minute). All patients were in sinus rhythm during the investigations.

Table 1. Patients characteristics and catheterization data*

<table>
<thead>
<tr>
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<th></th>
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</thead>
<tbody>
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<td>Number of patient</td>
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</tr>
<tr>
<td>IPAH</td>
<td>35</td>
</tr>
<tr>
<td>PHSSc</td>
<td>11</td>
</tr>
<tr>
<td>Male vs. female</td>
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</tr>
<tr>
<td>Age (yrs)</td>
<td>47 ± 16</td>
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</table>

<table>
<thead>
<tr>
<th>Functional status:</th>
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<tbody>
<tr>
<td>NYHA</td>
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<td>6 min walk distance (m)</td>
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<table>
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<tr>
<td>100 ms &lt; QRS &lt; 120 ms</td>
<td>8</td>
</tr>
<tr>
<td>QRS &gt; 120 ms</td>
<td>3</td>
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</table>

<table>
<thead>
<tr>
<th>Hemodynamic variables:</th>
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</tr>
<tr>
<td>dPap (mmHg)</td>
<td>37 ± 13</td>
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<tr>
<td>mPap (mmHg)</td>
<td>55 ± 16</td>
</tr>
<tr>
<td>Pcwp (mmHg)</td>
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</tr>
<tr>
<td>SvO₂ (%)</td>
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</tr>
<tr>
<td>CO (l/min)</td>
<td>4.3 ± 1.3</td>
</tr>
<tr>
<td>PVR (dyn·s·cm⁻⁵)</td>
<td>999 ± 604</td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>82 ± 15</td>
</tr>
</tbody>
</table>

Definition of abbreviations: iPAH = idiopathic pulmonary arterial hypertension; PHSSc = pulmonary hypertension related to systemic sclerosis; NYHA = New York Heart Association functional class; Pra = right atrial pressure; sPrv = systolic right ventricular pressure; dPrv = diastolic right ventricular pressure; sPap = systolic pulmonary artery pressure; dPap = diastolic pulmonary artery pressure; mPap = mean pulmonary artery pressure; Pcwp = pulmonary capillary wedge pressure; SvO₂ = mixed venous oxygen saturation; CO = cardiac output; PVR = pulmonary vascular resistance; HR = heart rate. * Values are expressed as mean ± SD.
MRI measurements

Mid-ventricular end-diastolic, end-systolic and early diastolic short-axis cine MR images are shown in Figure 1. The images A - C represent a control subject and images D - F represent a PAH patient (mPap = 76 mmHg). The individuals were matched for age (35 years), gender (female) and body surface area (1.8 m²). The images of the patient show distinct RV wall thickening and a larger RV lumen area in end-diastole and end-systole compared to the RV of the control subject. The LV of the patient compared to the LV of the control subject shows a smaller end-diastolic and end-systolic LV lumen area. The interventricular septum bends towards the LV during contraction and is maximal in early diastole (at 352 ms trigger delay from the R-wave of the ECG).

The parameters measured with MRI are summarized in Table 2. Compared to control patients had a decreased SV. Although heart rate was increased, CI was lower. Furthermore, patients had on average a dilated hypertrophied RV accompanied by a decrease in RV ejection fraction. For the left ventricular parameters, EDV was decreased in comparison with the control group, ESV was within normal range, and ejection fraction was lower. In all control subjects and four patients the position of the interventricular septum remained unaltered during the cardiac cycle and in two patients the septum flattened during diastole.

![Figure 1](image-url)

**Figure 1.** Mid-ventricular short-axis magnetic resonance images, of a control subject (A-C) and a patient with severe PAH mPap 76 mmHg (D-F). The images were acquired at end-diastole, end-systole and approximately 100 ms after end-systole. The temporal frames at the top (A-C) from left to right are in ms from the ECG R-wave: 0 ms, 317 ms and 421 ms, with an RR-interval of 920 ms. The temporal frames at the bottom (D-F) from left to right are in ms from the ECG R-wave: 0 ms, 250 ms and 352 ms, with an RR-interval of 640 ms. Right ventricular wall thickening and a larger lumen area in the PAH patient is seen by comparing panels A-C with panels D-F. In the early diastolic image F, maximal leftward ventricular septal bowing is shown.
Impaired left ventricular filling due to right to left ventricular interaction

To investigate the influence of LVEDV, RVEDV and RV afterload on SV, a correlation analysis was performed. Within the PAH patient group SV was related to LVEDV ($r = 0.62$, $p < 0.001$), but not related to RVEDV, as shown in Figure 2. Furthermore, SV was not correlated to mean pulmonary artery pressure ($r = -0.24$, NS).

LV PFR was decreased in PAH patients compared with control subjects (Figure 3). The LV volume curve shows that PAH patients start LV filling with approximately the same LVEDV fraction as control subjects. However, in patients early filling is slower: they reach 75% of LVEDV in approximately 80% of the RR-interval while controls reach 75% of LVEDV only in 60% of the RR-interval.

In patients LV filling is a more gradual process, while in controls after initial rapid filling a plateau is reached in mid-diastole (70 to 85% of the RR interval). The same phenomena are more explicitly shown in Figure 3B: PFR in patients is about two thirds of PFR in controls. However, in mid-diastole (70% to 85% of RR-interval) LV filling rate in patients is larger than in controls. In this graph is also shown that in patients the time onset of PFR (TPR) occurred after the time of maximal leftward septum curvature (TC). For the total patient group the time of maximal curvature was $389 \pm 92$ ms after the R-wave of the ECG, whereas the time to peak filling rate was $425 \pm 78$ ms, $p < 0.01$.

### Table 2. Comparison of MRI data of controls and PAH patients

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 18)</th>
<th>PAH' (n = 46)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVI (ml/m²)</td>
<td>41 ± 10</td>
<td>28 ± 13</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>71 ± 10</td>
<td>81 ± 16</td>
<td>$&lt; 0.05$</td>
</tr>
<tr>
<td>CI (l/min·m²)</td>
<td>3.0 ± 0.7</td>
<td>2.0 ± 0.9</td>
<td>$&lt; 0.01$</td>
</tr>
<tr>
<td><strong>Right ventricle</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>72 ± 22</td>
<td>96 ± 27</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>ESVI (ml/m²)</td>
<td>35 ± 14</td>
<td>70 ± 27</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>EF (%)</td>
<td>48 ± 10</td>
<td>29 ± 11</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>MI (g/m²)</td>
<td>22 ± 5</td>
<td>50 ± 13</td>
<td>$&lt; 0.001$</td>
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<td><strong>Left ventricle</strong></td>
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<td></td>
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<tr>
<td>EDVI (ml/m²)</td>
<td>61 ± 14</td>
<td>46 ± 14</td>
<td>$&lt; 0.01$</td>
</tr>
<tr>
<td>ESVI (ml/m²)</td>
<td>20 ± 6</td>
<td>20 ± 10</td>
<td>NS</td>
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<tr>
<td>EF (%)</td>
<td>67 ± 7</td>
<td>56 ± 13</td>
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</tr>
<tr>
<td>MI (g/m²)</td>
<td>62 ± 13</td>
<td>73 ± 12</td>
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<tr>
<td>Curvature (cm⁻¹)</td>
<td>0.35 ± 0.08</td>
<td>-0.13 ± 0.15</td>
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<td>PFR (ml/s)</td>
<td>541 ± 248</td>
<td>216 ± 90</td>
<td>$&lt; 0.001$</td>
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<td>PFR/edv (s⁻¹)</td>
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<td>TPR</td>
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<td>0.59 ± 0.11</td>
<td>NS</td>
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**Definition of abbreviations:** SVI = stroke volume index; HR = heart rate; CI = cardiac index; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; EF = ejection fraction; MI = myocardial mass index; Curvature = interventricular septum curvature, a negative value indicates that the curvature is towards the left ventricular cavity; PFR = left ventricular peak filling rate; PFR/edv = left ventricular peak filling rate normalized for left ventricular end-diastolic volume; TPR = time to left ventricular peak filling rate normalized to RR-interval; * Values are expressed as mean ± SD. † PAH group = patients with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension related to systemic sclerosis.
The filling rate at the time of maximal septum curvature (42 ± 98 ml/s) was correlated to septum curvature ($r = 0.64$, $p < 0.01$) and to LVEDV ($r = 0.65$, $p < 0.001$).

In a subset of 5 PAH patients and 5 controls LV filling was measured throughout diastole, thus including the last part of diastole until the next heart beat. In these data the relative contribution of the atrial contraction can be quantified more explicitly. Figure 4 presents the diastolic LV volume curve (4A) and the corresponding time derivative, LV filling rate (4B). Figure 4A shows that in patients LV filling is slow and gradual. In controls LV volume increases rapidly in early diastole, reaches a plateau in mid-diastole and finally increases rapidly due to atrial contraction. Figure 4B shows in patients the slow and gradual filling in early and mid-diastole. However in the late diastolic phase (80-100% of RR-interval), filling rate of patients exceeds that of controls and the
Impaired left ventricular filling due to right to left ventricular interaction

contribution of the atrial contraction is relatively more important in the LV filling process.

**TEE measurements**

TEE measurements were performed in 20 patients to assess left atrial filling. The ratio of early mitral peak flow (E = 54 ± 15 cm/s) and atrial mitral peak flow (A = 67 ± 15 cm/s) was reversed (E/A = 0.81 ± 1.01). The calculated pressure gradient during early mitral peak flow (ΔP_E) was 1.16 ± 0.10 mmHg and 1.77 ± 0.09 mmHg during atrial peak flow (ΔP_A). Compared with literature (21;22) concerning pulmonary venous flow, systolic (PVF_{syst} = 59 ± 16 cm/s), diastolic (PVF_{dia} = 42 ± 10 cm/s) pulmonary venous flow and systolic to diastolic flow ratio (PVF_{syst}/PVF_{dia} = 1.5 ± 0.5) showed no abnormalities. Peak pulmonary venous atrial reversed flow (PVF_A = 35 ± 10 cm/s) was increased. Linear regression analysis showed that PVF_{syst} was not related to SV or mean pulmonary artery pressure, and there was no significant correlation between PVF_{dia} and PFR. Furthermore, PVF_{syst} and PVF_{dia} were not related to LVEDV.

**Discussion**

The contribution of the left ventricle to heart failure in PAH patients is unclear and controversial. In this study we have demonstrated that the reduction in stroke volume in PAH patients is related to the filling state of the left ventricle at end-diastole, which is reduced due to an abnormal filling pattern. The main mechanism of left ventricular under filling was leftward interventricular septum displacement.

**Series versus direct ventricular interaction**

Impaired LV filling in RV pressure overload might be the result of two mechanisms: series and direct interaction (7;9;10). Under normal conditions series interaction, i.e. increased RV afterload

---

*Figure 4.* The average diastolic LV volume curve (A) and the average diastolic LV filling rate curve (B) in a random subgroup of 5 PAH patients (triangles) and 5 controls (squares), measured and analyzed during all of diastole. On the y-axis LV volume (A) and LV filling rate (B) were normalized for LVEDV, and on the x-axis time in the cardiac cycle was normalized for the RR-interval.
leading to a decrease in RV output and thus to a decrease in left atrial and LV filling subsequently, is the dominant physiological mechanism. In direct interaction, substantial RV dilatation and hypertrophy might compress the LV, thereby impairing LV filling. Either mechanism results in a reduced LV end-diastolic volume and stroke volume. In PAH, series and direct interaction might occur concomitantly. Although our results cannot distinguish these two mechanisms completely, the data provides several arguments that direct ventricular interaction contributes significant to LV filling impairment. First, in PAH patients early diastolic filling rate at the time of maximal septum curvature was closely related to interventricular septum curvature. Second, early diastolic filling rate at the time of maximal septum curvature was correlated to LV end-diastolic volume. The latter argues with the hypothesis that early diastolic filling is less important, because early filling impairment could be compensated towards end-diastole. Finally, left atrial filling was normal and not related to LV end-diastolic volume and thus could not explain the impaired filling or under filling of the left ventricle.

Mechanisms of direct ventricular interaction

Two mechanisms of direct ventricular interaction have been identified from previous research. These are 1) Direct ventricular interaction mediated by the pericardium and 2) interventricular asynchrony. Since both ventricles are enclosed within a relatively non-distensible pericardium, increases in RV volume may occur at the expense of LV volume (9). While a reduction of RV volume paradoxically increases LV volume (23). Interventricular asynchrony describes the effect of a slow, prolonged decay of RV pressure, causing higher pressure in the RV than in the LV in early diastole (24).

The pericardium

Animal studies by Elzinga et al. provided early evidence that the pericardium plays an important role in right-left ventricular interaction (7). Recently, Baker and Belenkie (10;11) studied the effect of acute RV pressure overload on LV output in dog hearts left in situ, by constricting the main pulmonary artery. Opening of the pericardium in the animal models facilitated LV filling leading to an increase of LV end-diastolic volume and consequently, cardiac output. However, in contrast with the animal studies, RV pressure overload in the PAH patients developed gradually and was chronic rather than acute. Pericardiotomies performed by Blanchard et al. (25) in patients with chronic RV pressure overload due to pulmonary emboli, showed that the pericardium has little influence on cardiac and interventricular septum deformations and concluded that the human pericardium is capable of adapting over time to cardiac geometry alterations. For this reason it is unclear whether pericardial constraint plays a significant role in mediating direct ventricular interaction in PAH patients.

Ventricular asynchrony

Evidence that interventricular asynchrony might play a role in PAH can be obtained from the ECG which showed frequently an (in)complete right branch block configuration in PAH. Furthermore,
Impaired left ventricular filling due to right to left ventricular interaction

research on the LV in heart failure patients showed that interventricular asynchrony is present in a substantial proportion regardless of the QRS duration (26). However, only a limited number of studies exist that found evidence for the presence of mechanical interventricular asynchrony in PH.

Earlier research performed by Stojnic et al. showed that beside a reduction of early LV diastolic filling velocity and an increase in LV filling velocity during atrial contraction, the time of RV pressure decline was prolonged compared to the LV (24). They concluded that diastolic LV filling impairment is mediated by deformation of the interventricular septum towards the LV cavity and is caused by a right-left ventricular asynchrony. Invasive data from our own group showed the presence of right-left ventricular asynchrony (20) in PAH patients. Synchronous RV and LV pressure measurements in PAH patients showed that a significant right to left transseptal pressure gradient was present at the time of maximal leftward septal displacement measured by MRI. Recently, tissue Doppler imaging in patients with pulmonary hypertension provides circumstantial evidence of the presence of mechanical asynchrony between the RV free wall and the interventricular septum, and between the RV and LV free wall (27;28). These data suggest that ventricular mechanical asynchrony might play a role in mediating direct ventricular interaction in PAH patients.

Study limitations
The major limitation of this study is, that although we found evidence that direct ventricular interaction contributes significantly to the hemodynamic deterioration of PAH patients, the separate contribution of series and direct interaction on LV filling could not be quantified. Furthermore, we were not able to measure pulmonary venous flow and LV filling simultaneously. However, neither MRI nor TEE is able to measure pulmonary venous flow and LV filling simultaneously.

Conclusion
In PAH, direct ventricular interaction mediated by the interventricular septum impairs LV diastolic filling, which results in an under filling of the left ventricle. The close relation between left ventricular end-diastolic volume and stroke volume, in the absence of such a relation for right ventricular end-diastolic volume, provides evidence that under filling of the left ventricle contributes to a decreased stroke volume.
Chapter 4

References


Impaired left ventricular filling due to right to left ventricular interaction

Chapter 5

Interventricular mechanical asynchrony in pulmonary arterial hypertension: Left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling


Journal of the American College of Cardiology
Abstract

Objective: To explore in pulmonary arterial hypertension (PAH) whether the cause of interventricular asynchrony lies in onset of shortening or duration of shortening.

Background: In PAH, leftward ventricular septal bowing (LVSB) is probably caused by a left-to-right (L-R) delay in myocardial shortening.

Methods: In 21 PAH patients (mean pulmonary arterial pressure 55±13 mmHg and ECG-QRS width 100±16 ms), MRI myocardial tagging (14 ms temporal resolution) was applied. For the Left Ventricular (LV) free wall, septum and Right Ventricular (RV) free wall, the onset time (T_onset) and peak time (T_peak) of circumferential shortening were calculated. RV wall tension was estimated by the Laplace law.

Results: T_onset was 51±23, 65±4 and 52±22 ms for LV, septum and RV respectively. T_peak was 293±58, 267±22 and 387±50 ms for LV, septum and RV. Maximum LVSB was at 395±45 ms, coinciding with septal overstretch and RV T_peak. The L-R delay in T_onset was -1±16 ms (p = 0.84), and the L-R delay in T_peak 94±41 ms (p < 0.001). The L-R delay in T_peak was not related with the QRS width, but was associated with RV wall tension (p < 0.05). The L-R delay in T_peak correlated with leftward septal curvature (p < 0.05), and correlated negatively with LV end-diastolic volume (p < 0.05) and SV (p < 0.05).

Conclusion: In PAH, the L-R delay in myocardial peak shortening is caused by lengthening of the duration of RV shortening. This L-R delay is related to LVSB, decreased LV filling and decreased stroke volume.
**Introduction**

In pulmonary arterial hypertension (PAH), leftward ventricular septal bowing (LVSB) is most prominent during early left ventricular (LV) diastole (1-3), and impairs LV filling (4-7). LVSB has been assessed by cine MRI and echocardiography (1-8), and can be quantified by the radius of leftward curvature (9). By MRI and tissue Doppler imaging (6;10;11), a right ventricular (RV) delay in the time to peak strain was observed in PAH. Such a left-to-right delay induces a left-to-right transseptal pressure gradient which may be the mechanism causing LVSB (12). However in these studies it was not yet clear whether this delay was caused by delayed RV onset or prolonged RV shortening.

The cause of either delayed or prolonged RV shortening is unknown, and knowledge of this cause could have implications for treatment. A first potential mechanism is an electrical conduction delay: RV overload and concomitant remodeling may well lead to a (partial) right bundle branch block, left-to-right electrical dyssynchrony and subsequent mechanical dyssynchrony. This would become manifest as a delayed RV time to onset of shortening in comparison to the LV. An alternative mechanism could be initiated directly by the mechanical pressure and volume overload, inducing increased RV wall tension and prolonged RV myocardial shortening. In this case, the time to *onset* of shortening would be similar for both ventricles, whereas the time to *peak* shortening of the RV wall would be delayed compared to the LV.

For the measurement of the left-to-right differences in the timing of shortening, MRI tagging and strain analysis provide a tool for accurate regional mapping of the onset and peak times in the myocardial wall (3). By this technique, any potential difference between RV and LV in onset times and peak times, to be denoted by the L-R onset delay and the L-R peak delay, can be measured.

The aim of this study is to explore in PAH whether the cause of the L-R delay lies in the onset of shortening, in the duration of shortening, or in both. The relative roles of conduction delay and prolonged shortening due to overload may then be revealed. In addition, the functional impact of the L-R mechanical asynchrony is determined by assessing its association with LVSB, LV filling and stroke volume.

**Methods**

**Patients and control subjects**

Twenty-one pulmonary hypertension patients, referred to the VU University Medical Center for treatment, were recruited. Eleven healthy control subjects were included (age 38 ± 9 years, 6 females), with normal ECG and QRS width of 80±2 ms. In 2 control subjects, the pulmonary artery pressure was measured invasively, resulting in 24 ± 1, 8 ± 4 and 16 ± 2 mmHg for systolic, diastolic and mean values.

**Image acquisition**

A 1.5 T Siemens ‘Sonata’ whole body MRI system, equipped with a 6-element phased-array coil, was used (Siemens Medical Solutions, Erlangen, Germany). The Siemens EKG gating system was
used, with no known delay between the true QRS and the QRS used to trigger the sequence. MRI myocardial tagging with high temporal resolution (14 ms) was applied with Complementary Spatial Modulation of Magnetization (7 mm tag distance) and steady state free precession imaging. Parameters: three phase-encoding lines per beat, TR 4.7 ms, TE 2.3 ms, no view sharing, flipangle 20 deg, voxel size 1.2 x 3.8 x 6.0 mm$^3$. In all patients and control subjects this tagging cine was acquired in the mid-ventricular short-axis plane (13;14). In a subset of 9 patients (nrs 1 through 8 and 10) this tagging cine was also acquired in the basal and apical short-axis planes, in order to explore any effect of the longitudinal level on the timing of strain. After the tagging acquisitions, the LV and RV were covered by a stack of short-axis cine MRI images, using steady state free precession imaging with a temporal resolution between 25 and 35 ms. In addition, cine images were acquired in the LV 3-chamber view showing the aortic and mitral valves, and through the RV outflow tract showing the pulmonary valves. Finally, the flow was measured in the main pulmonary artery by MRI velocity quantification (temporal resolution 22 ms, velocity sensitivity 120 cm/s).

Timing parameters derived from strain
The tagged images were analyzed using the Harmonic Phase procedure (15). Circumferential shortening was calculated over time during the cardiac cycle. For the LV free wall, septum and RV free wall, the onset time ($T_{\text{onset}}$) and peak time ($T_{\text{peak}}$) of circumferential shortening were calculated related to the ECG-R wave by automated routines (13). Overstretch is circumferential lengthening beyond end-diastolic value (or ‘positive strain’). Overstretch was observed in the septum and was quantified by the peak lengthening, and the time to peak lengthening.

![Figure 1](image)

**Figure 1**: The RV free wall is taken between the thick white lines and the LV free wall between the thin white lines. The septum is between the anterior and posterior ‘x’ signs. The anterior, mid and posterior points in the septum marked with ‘x’ were used to calculate the septal curvature.
LV free wall, RV free wall and septum definitions
The LV free wall was delineated as shown in fig 1. The two segments of the LV wall that were in direct continuity with the septum were not included as part of the LV free wall, as shown. The RV free wall was delineated in the same way. The complete septum was taken for the calculation of the septal strain, from the anterior till the posterior connections with the ventricular wall. For the LV free wall, RV free wall and septum the strains and strain timing parameters were derived. The difference between RV and LV in time to onset of shortening is denoted by the L-R delay in T_onset, and the difference in T_peak by the L-R delay in T_peak.

Timing parameters of the valves
The time to aortic valve closure was derived from the 3-chamber cine. The time to pulmonary valve closure was derived from the RV outflow tract cine. In patients nrs. 8 through 11 this pulmonary valve timing was derived from the most basal short-axis cine that showed the valves during the last part of systole.

Global LV and RV parameters
The stack of short-axis cine images was used for the calculation of the LV and RV end-diastolic volumes, and the RV end-systolic volume. RV stroke volume was measured from the flow map in the main pulmonary artery. The maximal leftward septal curvature was measured at the most basal short axis cine slice that still showed the LV and RV myocardium through the cardiac cycle. The septal coordinates were marked at the anterior and posterior insertions into the LV wall, and at the mid of the septum, as shown in Figure 1. From these coordinates the curvature was calculated (9).

RV wall tension
Our estimation of RV wall tension starts from the law of Laplace for a thin-walled sphere (16): Wall tension = 0.5 x Pressure x Radius
The RV pressure during shortening is estimated by the systolic pulmonary artery pressure (PAP). The RV-radius of curvature is difficult to measure directly because of the RV irregular shape. Therefore, we estimate this radius from the RV end-systolic volume (ESV) by assuming that this volume can be described by a sphere in PAH patients. Then the mean RV-radius is 0.620 x (RV-ESV)^1/3. Finally, to be able to compare different patients with different body sizes, the RV radius is normalized to BSA (body surface area). The estimation of RV wall tension then becomes: RV wall tension = 0.5 x PAP-systolic x RV-radius / BSA

Statistics
Values are expressed as mean ± SD. First, the timing parameters were tested for a normal distribution by the Shapiro-Wilks test. Then, comparisons between LV and RV timing parameters were performed using the paired-samples t-test (2-tailed). By the same test, the T_peak in the RV wall was compared with the times of LVSB, septal overstretch, and pulmonary valve closure.
Comparisons between patients and controls were performed by independent samples t-testing (2-tailed). The relations between the L-R delay in $T_{peak}$ versus ECG-QRS width, PAP and RV wall tension were tested by linear regression. The relations between septal curvature, stroke volume (SV) and LV end-diastolic volume (LVEDV) versus the L-R delay in $T_{peak}$ were also tested by linear regression. In these regression tests, the L-R delay in $T_{peak}$ was normalized for the R-R interval (RR) of the individual patient.

The interobserver variation was determined for the $T_{peak}$ of the RV by Bland-Altman analysis, for a subset of 10 patients.

**Results**

**Patient characteristics**

Sixteen patients were diagnosed as having idiopathic PAH, whereas 5 had chronic thromboembolic PH. The systolic, diastolic and mean pulmonary artery pressures were 87 ± 20, 33 ± 9 and 55 ± 13 mm Hg respectively, as measured via right heart catheterization with a Swan-Ganz catheter.

<table>
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IPAH is Idiopathic Pulmonary Arterial Hypertension, CTEPH is Chronic Thrombo-Embolic Pulmonary Hypertension, PAP is pulmonary arterial hypertension, S/D/M is systolic, diastolic, mean. (inc.) RBBB is (incomplete) right bundle branch block. n.a. means that the value is not measured within 1 week of the MRI investigation. ERA is endothelin receptor antagonist.
Interventricular mechanical asynchrony in pulmonary arterial hypertension

Figure 2: 3-Chamber images (above), short-axis images (mid) and short-axis tagged images (below), at the time of aortic valve closure at trigger delay of 252 ms (left) and the time of peak RV shortening at 341 ms (right). The 3-chamber images show that maximal leftward septal bowing occurs at 341 ms, well after aortic valve closure. In the tagged image at 341 ms, the distance of the tagging lines in the RV free wall show further shortening (thick white arrows), while the tagging lines in the LV free wall show relaxation.
The medication at the time of the MRI is listed in Table 1. The ECG-QRS width was 100 ± 16 ms. Based on the ECG morphology, 3 patients had an incomplete right bundle branch block, and one patient had a complete right bundle branch block.

RVSV was 53 ± 19 ml, RVEDV 202 ± 69 ml, RV free wall mass 91 ± 56 g, LV mass 114 ± 27 g, LVEDV 105 ± 28 ml, LVEF 51 ± 12%, BSA 1.85 ± 0.26 m² and leftward septal curvature was 0.14 ± 0.05 cm⁻¹. The LVEDV in the patients was smaller than in the controls (105 ± 28 ml vs. 158 ± 36 ml, \( p = 0.001 \)).

**Images and strains**

Figure 2 shows 3-chamber cine images, short-axis cine images and short-axis tagged images at the time of aortic valve closure, and at the time of maximal LVSB. In the patients, peak circumferential shortening of the LV and RV free walls was -14 ± 4% and -14 ± 3% respectively (\( p = 0.88 \)). Peak LV circumferential shortening in the patients was smaller than in the controls (-14 ± 4% vs. -20 ± 2%, \( p < 0.001 \)). For the septum, peak shortening was -11 ± 3%, and the maximal overstretch 6 ± 2%. Figure 3A shows the circumferential shortening curves during the cardiac cycle for the LV and RV free walls and the septum. LV and RV start simultaneously, but the RV reaches its peak later than the LV. The septum shows overstretch (positive shortening) at the same time when the RV reaches its peak shortening. In Figure 3B, the same plot is given for a control subject. In this control, the RV peak is not later than the LV peak, and the septum does not overstretch.
Timing parameters

The results of the timing parameters are given in figure 4 and table 2. In table 2 the data from the control subjects are included. The differences between the timing parameters are presented in

As shown in Table 3, there is no L-R delay in T\(_{\text{onset}}\) in contrast to the large L-R delay in T\(_{\text{peak}}\) of 94 ± 41 ms (p < 0.001). In addition, T\(_{\text{peak}}\)\(_{\text{RV}}\) is greater than T\(_{\text{pulmcl}}\) by 59 ± 40 ms, meaning that the RV free wall shows considerable post-systolic shortening, which does not contribute to ejection. The time of septal overstretch (T\(_{\text{stretch}}\)) is not different from the T\(_{\text{peak}}\)\(_{\text{RV}}\) (p = 0.93). Also the time of LVSB and the T\(_{\text{peak}}\)\(_{\text{RV}}\) are not different (p = 0.60). In the patients with a right bundle branch block, the L-R delay in T\(_{\text{peak}}\) was not different from the L-R delay in patients without a right bundle branch block. In the control subjects, not any L-R delay in timing was observed.

Regression analysis of timing parameters

By regression analysis, there was no relationship between the L-R delay in T\(_{\text{peak}}\) and the L-R delay in T\(_{\text{onset}}\) (p = 0.91). Also, the L-R delay in T\(_{\text{peak}}\) was not associated with the ECG-QRS width (p = 0.65), and not with systolic pulmonary artery pressure (Table 4).

As shown in Table 4 and Figure 5, there was an association between the L-R peak delay and RV wall tension (r = 0.55, p = 0.01). The L-R delay in T\(_{\text{peak}}\) was related to leftward septal curvature (p < 0.05), and was negatively related to LVEDV (r = 0.50, p = 0.02, Figure 6) and RV stroke volume (r = 0.49, p = 0.023), as shown in Table 4.

**Figure 4**: Timing parameters presented by mean values and standard deviations (error bars). L, R and S denote left ventricle, right ventricle and septum, respectively. T\(_{\text{onset}}\) and T\(_{\text{peak}}\) are onset and peak times of circumferential shortening. The time of maximal leftward septal bowing (T\(_{\text{LVsb}}\)) coincides with T\(_{\text{peak}}\). T\(_{\text{aortcl}}\) and T\(_{\text{pulmcl}}\) are the closing times of aortic and pulmonary valves.
### Table 2. Results of timing parameters in 21 patients and 11 healthy control subjects

<table>
<thead>
<tr>
<th>Timing parameter (ms)</th>
<th>Abbreviation</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between two ECG R-waves</td>
<td>RR</td>
<td>770 ± 142</td>
<td>989 ± 129</td>
</tr>
<tr>
<td>Time to onset of shortening of LV free wall</td>
<td>TonsetLV</td>
<td>51 ± 23</td>
<td>29 ± 25</td>
</tr>
<tr>
<td>Time to onset of shortening of RV free wall</td>
<td>TonsetRV</td>
<td>52 ± 22</td>
<td>44 ± 32</td>
</tr>
<tr>
<td>Time to onset of shortening of septum</td>
<td>TonsetS</td>
<td>65 ± 4</td>
<td>54 ± 23</td>
</tr>
<tr>
<td>Time to peak of shortening of LV free wall</td>
<td>TpeakLV</td>
<td>293 ± 58</td>
<td>386 ± 68</td>
</tr>
<tr>
<td>Time to peak of shortening of RV free wall</td>
<td>TpeakRV</td>
<td>387 ± 50</td>
<td>350 ± 55</td>
</tr>
<tr>
<td>Time to peak shortening of septum</td>
<td>TpeakS</td>
<td>267 ± 22</td>
<td>339 ± 37</td>
</tr>
<tr>
<td>Time to overstretch of septum</td>
<td>TstretchS</td>
<td>410 ± 16</td>
<td>not observed</td>
</tr>
<tr>
<td>Time to leftward ventricular septal bowing</td>
<td>Tlvsb</td>
<td>395 ± 45</td>
<td>not observed</td>
</tr>
<tr>
<td>Time to pulmonary valve closure</td>
<td>Tpulmcl</td>
<td>328 ± 36</td>
<td>375 ± 36</td>
</tr>
<tr>
<td>Time to aortic valve closure</td>
<td>Taortacl</td>
<td>311 ± 29</td>
<td>354 ± 16</td>
</tr>
</tbody>
</table>

### Table 3. Two-samples t-tests (2-tailed) between timing parameters of the patients

<table>
<thead>
<tr>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Difference (ms)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TonsetLV</td>
<td>TonsetRV</td>
<td>-1 ± 16</td>
<td>0.84</td>
</tr>
<tr>
<td>TonsetLV</td>
<td>TonsetS</td>
<td>-4 ± 16</td>
<td>0.48</td>
</tr>
<tr>
<td>TpeakLV</td>
<td>TpeakRV</td>
<td>-94 ± 41</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>TpeakLV</td>
<td>TpeakS</td>
<td>38 ± 27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tlvsb</td>
<td>TpeakRV</td>
<td>8 ± 34</td>
<td>0.60</td>
</tr>
<tr>
<td>TstretchS</td>
<td>TpeakRV</td>
<td>-1 ± 28</td>
<td>0.93</td>
</tr>
<tr>
<td>Tpulmcl</td>
<td>TpeakRV</td>
<td>-59 ± 40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Taortacl</td>
<td>TpeakLV</td>
<td>14 ± 46</td>
<td>0.25</td>
</tr>
<tr>
<td>Taortacl</td>
<td>Tpulmcl</td>
<td>-17 ± 23</td>
<td>0.08</td>
</tr>
</tbody>
</table>

S stands for the septum. Tonset and Tpeak are onset and peak times of circumferential shortening. Tlvsb is time of maximal LVSB. Taortacl and Tpulmcl are the closure times of aortic and pulmonary valves. In the healthy control subjects, not any of the above t-tests resulted in a significant difference.

### Table 4. Results of linear regression analysis.

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variable</th>
<th>p</th>
<th>r</th>
<th>slope</th>
<th>intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>(T_{onset}RV-T_{onset}LV)/RR</td>
<td>QRS width (ms)</td>
<td>0.99</td>
<td>0.1</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>(T_{onset}RV-T_{onset}LV)/RR</td>
<td>QRS width (ms)</td>
<td>0.65</td>
<td>0.1</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>(T_{peak}RV-T_{peak}LV)/RR</td>
<td>sPap (mmHg)</td>
<td>0.11</td>
<td>0.36</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>(T_{peak}RV-T_{peak}LV)/RR</td>
<td>RV wall tension (mmHg.cm.m^{-2})</td>
<td>0.018</td>
<td>0.51</td>
<td>0.123</td>
<td>1.99</td>
</tr>
<tr>
<td>curvature (cm^{-2})</td>
<td>(T_{peak}RV-T_{peak}LV)/RR</td>
<td>0.03</td>
<td>0.64</td>
<td>0.73</td>
<td>0.05</td>
</tr>
<tr>
<td>SV (ml/m^2)</td>
<td>(T_{peak}RV-T_{peak}LV)/RR</td>
<td>0.0053</td>
<td>0.59</td>
<td>-1.69</td>
<td>74.7</td>
</tr>
<tr>
<td>LVEDV (ml/m^2)</td>
<td>(T_{peak}RV-T_{peak}LV)/RR</td>
<td>0.02</td>
<td>0.50</td>
<td>-2.13</td>
<td>132.4</td>
</tr>
</tbody>
</table>

RR is the ECG-derived time interval between 2 heartbeats. n.s. is non-significant. The large p values and low r values for the relations versus QRS width, mean that the QRS width is not related to the L-R asynchrony in mechanical timing.
Regional analysis
For the subset of 9 patients with base, mid and apical coverage, the L-R difference in $T_{peak}$ was 85 ± 35 ms, 110 ± 51 ms, and 48 ± 57 ms at basal, mid and apical levels respectively. The effect of the level was not significant. Also, the $T_{peak}$ was measured in the RV anterior, RV lateral and RV inferior subregions; no effect of these subregions was found.

Reader agreement
The interobserver variation in the $T_{peak}$ of the RV was given by a correlation coefficient of 0.88 with $p < 0.001$, and a bias of -5 ms with 95% confidence limits of agreement of -47 and +37 ms respectively.

Discussion
The results showed that in PAH there is a 94 ms L-R delay in $T_{peak}$ shortening, which is caused by lengthening of the duration of RV shortening rather than a delay in the onset of RV shortening.

Cause of L-R asynchrony in $T_{peak}$
Because the L-R peak delay was not related to a L-R onset delay, neither with the QRS width, it is unlikely that electrical conduction delay would be the only dominant factor responsible for the L-R peak delay. Instead, the mechanism of the prolonged RV systole in PAH is probably the increased RV wall tension as shown by the correlation between L-R peak delay and RV wall tension.

![Figure 5: Linear regression between the L-R delay in $T_{peak}$ normalized for the R to R interval as dependent variable, and the RV wall tension.](image-url)
Chapter 5

(Figure 5). This mechanism is supported by measurements in rat cardiac trabeculae which provided evidence that an increased load leads to a reduction in the velocity of shortening and prolonged shortening of myocytes (17).

**Leftward Ventricular Septal Bowing**

The mechanism of LVSB is now better documented: maximal LVSB coincides with peak RV shortening and overstretch of the septal wall. Thus it is unlikely that there is compression of the septum, as suggested earlier (5). The overstretch indicates that LVSB is a result of higher pressure in the RV than in the LV, due to the ongoing shortening in the RV free wall whereas the LV free wall is already in its relaxation phase.

**Impaired RV systole**

The observed RVSV (53 ± 19 ml) is lower than normal reference values of 88 ± 19 ml (18), and showed a negative correlation with the L-R peak delay. This effect of the L-R peak delay can be explained: Due to the mechanical asynchrony between the RV free wall and the septum, RV contraction is very inefficient in its late phase. As shown in the results, the T\textsubscript{peak} of the RV free wall is 120 ms after the T\textsubscript{peak} of the septum, and when finally the RV free wall reaches its peak shortening, the septum is shifted to the left. The observation that the T\textsubscript{peak} RV is 59 ms later than closing of the pulmonary valves (post-systolic shortening) further illustrates the inefficiency of this last part of RV myocardial shortening. The effective systole of the RV is estimated to begin at the onset of RV shortening (mean 52 ms) and to run till pulmonary valve closure (mean 328 ms), thereby taking 276 ms. With 59 ms post-systolic shortening, total RV shortening time is 335 ms and thus (59/335)*100% = 18% of total RV shortening time is wasted and energy

![](figure6.png)

*Figure 6: Linear regression between LVEDV as dependent variable, versus the L-R delay in T\textsubscript{peak} normalized for the R to R interval.*
Interventricular mechanical asynchrony in pulmonary arterial hypertension

is dissipated in the non-functional LVSB. Thus the observed L-R asynchrony in PAH can be considered as an independent factor that has a negative effect on RVSV. This is in line with earlier Doppler-echo observations showing that RV dyssynchrony is related to RV dysfunction in PAH (10;11;19), and also in line with the architectural disadvantage of a leftward bowed septum (20).

In principle the loss of RV forward stroke volume might also be caused by tricuspid regurgitation. However we found no significant difference between the RVSV derived from (RVEDV - RVESV), and the RVSV derived from forward flow. This indicates that the volumetric contribution of tricuspid regurgitation to the loss of forward flow was minor.

Impaired LV diastole
As mentioned in the results, the L-R delay in T_peak predicted leftward septal curvature, and thereby had a negative effect on LVEDV. The negative relation between LVSB and LV filling was shown earlier in larger patient groups (7;12). This is confirmed in the present study, where the septum bowed maximally to the left at 395 ms, while the aortic valves have already been closed at 311 ms. The observed negative association between L-R delay in T_peak and LVEDV supports the concept that the L-R asynchrony plays a key role in LV filling impairment. The impaired LV filling and the ineffective RV systolic function both contribute to the loss of stroke volume, as displayed in the flowchart in Figure 7.

The measured values of LVEDV were shown to be smaller than the healthy control values. Also the observed LV free wall peak shortening was smaller than in the healthy control subjects. This is well explained by the Frank-Starling effect: the LV myocardial muscle fibers are not stretched to their optimal length and thus are not able to perform their optimal shortening. The underfilled LV further contributes to the leftward septal bowing and inefficient RV systole. In addition, Gurudevan et al. (2007) evaluated several different indicators of LV filling, and showed that the LV underfilling is in large part responsible for the impaired LV relaxation pattern (21).

Practical implications
In clinical practice, understanding the meaning of LVSB is relevant because it is much easier to measure than the strain-derived properties of LV, RV and septal wall. LVSB can directly be measured and timed from MRI cine imaging (9) or from echocardiography. This easily obtained timing of maximal LVSB coincides with the RV time to peak shortening. The time to LV peak circumferential shortening can be estimated by the time of aortic valve closure. Thus the L-R delay in peak shortening can be estimated from the time interval between aortic valve closure and LVSB. This provides an easy measure to follow individual PAH patients during treatment, also when MRI is not available.

Another potential implication can be derived from the key role that the L-R delay in peak shortening plays in the loss of LV and RV performance. Although conduction delay is not the cause of the L-R mechanical delay, the mechanical synchrony between the LV and RV may be
improved by earlier electrical activation of the RV free wall with pacing. This early activation will shift the RV contraction period to an earlier time in the cardiac cycle, and possibly also shorten it. Both effects may reduce RV post-systolic shortening, thereby improving both the RV efficiency and LV filling. However this has not been proven. Whether this might be an effective approach to improve cardiac function in PAH must be tested first in animals, before it might be considered in patients.

**Limitations**

The role of electrical conduction delay was indirectly estimated from the ECG-QRS width and the onset times of shortening. The true role of conduction delay still needs more exploration. The RV load was estimated by the wall tension. The assumption that the RV in PAH can be described by a sphere needs confirmation. The estimation may be improved by taking the wall thickness into account in order to calculate wall stress. However the RV wall thickness is difficult to define due to its trabeculated endocardial border.
Conclusion
In PAH, no L-R delay was observed in the onset times of shortening, while a large L-R delay was observed in the times to peak shortening. Thus the L-R delay in myocardial peak shortening is caused by prolonged RV shortening. An increased RV wall tension, rather than electrical conduction delay, is related to this interventricular mechanical asynchrony. As wall tension is the product of pressure and radius, it means in practice that those PAH patients with an increased RV pressure combined with an enlarged RV volume will have increased RV wall tension and thereby more L-R mechanical asynchrony in $T_{\text{peak}}$. This asynchrony is associated with leftward septal bowing, LV underfilling and decreased RV stroke volume.
Chapter 5

References


Chapter 6

The atrium compensates for impaired right ventricular function in pulmonary hypertension


Submitted
Abstract

Objective: To investigate the function of the right atrium in relation to right ventricular structure and function in pulmonary hypertension.

Methods and results: MRI measured structure and function of the right atrium and ventricle in 14 pulmonary hypertension patients and 11 controls. Reservoir volume defines right atrial blood inflow with the tricuspid valve closed, and conduit volume the blood inflow with the tricuspid valve open. Conduit-to reservoir volume ratio quantified right atrial function. Compared to controls, patients had larger right atria (42 [31-55] vs. 25 [17-30] ml/m$^2$, $p = 0.001$), comparable reservoir volume (27 [20-30] vs. 25 [21-28] ml/m$^2$, $p = 0.792$), and decreased conduit volume (4 [2-9] vs. 13 [10-18] ml/m$^2$, $p = 0.003$). In PH conduit-to-reservoir volume ratio is reduced (0.14 [0.08-0.92] vs. 0.61 [0.39-0.72], $p = 0.002$), and atrial contractile function is enhanced (43 [33-63] vs. 27 [18-29] %, $p=0.002$). In patients, right atrial maximum volume was related to right ventricular end-diastolic volume index ($r = 0.63$, $p = 0.022$). Conduit-to-reservoir volume ratio was related to right ventricular ejection fraction ($r = -0.71$, $p = 0.005$), and inversely related to right ventricular isovolumic relaxation function ($r = -0.63$, $p = 0.015$) Conclusion: In pulmonary hypertension, the right atrium is larger, conduit-to reservoir volume ratio smaller and atrial contractile function is enhanced, probably as a result of a compensatory mechanism for impaired right ventricular diastolic and systolic function.
The atrium compensates for impaired right ventricular function in pulmonary hypertension

Introduction
The right atrium (RA) transfers a large amount of volume to the right ventricle (RV) at low pressures. Different volumes can describe RA function. 1) Reservoir volume, i.e. the blood flow into the right atrium during ventricular systole with the tricuspid valve closed. 2) Conduit volume, i.e. the amount of blood that directly flows from the veins into the ventricle. In general, global RA function can be quantified by the ratio of conduit-to-reservoir volume ratio (1-3). Left atrial function is an important determinant of left ventricular function in left heart disease and can affect cardiac performance(4;5). It has been shown that impaired left ventricular relaxation reduces conduit volume(4), leading to left atrial dilatation and augmentation of contractile function.(6) In pulmonary hypertension (PH) increased afterload affects the RV, which results in hypertrophy, and impaired RV diastolic function.(7) Recently, the animal studies by Gaynor et al. demonstrated the adaptive capacity of the RA (1;2) in response to RV pressure overload. Where previous research in PH patients focused on the RV, the RA, (8) or the predictive value of either, (9;10) no studies have investigated the combined pathophysiology of both right heart chambers in PH patients. Thus, whether RA volumes and function are related to RV hypertrophy, dilatation and function is not clear in PH patients. To be able to elucidate the adaptive capacity of the RA in PH patients, merely omitting the use of geometrical assumptions, measurements of RA volumes by magnetic resonance imaging is a prerequisite.

The aim of the present MRI study was to compare RA volumes and function of PH patients with controls, and to investigate the relation of RA maximum volume and function with RV structure and function.

Methods

Study design
A total of 14 PH patients and 11 healthy controls were studied. All patients had a mean pulmonary artery pressure > 25 mmHg, pulmonary capillary wedge pressure < 15 mmHg at right heart catheterization and normal systemic blood pressure. PH due to left sided heart diseases, interstitial lung disease or hypoxemia, was excluded by further diagnostic work-up (echocardiography, high resolution CT-scan and lung function test) following the 2003 Venice consensus guidelines on the diagnosis and treatment of pulmonary arterial hypertension.(11) The different etiologies of PH were distributed as follows, idiopathic pulmonary arterial hypertension (n = 6), pulmonary arterial hypertension related to the limited type of systemic sclerosis (n = 4), and PH due to chronic thrombo-embolic disease (n = 4). The study was approved by the Institutional Review Board on Research Involving Human Subjects of the VU University Medical Center, Amsterdam, the Netherlands. Written informed consent was obtained from all patients and controls.

MRI measurements
All patients and controls underwent an MRI-scan. Measurements were performed on a Siemens 1.5T Sonata scanner (Siemens Medical Solutions, Erlangen, Germany), using a six-element phased
array cardiac receiver coil, according to the MRI protocol described previously.(12) Perpendicular to the four-chamber view at end-diastole, a stack of consecutive short-axis breath hold cine images was acquired, using the LV two-chamber as a second localizer. Image parameters were: Temporal resolution of 34 ms, echo time of 1.6 ms, an image resolution of 280 x 340 mm and a slice thickness of 10 mm. From the stack of parallel short-axis cine images, quantitative analysis of volumes and geometry was performed by manually drawing of endocardial and epicardial borders on each slice, using the MR Analytical Software System (Medis, Leiden, the Netherlands). Endocardial contours were drawn on the diastolic images. RA minimal and maximal volumes and RV end-diastolic volume were obtained by the sum of the endocardial areas multiplied by slice thickness. The epicardial contour was drawn to assess RV wall volume. The value was multiplied by 1.05 g/ml, specific gravity of muscle, to obtain myocardial mass. Figure 1 shows the four-chamber view of a patient (A-B). The lines indicate the image planes at which atrial cine images were acquired (C-D).

**Definition of right atrial structure and function**

Figure 2A shows an example of RV and RA volume during the cardiac cycle in a PH patient. *Right atrial minimum volume* (RA_{min}) occurs at end-diastole preceding tricuspid valve closing.

---

**Figure 1.** Abbreviations: RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle; Ao = aorta; MPA = pulmonary artery. Top panels (A-B) show an MRI four-chamber view of a patient acquired at end-diastole and end-systole. The lines indicate the image planes at which atrial cine images were acquired. The lower panels (C-D) show an MRI mid-atrial cine image at end-diastole and end-systole. Note that both RA and LA area is increased at end-systole shown in B and D when compared to A and C.
Right atrial maximum volume (RA_{max}) occurs at end-systole preceding pulmonary valve closing. Reservoir volume is defined as the blood flow into the RA with the tricuspid valve closed. Conduit volume defines the blood that flows into the RA and directly into the RV. Because tricuspid insufficiency might have a significant effect on measurements of reservoir and conduit volumes, direct measurements of inferior and superior vena cava flow were used to assess reservoir and conduit volumes (Figure 2B). The area under the curve during systole represents reservoir volume, while the area under the curve during diastole corresponds to conduit volume. RA function was defined as the ratio of conduit-to-reservoir volume ratio. RA contractile function was defined as the difference between RA pre-contractile volume and RA_{min}, expressed as a percentage of stroke volume. If backflow was observed in the vena cavae during atrial contraction, RA contractile function was calculated as follows: 100* (RA pre-contractile volume - RA_{min} - backflow volume)/stroke volume.

Catheterization
Diagnostic right heart catheterization was performed with a balloon tipped, flow directed 7F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp; Irvine, CA). The patient was in a stable condition lying supine and breathing room air. Right atrial, right ventricular, pulmonary artery and pulmonary capillary wedge pressures were measured. Blood was sampled, with the catheter positioned in the main pulmonary artery. Arterial oxygen saturation was measured from blood sampled from the radial or femoral artery. Cardiac output was assessed by the Fick method and pulmonary vascular resistance was calculated using the formula: (mPap-Pcwp)/cardiac output, where mPap is the mean pulmonary artery pressure and Pcwp is the pulmonary capillary wedge pressure.

Figure 2. (A) Right ventricular (RV) and right atrial volume curve (RA) of a PH patient (mPap = 32 mmHg). The graph starts at end-diastole (ED), which corresponds with minimum right atrial volume. End-systole (ES) corresponds to maximum right atrial volume. Pre-contractile volume (PCV) corresponds to the volume prior to atrial contraction. (B) Flow measurements in the vena cava inferior (VCI) and vena cava superior (VCS) to assess right atrial reservoir and conduit volumes accurately in patients. The area under the curves displays volume throughout the cardiac cycle.
**Data analysis**

SPSS 12.0 (SPSS, Chicago IL) was used for statistical analyses and \( p < 0.05 \) was considered statistically significant. Results are reported as median and interquartile range, unless otherwise indicated. Mann-Whitney test was performed for comparison of continuous values between controls and patients. Pearson's correlation test was used to assess significant correlations between RA structure and function with parameters of RV structure and function.

**Results**

The PH patients had an average age of 46±14 years and a male to female ratio of 6/8. The controls had an average age of 43±12 years and a male to female ratio of 4/7.

Table 1 summarizes the functional status of the patients and the hemodynamic data obtained at right heart catheterization. The hemodynamic data yielded characteristics of RV pressure overload. RA volumes of PH patients and controls are shown in Figure 3.

PH patients had a dilated RA, as shown by larger minimal (PH patients: 42 [31-55] vs. control: 25 [17-30] ml/m\(^2\), \( p = 0.001 \)) and maximal (PH patients: 75 [53-85] vs. control: 52 [43-54] ml/m\(^2\), \( p = 0.001 \)) RA volumes. Reservoir volume was not different between PH patients and controls (PH patients: 27 [20-30] vs. control: 25 [21-28] ml/m\(^2\), \( p = 0.792 \)). Conduit volume was significantly decreased (PH patients: 4 [2-9] vs. control: 13 [10-18] ml/m\(^2\), \( p = 0.003 \)). Conduit-to-reservoir volume ratio was decreased in PH patients, consequently (PH patients: 0.14 [0.08-0.92] vs. control: 0.61 [0.39-0.72], \( p = 0.002 \)). RA contractile function was augmented in PH patients when compared to controls (PH patients: 43 [33-63] vs. controls: 27 [18-29] \%, \( p = 0.002 \)). Table 2 summarizes RV characteristics of PH patients and controls and shows that PH patients had dilated

<table>
<thead>
<tr>
<th>Table 1. Patients characteristics and hemodynamic data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic variables:</strong></td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td><strong>Functional status:</strong></td>
</tr>
<tr>
<td>NYHA (II:III:IV)</td>
</tr>
<tr>
<td>6 min walk distance (m)</td>
</tr>
<tr>
<td><strong>Hemodynamic variables:</strong></td>
</tr>
<tr>
<td>Pra (mmHg)</td>
</tr>
<tr>
<td>dPrv (mmHg)</td>
</tr>
<tr>
<td>sPrv (mmHg)</td>
</tr>
<tr>
<td>mPap (mmHg)</td>
</tr>
<tr>
<td>Pcwp (mmHg)</td>
</tr>
<tr>
<td>SvO(_2) (%)</td>
</tr>
<tr>
<td>CO (l/min)</td>
</tr>
<tr>
<td>PVR (dyn⋅s⋅cm(^{-2}))</td>
</tr>
<tr>
<td>HR (min(^{-1}))</td>
</tr>
</tbody>
</table>

NYHA = New York heart association class; Pra = mean right atrial pressure; dPrv = right ventricular diastolic pressure; sPrv = right ventricular systolic pressure; mPap = mean pulmonary artery pressure; Pcwp = pulmonary capillary wedge pressure; SvO\(_2\) = mixed venous oxygen saturation; CO = cardiac output; PVR= pulmonary vascular resistance; HR = heart rate.
The atrium compensates for impaired right ventricular function in pulmonary hypertension.

Correlation analyses showed that RA maximum volume was not related to RVMI (\(r = 0.19, \ p = 0.53\)) but significantly related to RVEDVI (\(r = 0.63, \ p = 0.022\)). Furthermore, RA conduit-to-reservoir volume ratio was inversely related to RV isovolumic relaxation time (\(r = -0.63, \ p = 0.05\)) and related to RV ejection fraction (\(r = 0.7, \ p = 0.005\)), as is illustrated in Figure 4.

Discussion

In this study MRI measured RA volumes and function. In comparison with controls the RA in PH patients was larger and RA conduit volume was decreased. Since RA reservoir volume was not significantly different between PH patients and controls, decreased RA conduit-to-reservoir volume ratio results. There was a significant contribution of RA contraction to RV filling when compared to controls. Furthermore, RA dilatation was associated to RV dilatation, and RA conduit-to-reservoir volume ratio was inversely related to RV diastolic function, and related to RV systolic function.

Table 2. Comparison of MRI data of controls and PH patients

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 11)</th>
<th>PH (n = 14)</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDVI (ml/m(^2))</td>
<td>76 [61-89]</td>
<td>90 [69-117]</td>
<td>0.033</td>
</tr>
<tr>
<td>SVI (ml/m(^2))</td>
<td>37 [35-40]</td>
<td>28 [25-34]</td>
<td>0.019</td>
</tr>
<tr>
<td>Mass (g/m(^3))</td>
<td>24 [20-30]</td>
<td>42 [36-63]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVRT (%)</td>
<td>5 [3-9](^*)</td>
<td>16 [9-20]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF (%)</td>
<td>52 [45-57]</td>
<td>31 [25-43]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Definition of abbreviations: EDVI = end-diastolic volume index; SVI = stroke volume index; Mass = mass index; IVRT = isovolumic relaxation time as percentage of ECG RR-interval; EF = ejection fraction. \(^*\) Assessed in 5 controls.
Chapter 6

Right atrial dilatation

RA dilatation is one of the hallmarks on echocardiography in PH and has shown to be prognostic in idiopathic pulmonary arterial hypertension patients.(9) In this study RA dilatation, as quantified by MRI measured $R_{\text{A, max}}$ volume, was present in all PH patients when compared to the controls. In general, the physiological response to increased ventricular afterload is myocardial hypertrophy,(3) which is associated with reduced ventricular compliance and diastolic dysfunction.(4) In addition, increased ventricular afterload might also affect diastolic function.(5) In patients with systemic hypertension left ventricular wall thickness was associated with left atrial dilatation.(6) In the present study there was no relation between RA size and RV myocardial mass. This finding might suggest that increased ventricular afterload was the main determinant of RV diastolic dysfunction and thus RA dilatation in the present study. The latter is supported by previous research in patients with PH due to large vessel thromboembolic occlusion.(7;8) These studies showed that an acute reduction in RV afterload after thrombo endarterectomy was associated with a decrease of RV and RA dimensions. The relation between $R_{\text{A, max}}$ and RVEDVI in the present study is in agreement with the findings by Ditttrich (17) and Mahmud (18) that changes in afterload affect both RV and RA dimensions. Furthermore, the presence of tricuspid regurgitation might potentially cause RA dilatation. Although we did not investigate the influence of tricuspid regurgitation on RA size, the relation of $R_{\text{A, max}}$ and RVEDVI suggests an effect of tricuspid regurgitation on RA size, since the greater prevalence of tricuspid regurgitation in dilated right ventricles. Thus RA dilatation in PH patients might be the result of increased right ventricular afterload associated diastolic dysfunction and tricuspid regurgitation.

Increased RA size on echocardiography has shown to predict worse prognosis in PH patients.(9) For the left atrium measurements of volumes have shown to be superior for prediction of

![Figure 4](image.png)

**Figure 4.** Correlation of right atrial conduit-to-reservoir ratio (C/R) with right ventricular isovolumic relaxation time expressed as a percentage of the ECG RR-interval (Top), and right ventricular ejection fraction (Bottom) in pulmonary hypertension patients ($n = 14$).
The atrium compensates for impaired right ventricular function in pulmonary hypertension

cardiovascular outcome. (19) Future studies should investigate, whether the same holds for RA volume in PH patients, which can also be assessed by echocardiography.

Proposed mechanism of right atrial adaptation
Information on pathophysiological changes of the RA in PH patients is scarce. Chronically increased RV afterload affects RV relaxation and filling. (20-22) Hence, the RA should compensate to maintain RV filling. We found no difference in reservoir volume between patients and controls. Since conduit-to-reservoir volume ratio was inversely related to isovolumic relaxation, decreased RA conduit volume can be attributed to RV diastolic dysfunction. This finding is in agreement with experimental research on the RA in relation to RV pressure overload and studies on the left atrium. (1;2;4) Because of the smaller conduit volume, RV filling is more dependent upon RA contractile function in PH patients.

For the left atrium it has been shown that reservoir volume is determined by 1) elastic recoil of the atrium after contraction, and 2) by the suction effect caused by left ventricular base systolic descent during ventricular contraction. (3) Since RV systolic function was impaired, tricuspid annular plane descent might have been diminished and reservoir volume is presumably preserved by the atrial contraction associated elastic recoil. The latter may suggest the presence of increased RA distensibility in PH patients, which was not investigated in the present study, but is supported by previous experimental work on the right atrium. (2)

Both RV diastolic and systolic function are related to RA function. This suggests that the adaptive capacity of the RA tries to maintain filling of the RV and preserve RV systolic function. The relation between isovolumic relaxation time and RA function might be explained by the influence of impaired relaxation on conduit volume. The inversed relation between RA conduit-to-reservoir volume ratio and RV ejection fraction implies that due to decreased conduit volume, reservoir volume, and thus RA contractile function, is more important for RV filling and systolic function. However, both reservoir and conduit volume are determined by systolic ventricular contraction and ventricular elastic recoil. (3) Even in the absence of an atrio-ventricular pressure gradient, diastolic ventricular suction contributes to ventricular filling. (23) Other studies have shown that impaired ventricular contraction is associated with diminished elastic recoil and ventricular diastolic suction consequently. (24-26) Similar pathophysiological mechanisms may hold for the RV, since diastolic suction has been identified in the human RV (27) and has been confirmed in an elegant animal study by Sun et al (28). This complex interplay of RA and RV function underscores the importance of global right heart function in PH patients.

Limitations
In this study we measured RA pressures during right heart catheterization. Although we would have been able to calculate RA distensibility in the patients, the lack of normal values and interventions that influence distensibility, made us decide to use only the MRI data.

RA reservoir volume was probably underestimated in all subjects, because we did not measure coronary sinus flow. In the present study RA volumes defined structure and function. When
compared to echocardiography, MRI might be more accurate with respect to atrial volume measurements (29), but echocardiography remains a practical tool. We are aware of the small sample size. Despite this limitation we think our data shows the important role of the RA in PH patients. The prognostic value of RA volume and function can only be investigated in a larger study group, and should be compared to other prognostic MRI parameters. (10)

**Conclusion**

In PH patients the RA adapts to structural and functional change of the RV. The predominant structural change of the RA in PH patients is dilatation. The function of the RA is to compensate impaired ventricular filling and preserve systolic function.
The atrium compensates for impaired right ventricular function in pulmonary hypertension

References


The atrium compensates for impaired right ventricular function in pulmonary hypertension
Non-invasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension


Chest 2007 Dec; 132(6): 1906-12
Abstract

Aims: Decreased total compliance of the pulmonary vascular bed is associated with increased mortality in pulmonary arterial hypertension (PAH). We investigated whether proximal pulmonary artery stiffness, in terms of area distensibility ($\Delta A/\Delta P\cdot A$) and non-invasively assessed relative area change (RAC) calculated as $\Delta A/A$, predicts mortality in PAH. Methods and Results: Eighty-six subjects underwent right heart catheterization and an MRI-scan to assess area distensibility and RAC. Patients were followed up to 48 months. Kaplan-Meier plot and Cox proportional hazards regression analyses assessed the predictive value of area distensibility and RAC. In 70 patients, the diagnosis PAH was confirmed and 16 subjects served as controls. In comparison with controls, proximal pulmonary arteries of patients were distended (685±214 vs. 411±153 mm$^2$, $p<0.001$), less distensible ($\Delta A/\Delta P\cdot A$: 0.46±0.38$\cdot 10^{-2}$ mmHg$^{-1}$ vs. 3.69±1.96$\cdot 10^{-2}$ mmHg$^{-1}$, $p<0.0001$), and RAC was smaller (20±0 vs. 58±21 %, $p<0.0001$). RAC showed an inverse curvilinear relation with mean pulmonary artery pressure ($R^2 = 0.47$). Eighteen patients (26%) died because of cardiopulmonary causes. Patients with a pulmonary artery RAC $\leq$ 16% had a worse prognosis than those with a value $>$16% (log-rank, $p<0.001$). The RAC predicted mortality better than area distensibility. Conclusion: Non-invasively measured pulmonary artery RAC, predicts mortality in PAH.
Introduction
The pulmonary circulation is a low-pressure, low-resistance and highly distensible system.
Recently, the work by Mahapatra et al. has shown that total compliance of the pulmonary vascular bed, defined as the ratio of stroke volume and pulse pressure, predicts mortality in pulmonary arterial hypertension (PAH) (1,2). A large part of total vascular bed compliance is located in the proximal arterial branches (3). Therefore, the predictive value of pulmonary vascular bed compliance in chronic PAH also pertains to increased stiffness of the proximal pulmonary artery. PAH is a disease of the small distal pulmonary arteries, characterized by vascular narrowing leading to a rise in pulmonary vascular resistance and, as a result pulmonary artery pressure. Increased pressure causes distension and stiffening of the proximal pulmonary artery (4-6), and might also result in vessel wall remodeling (7), which on itself may influence stiffness. Thus both, pressure and changes in the vessel wall, contribute to proximal pulmonary artery stiffening.

Vessel wall stiffness (β) can be calculated from the equation proposed by Hayashi (8) and Kawasaki (9); \[ \beta = \left[ \ln \left( \frac{P_s}{P_d} \right) \right] / \left( 2 \Delta A/A \right), \] where \( P_s \) and \( P_d \) is the ratio of systolic and diastolic pressure, and \( \Delta A/A \) is the relative cross-sectional area change of the vessel. In addition, previous research has shown a strong linear relation between \( P_s \) and \( P_d \) across a wide range of pulmonary artery pressures (10). This implies that the ratio \( P_s/P_d \) is constant, so that \( \Delta A/A \), the Relative Area Change (RAC) is inversely proportional to the stiffness constant \( \beta \), and represents pulmonary artery elasticity. The RAC, (maximum area – minimum area)/ minimum area, can be obtained non-invasively (e.g., by MRI) (11-14). These studies have shown that in pulmonary hypertension RAC is decreased, but whether this MRI measure predicts mortality in PAH has not been investigated. Therefore we studied whether this non-invasive MRI measure of pulmonary artery stiffness is able to predict mortality in PAH.

Methods
Patient selection
All patients referred to our institute for the evaluation and treatment of PAH in the period from September 2001 to September 2005 were considered for enrollment in to this study. The diagnosis of PAH was assessed according to the 2003 Venice consensus guidelines on the diagnosis and treatment of PAH (15). All persons underwent an MRI scan of the heart and large pulmonary vessels within one week of initial right heart catheterization. The selection of patients depended upon whether the diagnosis of PAH could be confirmed and the ability to perform an MRI scan. Patients with evidence of left sided heart disease on echocardiography or increased wedge pressure, interstitial lung disease or chronic thrombo-embolic pulmonary hypertension were excluded from the study. Individuals with a mean pulmonary artery pressure < 25 mmHg during right heart catheterization and without any evidence of congenital heart disease were regarded as controls. We assessed outcomes through chart review and computerized search of the institutional pulmonary hypertension database. Since all patients are under treatment and
monitored in our institution there was a 100% follow-up. The Institutional Review Board on Research Involving Human Subjects of the VU University Medical Center approved this study. Written informed consent was obtained from all subjects.

**MRI measurements**

The MR images were acquired with a 1.5 T Siemens Sonata whole body system (Siemens Medical Solutions, Erlangen, Germany), equipped with a circularly polarized phased-array body coil. The image plane for measuring relative area change was chosen orthogonal in the middle of the relatively straight right pulmonary artery (Figure 1A). Cine imaging of the right pulmonary artery cross-section (Figure B and C) was performed with a steady state free precession sequence. With this sequence, the contrast between blood and the vessel wall is mainly dependent on the
Non-invasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension

tissue to blood $T_1/T_2$ ratio. On the MR cine images the vessel cross-section can accurately be delineated through all phases of the cardiac cycle (Figure 1 B and C) and was obtained by manual delineation of the vessel wall in Medis Flow (Medis, Leiden, The Netherlands).

**Cardiac catheterization**
Diagnostic right heart catheterization was performed with a balloon tipped, flow directed 7F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp; Irvine, CA). The patient was in a stable condition, lying supine and breathing room air. Right atrial, right ventricular, pulmonary artery and pulmonary capillary wedge pressures were measured. Blood was sampled, with the catheter positioned in the main pulmonary artery. Arterial oxygen saturation was measured from blood sampled from the radial or femoral artery. Cardiac output was assessed by the Fick method and pulmonary vascular resistance was calculated using the formula: $(mPap-Pcwp)/\text{cardiac output}$, where $mPap$ is the mean pulmonary artery pressure and $Pcwp$ is the pulmonary capillary wedge pressure.

**Measures of pulmonary artery stiffness**
*Total Pulmonary arterial compliance* was calculated as the ratio of stroke volume and pulse pressure $(SV/PP)$, where pulse pressure is calculated as the difference of systolic and diastolic pulmonary artery pressure. *Pulmonary artery area distensibility* was calculated as the ratio of the relative area change and pulse pressure $(\Delta A/A \cdot PP)$. The relative area change $(\Delta A/A)$ is calculated as $(\text{maximum area} - \text{minimum area}) / \text{minimum area}$.

**Data analysis**
SPSS 12.0 (SPSS, Chicago IL) was used for statistical analyses. Results are reported as mean ± SD for descriptive statistics. Student’s $t$-test was used to compare continuous variables between the PAH group and the control group, and between survivors and non-survivors. Linear least-squares analysis was used to fit the relation between RAC and mean pulmonary artery pressure and linear regression analysis was performed to assess the relation between systolic and diastolic pulmonary artery pressure. Survival curves were derived by Kaplan-Meier method. The patients were separated (arbitrarily divided by the median) into two groups. Groups were compared by means of the log-rank test. The interval from initial evaluation until death or four years was regarded as follow-up period. The hazard ratio with 95% confidence interval was calculated using the Cox proportional hazards regression for candidate predictors: i.e. age, six-minute walk distance, right atrial pressure, mean pulmonary artery pressure, pulmonary artery pulse pressure, mixed venous oxygen saturation, cardiac index, pulmonary vascular resistance, area distensibility and RAC. A bivariate model of RAC with the significant predictors of mortality assessed in the univariate Cox analysis was investigated. In addition, the prognostic information of RAC and pulse pressure was analyzed. Receiver-operator curves were constructed based on the sensitivity and specificity for each significant predictor of mortality to predict survival. A $p<0.05$ was considered statistically significant.
Chapter 7

Results

Seventy PAH patients and sixteen subjects without pulmonary hypertension were included in this study. Table 1 summarizes patient characteristics, etiologies and hemodynamics. The majority of patients were female and diagnosed as idiopathic PAH and right heart catheterization data yielded characteristics of right ventricular pressure overload. In the 16 control subjects the diagnosis pulmonary hypertension was excluded by right heart catheterization. The controls appeared to be younger, but this was not statistically significant. Other characteristics and hemodynamics are shown in Table 1. None of these persons had a congenital heart defect.

Table 1. Characteristics and hemodynamic variables according to survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
<th>Survivors</th>
<th>Non-survivors</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>70</td>
<td>52</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Male vs. female</td>
<td>15/55</td>
<td>12/40</td>
<td>3/15</td>
<td>3/16</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50 ± 15</td>
<td>48 ± 14</td>
<td>54 ± 16</td>
<td>41±15</td>
</tr>
<tr>
<td>6 min walk distance (m)</td>
<td>356 ± 140</td>
<td>388 ± 125</td>
<td>253 ± 142^</td>
<td>-</td>
</tr>
<tr>
<td>Etiology:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPAH</td>
<td>49</td>
<td>39</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>16</td>
<td>10</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>HIV</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Other PAH</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Hemodynamics:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pra (mmHg)</td>
<td>8 ± 5</td>
<td>8 ± 4</td>
<td>11 ± 6^</td>
<td>5 ± 2^</td>
</tr>
<tr>
<td>dPrv (mmHg)</td>
<td>11 ± 7</td>
<td>10 ± 7</td>
<td>14 ± 7</td>
<td>4 ± 3^</td>
</tr>
<tr>
<td>sPrv (mmHg)</td>
<td>86 ± 23</td>
<td>87 ± 24</td>
<td>82 ±17</td>
<td>28 ± 9^</td>
</tr>
<tr>
<td>dPap (mmHg)</td>
<td>33 ± 12</td>
<td>32 ± 12</td>
<td>35 ± 12</td>
<td>9 ± 4^</td>
</tr>
<tr>
<td>sPap (mmHg)</td>
<td>84 ± 21</td>
<td>85 ± 23</td>
<td>83 ± 12</td>
<td>24 ± 8^</td>
</tr>
<tr>
<td>mPap (mmHg)</td>
<td>53 ± 14</td>
<td>53 ± 15</td>
<td>54 ± 12</td>
<td>15 ± 5^</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>51 ± 15</td>
<td>52 ± 16</td>
<td>48 ± 12</td>
<td>15 ± 6^</td>
</tr>
<tr>
<td>SvO_2 (%)</td>
<td>62 ± 10</td>
<td>64 ± 9</td>
<td>55 ± 12^</td>
<td>78 ± 10^</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>81 ± 21</td>
<td>79 ± 15</td>
<td>87 ± 12</td>
<td>80 ± 8</td>
</tr>
<tr>
<td>CI (l/min⁻¹·m⁻²)</td>
<td>2.5 ± 0.8</td>
<td>2.6 ± 0.8</td>
<td>2.1 ± 0.8*</td>
<td>4.8 ± 1.7^</td>
</tr>
<tr>
<td>PVR (dyn·s·cm⁻⁵)</td>
<td>923 ± 501</td>
<td>839 ± 455</td>
<td>1228 ± 581*</td>
<td>113 ± 35^</td>
</tr>
<tr>
<td>SV/PP (ml·mmHg⁻¹)</td>
<td>1.25 ± 0.78</td>
<td>1.37 ± 0.86</td>
<td>0.92 ± 0.38*</td>
<td>7.87 ± 2.74^</td>
</tr>
<tr>
<td>Medication:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosentan</td>
<td>36</td>
<td>31</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>18</td>
<td>7</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Remodulin</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Combination</td>
<td>7</td>
<td>7</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Definitions of abbreviations: IPAH = idiopathic pulmonary arterial hypertension; Pra = right atrial pressure; dPrv = diastolic right ventricular pressure; sPrv = systolic right ventricular pressure; dPap = diastolic pulmonary artery pressure; sPap = systolic pulmonary artery pressure mPap = mean pulmonary artery pressure; PP = pulmonary artery pulse pressure; SvO_2 = mixed venous oxygen saturation; HR = heart rate; CI = cardiac index; PVR = pulmonary vascular resistance; SV/PP = pulmonary arterial compliance; Combination = Bosentan and Sildenafil.* p< 0.05, † p< 0.01 (non-survivors vs. survivors); ‡ p< 0.01 (patients vs. controls).
Non-invasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension

Measures of pulmonary artery stiffness

MRI analysis showed that compared to controls maximal (PAH 685±214 vs. controls 411±153 mm², p< 0.001) and minimal (PAH 580±202 vs. controls 262±96 mm², p< 0.001) cross-sectional areas were larger in PAH patients. Figure 2 shows that in the PAH group area distensibility (0.46±0.38·10⁻² vs. 3.69±1.96·10⁻² mmHg⁻¹, p< 0.001) and RAC (20±10 vs. 58±21 %, p< 0.001) were decreased, when compared to controls. The relation between mean pulmonary artery pressure and RAC in controls and patients is inverse and curvilinear (Figure 3). There was a significant relation between systolic and diastolic pulmonary artery pressure r = 0.85, p< 0.001 and best described by y = 0.41x - 1.5.

Figure 2. Average right pulmonary artery area distensibility and relative area change and in controls and pulmonary arterial hypertension (PAH) patients * p< 0.001.

Figure 3. Curvilinear relationship of mean pulmonary artery pressure and relative area change, in the total study group (n = 86).
Chapter 7

Survival analyses

No patients were lost to follow-up. From the 70 PAH patients eighteen (26%) died due to right heart failure and none of the patients died of causes other than cardiopulmonary. The cause of death was ascertained when clinical signs of right heart failure were observed by one of the attending physicians specialized in the treatment of PAH.

Average survival was 6 months (range 0-48). The baseline six-minute walk distance, cardiac index and mixed venous oxygen saturation was significantly lower in non-survivors than in survivors (Table 2). Furthermore, right atrial pressure and pulmonary vascular resistance was higher in the non-survivors (Table 2). In non-survivors maximal (non-survivors; 683±210 vs. survivors; 686±217 mmHg) and minimal (non-survivors; 604±209 vs. survivors; 573±201 mmHg) pulmonary artery cross-sectional area was not different from survivors. RAC was significantly lower when compared with survivors (non-survivors; 15±7 vs. survivors; 21±10 %, p<0.05).

Table 2. Univariate predictors of mortality in PAH patients (n = 70)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95 % CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>1.02</td>
<td>0.99-1.05</td>
<td>0.305</td>
</tr>
<tr>
<td>6 MWD (m)</td>
<td>0.99</td>
<td>0.98-0.99</td>
<td>0.004</td>
</tr>
<tr>
<td>Pra (mmHg)</td>
<td>1.09</td>
<td>1.01-1.18</td>
<td>0.025</td>
</tr>
<tr>
<td>mPap (mmHg)</td>
<td>1.01</td>
<td>0.98-1.04</td>
<td>0.595</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>0.99</td>
<td>0.95-1.02</td>
<td>0.344</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>0.93</td>
<td>0.90-0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI (l·min⁻¹·m⁻²)</td>
<td>0.58</td>
<td>0.15-0.98</td>
<td>0.045</td>
</tr>
<tr>
<td>PVR (dyn·s·cm⁻²)</td>
<td>1.00</td>
<td>1.00-1.02</td>
<td>0.014</td>
</tr>
<tr>
<td>SV/PP (ml·mmHg⁻¹)</td>
<td>0.30</td>
<td>0.10-0.90</td>
<td>0.032</td>
</tr>
<tr>
<td>Area distensibility</td>
<td>0.10</td>
<td>0.07-1.50</td>
<td>0.097</td>
</tr>
<tr>
<td>RAC (%)</td>
<td>0.87</td>
<td>0.79-0.96</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Definition of abbreviations: 6 MWD = six minute walk distance; Pra = right atrial pressure; mPap = mean pulmonary artery pressure; PP = pulmonary artery pulse pressure; SvO₂ = mixed venous oxygen saturation; CI = cardiac index; PVR = pulmonary vascular resistance; SV/PP = pulmonary arterial compliance; RAC = pulmonary artery relative area change.

Table 3. Bivariate predictors of mortality against ∆A/A in PAH patients (n = 70)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio of variable with ∆A/A</th>
<th>p value</th>
<th>Hazard ratio of ∆A/A with variable</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 MWD</td>
<td>0.99 [0.98-1.00]</td>
<td>0.028</td>
<td>0.92 [0.82-1.02]</td>
<td>0.124</td>
</tr>
<tr>
<td>Pra</td>
<td>1.07 [0.98-1.17]</td>
<td>0.115</td>
<td>0.90 [0.81-0.99]</td>
<td>0.027</td>
</tr>
<tr>
<td>SvO₂</td>
<td>0.95 [0.91-0.93]</td>
<td>0.011</td>
<td>0.92 [0.82-1.02]</td>
<td>0.102</td>
</tr>
<tr>
<td>CI</td>
<td>0.47 [0.18-1.24]</td>
<td>0.128</td>
<td>0.93 [0.84-1.03]</td>
<td>0.179</td>
</tr>
<tr>
<td>PVR</td>
<td>1.00 [1.00-1.01]</td>
<td>0.066</td>
<td>0.89 [0.79-0.99]</td>
<td>0.030</td>
</tr>
<tr>
<td>SV/PP</td>
<td>0.39 [0.12-1.25]</td>
<td>0.112</td>
<td>0.90 [0.81-0.99]</td>
<td>0.034</td>
</tr>
<tr>
<td>PP</td>
<td>0.97 [0.94-1.00]</td>
<td>0.119</td>
<td>0.87 [0.79-0.91]</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Definition of abbreviations: 6 MWD = six minute walk distance; Pra = right atrial pressure; SvO₂ = mixed venous oxygen saturation; CI = cardiac index; PVR = pulmonary vascular resistance; SV/PP = pulmonary arterial compliance; RAC = pulmonary artery relative area change

Survival analyses

No patients were lost to follow-up. From the 70 PAH patients eighteen (26%) died due to right heart failure and none of the patients died of causes other than cardiopulmonary. The cause of death was ascertained when clinical signs of right heart failure were observed by one of the attending physicians specialized in the treatment of PAH.

Average survival was 16 months (range 0-48). The baseline six-minute walk distance, cardiac index and mixed venous oxygen saturation was significantly lower in non-survivors than in survivors (Table 1). Furthermore, right atrial pressure and pulmonary vascular resistance was higher in the non-survivors (Table 1). In non-survivors maximal (non-survivors; 683±210 vs. survivors; 686±217 mmHg) and minimal (non-survivors; 604±209 vs. survivors; 573±201 mmHg) pulmonary artery cross-sectional area was not different from survivors. RAC was significantly lower when compared with survivors (non-survivors; 15±7 vs. survivors; 21±10 %, p<0.05).
Non-invasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension

The Kaplan-Meier survival curves for groups (divided by the median) for RAC is shown in Figure 4. PAH patients with a RAC \( \leq 6\% \) had a significantly lower survival rate than those with a RAC > 6\% (log-rank, \( p = 0.0006 \)). Univariate Cox regression analysis showed that RAC was a strong non-invasive predictor of mortality in contrast to area distensibility (Table 2). Furthermore, SV/PP as an invasive measure of pulmonary arterial compliance was also a predictor of mortality in this PAH group. The results of Table 3 showed that by means of bivariate Cox regression analysis RAC is the best predictor of mortality. Other known predictors of mortality did not add any prognostic information (Table 3). The receiver operator curve analysis (Figure 5) shows the significant predictors able to distinguish between survivors and non-survivors in this PAH group. Cardiac index (area under the curve: 0.67, \( p = 0.07 \)) and SV/PP (area under the curve: 0.65, \( p = 0.06 \)), both significant predictors in univariate Cox regression analysis (Table 2), could not distinguish between survivors and non-survivors.

Discussion

This MRI study shows that in PAH patients the pulmonary artery becomes distended and less distensible. In comparison with subjects without PAH, both area distensibility and RAC are significantly lower in PAH patients. Furthermore, it was shown that non-invasively measured RAC is a predictor of mortality.

Physiological response to increased pressure: distension and stiffening

In PAH patients, elevated pulmonary artery pressure distends the proximal pulmonary artery by circumferential stretch as was observed in this study by increased maximal and minimal pulmonary artery cross-sectional area. As a result, area distensibility and relative area change were decreased when compared with controls, as was shown in this study and previous MRI research (16-18). Interestingly, area distensibility differs more between patients and control...
subjects (Figure 2) than relative area change. This may result from the larger pulse pressure in the PAH patients. Yet the survival analysis shows that the area distensibility was a weaker predictor of mortality then the RAC.

The curvilinear relation between pulmonary artery pressure and RAC in this study shows similarities with previous data (9-2). A low pressure causes less distension, and corresponds to a larger RAC, whereas an elevated pressure distends the pulmonary artery, and is associated with a lower RAC. However, the scatter of the data points of the relation between mean pulmonary artery pressure and RAC (Figure 3) indicates that pressure is not the only factor determining pulmonary artery RAC. Elevated pulmonary artery pressure may also result in vessel remodeling, i.e. wall thickening, to normalize wall stress. Furthermore, the presence of pulmonary atherosclerosis has been shown characteristic of all conditions associated with severe chronic PAH (22). Thus the duration and the extent of increased pressure seem to play a crucial role in vessel wall remodeling of the large pulmonary arteries.

**Prognostic value of pulmonary artery stiffness**

The work performed in this study confirms the results of earlier studies (23;24), that total compliance of the pulmonary vascular bed is a predictor of mortality. In addition, our data shows that non-invasively measured RAC is a strong predictor of mortality while area distensibility is a less strong predictor. Furthermore, bivariate analysis revealed that other predictors of mortality added no prognostic information. Moreover, RAC was a predictor of mortality independent of pulmonary artery pulse pressure. The latter is remarkable, since prognostic measures of pulmonary artery stiffness; i.e. compliance and area distensibility require pressure measurements.

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**Figure 5.** Receiver operator curves for significant predictors of death in pulmonary arterial hypertension. Abbreviations: RAC = relative area change; 6MWD = six-minute walking distance; SVO$_2$ = Mixed venous oxygen saturation; Pra = right atrial pressure; PVR = pulmonary vascular resistance
Non-invasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension

However, the correlation between systolic and diastolic pulmonary artery pressure found in this study is in agreement with the work by Friedberg et al. (25). They found a gradient of $\alpha = 0.49$, while the gradient of the linear equation we found was approximately similar ($\alpha = 0.41$). Thus vessel wall elasticity as calculated by the Kawasaki equation (26), can be assessed by RAC measurements. Since pulmonary artery compliance constitutes an important part of the load on the right ventricle (27), a proximal stiff pulmonary artery may affect the ventricle by increased workload independently (6;28). The latter can be attributed to early wave reflection to the right ventricle (6), which may result in augmented myocardial load and oxygen demand. This has been shown for the systemic circulation, in which increased aorta stiffness is associated with increased left ventricular work and poor prognosis (29-32). In addition to the work by Mahapatra (33;34), the data in this study suggests that the amount of load on the right ventricle is partly due to stiffening of the large proximal pulmonary arteries. Furthermore, in our series of patients non-invasively assessed RAC, as a measure off stiffness, was a better marker of death than known prognostic variables.

Limitations

Patients with PAH associated to congenital heart disease were excluded, because it has been shown that the arrangement of the elastic tissue in the large pulmonary arteries in these patients are comparable to the aorta (22), and therefore might resemble similar properties with respect to vessel distensibility. Thus the results of this study might not be extrapolated to patient populations that include patients with PAH associated to congenital heart disease. The controls in this study were admitted to our hospital for the clinical evaluation of PAH. Therefore comparisons between controls and PAH patients should be interpreted with caution. Furthermore, control subjects were younger but this was not statistically significant. However, it appears that pulmonary artery RAC does not decrease with age (35). Pulmonary artery stiffness was not measured in the main pulmonary artery, but in the right pulmonary artery, while the main pulmonary artery may be the most important contributor to total distensibility of the pulmonary vascular bed. However, MRI measurement of the cross-sectional area of the main pulmonary artery is confounded by cardiac motion in the through-plane direction. Due to its conical shape this may result in artificial distension or constriction of the main pulmonary artery in the image plane. On the contrary, the right pulmonary artery, a relatively straight tube, is at the most affected by cardiac motion in the transversal direction, which does not result in artificial distension or constriction. Furthermore, relative area change of the right pulmonary artery has been shown to be on average similar to that of the main and left pulmonary artery (36). In this study we performed bivariate Cox proportional hazards regression analysis to investigate whether other known prognostic variables added any prognostic information to RAC. Multivariate analysis for survival was not performed because there were only eighteen deaths. However, future studies may elucidate the predictive value of non-invasively assessed RAC, not only with established predictors of mortality in PAH, but also with non-invasively assessed parameters of RV structure and function.
Conclusion
In patients with PAH increased pulmonary artery pressure causes distension and possibly wall remodeling, both resulting in stiffening of the proximal pulmonary arteries. Non-invasively assessed pulmonary artery RAC is a good predictor of mortality.
Non-invasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension

References


Chapter 7

Non-invasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension
Chapter 8

Pathophysiology and management of right ventricular failure in chronic pulmonary hypertension

C.T. Gan, A. Boonstra, P.E. Postmus and A. Vonk Noordegraaf

Abstract
Pulmonary hypertension is the most common cause of right ventricular failure. Under physiological conditions the right ventricle functions as a pump, which propels large amounts of blood against low pressures into the highly distensible pulmonary circulation. In chronic pulmonary hypertension, disease progression might eventually result in right ventricular failure and should be considered as a sign of insufficient right ventricular adaptation to the progressively increasing afterload. The pathophysiological mechanisms involved in right ventricular failure include systolic and diastolic dysfunction of the right ventricle, and interventricular interaction leading to a leftward shift of the interventricular septum and subsequent underfilling of the left ventricle. Insights into these mechanisms form the basis for the management of these critical ill patients. Since cardiopulmonary resuscitation is rarely successful and the role of ventilatory support is limited, palliative care focused on relief of respiratory distress and of the patient's discomfort is important in patients with end stage right ventricular failure.
**Introduction**

Pulmonary hypertension (PH) is the most common cause of right ventricular (RV) failure. PH is defined as a mean pulmonary artery pressure of more than 25 mm Hg at rest, or higher than 30 mmHg during exercise. From a clinical point of view, RV failure as a consequence of PH can occur 1) acutely in the non-adapted RV in patients with massive pulmonary embolism or 2) as a progressive process in chronic PH. In the latter case RV failure should be considered as a result of an insufficient adaptation of the RV to the progressively increasing RV afterload. The many causes of PH leading to this condition are summarized in Table 1 (1). This clinical classification of PH has been adapted from the World Health Organization consensus meeting on pulmonary arterial hypertension held in 2003. Although management strategies in patients with acute pulmonary embolism are well known, less is known about the management of RV failure as a consequence of chronic PH. Insights into the mechanisms of RV failure in these patients forms the basis of the approach to optimizing the clinical condition of these patients. In this review, we will focus on these mechanisms and based on that provide a scheme for the treatment of PH patients with life threatening RV failure.

**Physiological structure and function of the right ventricle and the response to increased pulmonary artery pressure**

The normal RV is crescent shaped and has a thin myocardial wall in contrast to the left ventricle, which is concentric and has a thick myocardium, as shown in Figure 1. The anatomical difference between the right and left ventricles originates from the properties of the vascular bed to which it is coupled. In the left ventricle, the highly resistant systemic circulation demands a ventricle able to generate flow at high pressures. The unique pulmonary circulation is a low-flow and low-pressure system, which enables the RV to pump a large amount of blood into the pulmonary circulation at low pressures. Therefore the RV can be regarded as a volume pump in contrast to the left ventricle, which functions as a pressure pump. The mean pulmonary artery pressure in the pulmonary circulation is approximately 10 mmHg. This low pressure is due to the thin-walled pulmonary vessels, the low vascular tone, and the large recruitment capacity of the pulmonary vascular bed. Under physiological conditions the recruitment capacity of the capillaries in the lungs is the main mechanism for the fall in pulmonary vascular resistance with an increase in pulmonary artery pressure.

When this recruitment capacity is lost, pulmonary vascular resistance rises. When there is a gradual increase in pulmonary vascular resistance, the RV adapts by thickening of the myocardial wall (Figure 1) (2). Myocardial hypertrophy is the physiological response to increased ventricular afterload and reduces myocardial wall stress, which is important in relation to the oxygen demand of the myocardium (3). Concomitantly with this increase in myocardial mass, the RV dilates to allow compensatory preload and preserve stroke volume.
### Tabel 1.

<table>
<thead>
<tr>
<th>WHO classification of pulmonary hypertension</th>
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<tbody>
<tr>
<td>1. Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>1.1 Idiopathic</td>
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<tr>
<td>1.2 Familial</td>
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<tr>
<td>1.3 Associated with:</td>
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<tr>
<td>(1) Collagen vascular disease</td>
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<tr>
<td>(2) Congenital systemic-to-pulmonary shunts</td>
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<tr>
<td>(3) Portal hypertension</td>
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<tr>
<td>(4) HIV infection</td>
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<tr>
<td>(5) Drugs/toxins: Anorexigens</td>
</tr>
<tr>
<td>(6) Other</td>
</tr>
<tr>
<td>1.4 Associated with venous or capillary involvement</td>
</tr>
<tr>
<td>(1) Pulmonary veno-occlusive disease</td>
</tr>
<tr>
<td>(2) Pulmonary capillary haemangiomatosis</td>
</tr>
<tr>
<td>1.5 Persistent pulmonary hypertension of the newborn</td>
</tr>
</tbody>
</table>

2 Pulmonary with left heart disease

2.1 Left-sided atrial or ventricular heart disease

2.2 Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung disease and/or hypoxaemia

3.1 Chronic obstructive pulmonary disease

3.2 Interstitial lung disease

3.3 Sleep-disordered breathing

3.4 Alveolar hypoventilation disorders

3.5 Chronic exposure to high altitude

3.6 Developmental abnormalities

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease

4.1 Thromboembolic obstruction of proximal pulmonary arteries

4.2 Thromboembolic obstruction of distal pulmonary arteries

4.3 Non-thrombotic pulmonary embolism (thrombus, parasites, foreign material)

5. Miscellaneous

Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumours, fibrosing mediastinitis)

Clinical classification of pulmonary hypertension adapted from the World Health Organization consensus meeting on Pulmonary Arterial Hypertension, Venice, June, 2003. Published in the Journal of the American College of Cardiology by Simmonneau et al.

#### The pathophysiology of right ventricular failure

In the past, RV failure was considered to be systolic dysfunction as a consequence of increased RV afterload. Currently, the role of RV diastolic dysfunction in chronic right heart failure has been recognised, and that, by the process of interventricular interdependency, left ventricular underfilling also contributes to the decreased stroke volume in these patients (4). Moreover, the critical role of increased pericardial constraint and impaired RV coronary perfusion on RV function has been recognized. The mechanisms of heart failure in patients with chronic pressure overload are summarized in Figure 2. The consequences for the heart of the mechanisms involved in the pathophysiology of RV failure are illustrated in Figure 3.
**Figure 1.** Short axis MR images of the heart in a control (left), and an idiopathic pulmonary arterial hypertension patient (right). Compared to the control the patient has a hypertrophied and dilated right ventricle (R). The left ventricle (L) is compressed and the interventricular septum is flattened.

**Figure 2.** Pathophysiological mechanisms involved in right ventricular heart failure.
Right ventricular systolic function

Progressive increase in pulmonary vascular resistance will lead to RV dilatation and impaired systolic function. For this reason progressive RV dilatation, defined as an increase of RV end-diastolic volume over time is a clear sign of RV failure and is a predictor of a poor prognosis (5). A reduced RV stroke volume concomitant with an increase in RV end diastolic volume results in a reduced RV ejection fraction, i.e. impaired RV systolic function. Ideally, RV function should be interpreted in the light of the pulmonary vascular bed to which it is coupled, and quantified by measures of pressure and volume. This concept of ventriculoarterial coupling between the right ventricle and the pulmonary vascular bed has been investigated in animal models (6-8) and patients with pulmonary artery hypertension (PAH) (9). These studies showed that RV pump function is reduced despite enhanced myocardial contractility, and in cases of RV failure, uncoupled from the pulmonary vascular bed.

Right ventricular diastolic function

Although most research has been focused on impairment of systolic function in RV failure, it is now recognized that diastolic dysfunction might play a role in RV failure. First, right atrial pressure, an indirect measure of RV diastolic function, is an important prognostic marker in patients with pulmonary arterial hypertension (10). Second, in PH animal models it has been shown that chronic RV pressure overload results in impaired diastolic function (11,12). Several echocardiography studies have revealed prolonged RV relaxation in PH patients (13-15). In addition, RV hypertrophy and increased pulmonary vascular resistance are associated with impaired myocardial relaxation during the diastolic phase (16). As a consequence, RV early diastolic filling is decreased and filling of the
Pathophysiology and management of right ventricular failure in chronic pulmonary hypertension

RV towards end-diastole becomes more important and is dependent upon right atrial contractile function.
In PH the right atrium is dilated and functions as a storehouse for blood rather than a conductor (17). Right atrial contractile function is particularly enhanced to maintain right ventricular filling. Atrial fibrillation, leading to a loss of contractile function of the atria, will thus have detrimental effects on RV function in PH and for this reason, should be corrected.

Ventricular interaction
A characteristic finding in RV pressure overload is the leftward movement of the interventricular septum, i.e. septal bowing. It has been shown that RV pressure overload leads to prolonged contraction of the RV free wall (18). At this time the left ventricle is already in its early diastolic phase, and RV pressure exceeds left ventricular pressure, as is illustrated in Figure 4. As a result, a transseptal pressure gradient results leading to this paradoxal septum movement (19). The consequence of this leftward septal bowing is not only an ineffective RV systolic contraction, but also impaired left ventricular filling in early diastole (20;21). As a result left ventricular end-diastolic volume, i.e. preload, is decreased in PH (4). According to the Frank–Starling mechanism decreased left ventricular preload will directly impair left ventricular output.

Decreased coronary perfusion
As a result of reduced left ventricular output, systemic blood pressure will decrease. Furthermore, increased right atrial pressure will impair venous drainage of the coronary arteries. As a consequence, decreased coronary artery flow may result (22). Since the myocardium demands more oxygen due to increased RV work, the imbalance between oxygen demand and supply will

Figure 4 Simultaneous measurements of right (dashed line) and left (solid line) ventricular pressures in a PH patient. Note that right ventricular pressure exceeds left ventricular pressure at approximately 0.35 seconds from the start of contraction.
result in ventricular ischaemia, which impairs RV global function. For this reason, RV failure will inevitably lead to chest pain (23) and increased troponin-t levels (24) in the blood, even in the absence of coronary artery disease.

Management
Principles of treatment of RV failure in chronic pressure overload can be derived from Figure 2 and are summarized in Table II. The principles of management can be divided into 1) reduction of RV afterload, 2) improvement of RV function, and 3) prevention of left ventricular underfilling.

Reduction of right ventricular afterload
Oxygen is widely used to support critically ill patients with severe PH in an attempt to correct hypoxaemia. Most importantly, even in chronic pulmonary arterial hypertension, hypoxic and non-hypoxic dependent pulmonary vasoconstriction still plays a role and is mainly caused by hypoxic pulmonary vasoconstriction due to low mixed venous oxygen saturation. Inhalation of 100% oxygen will increase mixed venous and arterial oxygen saturation (25). Therefore administration of high doses of oxygen may reduce pulmonary vascular resistance and correct hypoxaemia. In general, administration of pulmonary vasodilators is aimed at reducing RV afterload and improving cardiac output. In addition to oxygen therapy, inhalation of nitric oxide (NO) has beneficial effects on haemodynamics in idiopathic pulmonary arterial hypertension (26-28) and chronic thromboembolic PH (29). Several studies have shown the beneficial effect of NO on pulmonary artery pressure, pulmonary vascular resistance, cardiac output, stroke volume and mixed venous oxygen content in patients with other aetiologies of PH (30-31). The advantage NO inhalation or administration through an endotracheal tube is that it reduces pulmonary vascular resistance without decreasing systemic pressures, and improves ventilation-perfusion mismatch by increasing perfusion to those areas that are well ventilated (32). Recently we found that the combined inhalation of NO (20 ppm) and 100% oxygen can cause a reduction of more than 20 % in end-stage PAH, leading to a direct improvement of cardiac output (33). Prostacyclin is a potent pulmonary vasodilator and has shown to be effective in severe pulmonary arterial hypertension

Table 2. Management of right ventricular failure

Reduction of right ventricular afterload
- 100 % oxygen + 20 ppm NO
- Prostacyclin
- Sildenafil 50 mg

Improvement of right ventricular function
- Lisdexamethasone and spironolactone
- Electric cardioversion or amiodarone
- Dobutamine or milrinone: in normotensive patients and low cardiac output

Treatment of left ventricular underfilling
- Vasopressin, dopamine or noradrenaline: in hypotensive patients with low cardiac output
- Atrial balloon septostomy
Pathophysiology and management of right ventricular failure in chronic pulmonary hypertension

(24) with sustained long term beneficial effects (25,27) and thus is considered as the first choice of treatment in PAH patients in NYHA class 4. Since the drug acts as a non-selective vasodilator, significant shunt might occur in patients with underlying pulmonary diseases (34). For this reason prostacyclin should only be considered as a therapy in patients in WHO groups 1 or 4 PH, see Table 1. However careful monitoring is required, since systemic hypotension may result. Another potential pulmonary vasodilator which is more frequently used in the ICU is phosphodiesterase-5 inhibitor - sildenafil. This drug has been shown to be pulmonary-specific and improve haemodynamics in PH patients (35). In addition to the pulmonary vasodilator effect, it has been shown in an animal model that sildenafil has a chronic effect on the cardiomyocyte (36). Cyclic guanosine monophosphate (cGMP) is the common second messenger for the cardiovascular effects of nitric oxide (NO) and for natriuretic peptides, such as atrial or brain natriuretic peptide. Sildenafil increases cGMP levels by inhibiting the activity of phosphodiesterase-5 inhibitor. As a consequence NO and natriuretic peptide release of the cardiomyocyte is enhanced potentially leading to muscle relaxation. Although there are many reports showing the beneficial short-term effects of sildenafil in patients admitted to the ICU for right heart failure, prospective randomized controlled data from well-defined ICU patients are lacking. Therefore the question, ‘which patient will benefit from this treatment’, remains to be answered.

Improvement of right ventricular function

Forward failure due to impaired RV systolic function will lead to renal fluid retention in turn leading to an increase in intravascular volume. Initially, this status might lead to increased RV preload and augmented RV contractility. However, in advanced stages of RV failure, volume overload will lead to progressive RV dilatation, not only impairing RV contractile function but also contributing to left ventricular underfilling and resulting in decreasing cardiac output (Figure 2). For this reason, diuretics are required to balance intravascular volume and improve right and left ventricular function(37). Diuretics should preferably be administrated intravenously in the initial state, and titrated on renal function.

Because in PH patients both right and left ventricular filling are dependent upon the atrial contribution, restoring sinus rhythm is requisite. If electrical cardioversion is not possible, the use of amiodarone is warranted (38). The use of digoxin remains controversial and is not recommended based on limited data (39;40). Human data on the role of inotropes in RV failure is lacking. However, a study performed in dogs with RV pressure overload showed the beneficial effect of inotropes (41). Since RV pump function is enhanced in PH, inotropes might increase myocardial demand and lead to an impairment of RV function (Figure 2). However, in normotensive patients with decreased cardiac output inotropes may improve the patients’ haemodynamic status. In addition, low dose vasopressor therapy can be effective in patients with significant systemic hypotension (42). A potentially effective drug for the treatment of RV failure is levosimendan, since this drug can improve RV contractility and reduce RV afterload (43). In this study levosimendan restored ventriculoarterial coupling better than dobutamine in dogs with RV pressure overload. However, as yet there is little experience with this drug in patients with RV failure.
Treatment of left ventricular underfilling

Due to RV dilatation and systemic hypotension in the presence of increased RV systolic pressures, leftward septal bowing will occur and left ventricular filling and function will be impaired. Restoring left ventricular filling can thus be achieved in two ways. First, unloading of the RV by reducing its afterload or preload, and secondly, an increase in systolic left ventricular pressure, which prevents leftward septal bowing and maintains systemic pressure to preserve coronary perfusion. The ideal pressor agent for this purpose should improve peripheral perfusion without significantly increasing pulmonary vascular resistance. Norepinephrine, epinephrine, vasopressin and dopamine if given at low doses under haemodynamic monitoring have been shown to have favourable effects on haemodynamics in patients with acute pulmonary embolism and acute circulatory failure (44;45). Vasopressors may be started initially to compensate systemic hypotension and depending on the circumstances in which inotropes are used, it may compensate the vasodilatory effect. Vasopressin has been used to treat milrinone-induced hypotension without any negative effect on cardiac output and pulmonary artery pressure (46). An invasive method of improving left ventricular filling is atrioseptostomy. Atrioseptostomy can provide immediate relief of symptoms in end-stage PAH and might function as a bridge to lung transplantation (47). An atrioseptostomy in this setting creates a right-to-left shunt that increases cardiac output and, despite the fall in systemic arterial oxygen saturation, augments systemic oxygen transport. In addition, the shunt decompresses the heart and ameliorates RV failure. This option should only be considered in patients who are unstable despite being treated by conventional therapy and diuretics, and not performed in patients with a mean right atrial pressure of more than 20 mmHg because of high mortality risk (48).

Other pharmacological interventions

The use of anticoagulants has been shown to be beneficial in idiopathic PAH (49). In addition to the prophylaxis of pulmonary emboli, the use of anticoagulants may in theory prevent thrombosis-associated pulmonary vascular remodelling. There is limited information on the use of beta-blockers and ACE-inhibitors in PH patients. Recently, a study by Provencher et al. showed the deleterious effects of beta-blockers on exercise capacity and pulmonary haemodynamics in patients with portopulmonary hypertension (50). These deleterious effects were mainly associated to the negative chronotropic effect of beta-blockers. Since PAH patients have impaired stroke volume response in exercise (51;52), cardiac output might only be preserved or augmented by increased heart rate. Therefore administration in PAH patients is contraindicated. ACE-inhibition has shown to prevent vascular remodelling in an animal model (53). However, the systemic hypotensive effect makes the role of ACE-inhibitors in the treatment of RV failure less likely.

Future developments

The therapeutic options of levosimendan were investigated in a pilot study in patients with acute respiratory distress syndrome and showed a beneficial effect on RV performance due to their
pulmonary vasodilator effect (54). The use of this calcium sensitizer with potential pulmonary vasodilator properties needs further investigation.

**End-of-life decisions**

In end-stage disease dyspnoea is a consequence of circulatory impairment, therefore the role of ventilatory support is limited. In addition, mechanical ventilatory support in PH patients might potentially increase pulmonary vascular resistance and worsen RV filling (55). At the VU University Medical Center, invasive or non-invasive ventilation was initiated in seven patients. All patients were well-known at our center and had a progressive type of PH despite optimal treatment. Reasons for ventilation were: pneumonia (3), respiratory exhaustion in patients on the high urgency list for lung transplantation (2), and pulmonary veno-occlusive disease with increase of pulmonary oedema (2). Although most of the patients improved initially, none of them survived. These limited data indicate that the role of mechanical ventilation is limited, even in patients with an indication. Therefore, palliation of respiratory distress and maximum comfort should be regarded as important alternatives to invasive ventilation in the treatment of end-stage right heart failure in patients under optimal treatment. In addition, a large retrospective multicenter study showed that cardiopulmonary resuscitation is rarely successful in PH patients who have a cardiac arrest (44).

**Conclusion**

In patients with chronic PH, insights into the pathophysiological mechanisms involved in RV failure forms the basis of medical therapy. The management of these critically ill patients should be focused on reduction of RV afterload, improvement of global RV function and preservation of left ventricular filling. Invasive ventilation and cardiopulmonary resuscitation are not successful options in these patients.
Chapter 8

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Summary and future perspective
Pulmonary arterial hypertension (PAH) is a disease, which involves the small pulmonary vessels. In the past few years the efforts done to understand the pathobiology underlying this disease improved treatment and outcome. However prognosis remains grim in PAH. It has been recognized that mortality of PAH patients is directly associated to the function of the right ventricle; i.e. right heart failure in end-stage disease. During progression of the disease there is a transition from an adapted right ventricle, able to maintain its function in relation to the pressure overload, to a failing ventricle. Insight in this process and the role of the left ventricle, the atria and large pulmonary vessels are limited. The studies described in this thesis were aimed to improve our understanding of right ventricular failure in patients with pulmonary arterial hypertension and provide accurate measures for an early detection of right ventricle failure. Chapter 1 of this thesis gives an overview of the insights on the pathobiology, pathogenesis, and genes involved in PAH. Furthermore, the classification, diagnostic work-up and treatment of PAH are viewed.

The effect of pulmonary hypertension on the right ventricle is the increased afterload, which elevates myocardial wall stress. Brain natriuretic peptide and its biological inactive equivalent N-terminal pro-brain natriuretic peptide (NT-proBNP) are released by the cardiomyocytes due to increased wall stress. It has been shown that brain natriuretic peptide and NT-proBNP can monitor disease and treatment effects, and both are significant prognostic markers in PAH. However, insight in to changes in right ventricular structure and systolic function in relation to NT-proBNP are unknown. Chapter 2 presents a study about the temporal relationships of NT-proBNP with right ventricular structure and systolic function in thirty pulmonary hypertension patients. The results of the study showed that relative changes in NT-proBNP during treatment were correlated to the relative changes in right ventricular end-diastolic volume index (r = 0.59, p< 0.001), right ventricular mass index (r = 0.62, p< 0.001) and right ventricular ejection fraction (r = -0.81, p< 0.001). Elevated NT-proBNP levels over time reflects right ventricular dilatation concomitant to hypertrophy and deterioration of systolic function, and should be interpreted as a sign of right heart failure.

It has been recognised that systolic function is important in the overloaded right ventricle, however there is little insight in right ventricular diastolic function. There are arguments that right ventricular diastolic function may be impaired in pulmonary hypertension patients. First, due to increased right ventricular afterload myocardial relaxation and filling may be impaired. Second, right ventricular compensatory hypertrophy to increased afterload reduces ventricular compliance and may impair diastolic function. Therefore the aim of the study presented in chapter 3 was to investigate whether right ventricular diastolic function is impaired in pulmonary hypertension patients, and whether this impairment is related to right ventricular mass and afterload. Phodopodiesterase-5-inhibitor sildenafil was used to investigate whether an acute reduction of afterload improves right ventricular diastolic function. Finally, the relation between right ventricular diastolic function and cardiac parameters that reflect disease severity in pulmonary hypertension was assessed. Twenty-five patients and 11 controls were studied. Isovolumic relaxation time (IVRT), normalized early (E), atrium-induced (A) peak filling rate, and E/A, described diastolic function. Compared to controls,
patients had impaired right ventricular diastolic function in terms of prolonged isovolumic relaxation time (IVRT) (133.5±53.2 ms vs. 29.3±20.8 ms, p<0.001), decreased normalized early peak filling rate (E) (3.0±1.6 s⁻¹ vs. 6.4±2.5 s⁻¹, p<0.001) and E/A (1.1±0.7 vs. 5.3±4.9, p<0.001), and increased atrium-induced peak filling rate (A) (3.0±1.4 s⁻¹ vs. 1.5±0.9 s⁻¹, p = 0.001). IVRT was related to right ventricular mass (r = 0.56, p = 0.005) and pulmonary vascular resistance (r = 0.74, p<0.0001). In patients right ventricular diastolic dysfunction is related to right ventricular mass and afterload. Sildenafil improved right ventricular diastolic and systolic function. IVRT was correlated to NT-proBNP (r = 0.70, p<0.001), and inversely related to cardiac index (r = -0.70, p<0.001) and right ventricular ejection fraction (r = -0.69, p<0.001). Whether this effect is secondary to a reduction in afterload or a direct effect of sildenafil on the cardiomyocytes remains to be further investigated. Right ventricular diastolic function improves by reducing afterload. The correlations between diastolic function and prognostic parameters showed that impairment of the diastolic function is a major contributor to right ventricle failure.

Although the right ventricle is the main player in right ventricle failure, there is increasing evidence that the role of the left ventricle is largely underestimated in pulmonary hypertension. The hallmark of pulmonary hypertension on echocardiography is paradoxal septal movement; i.e. leftward ventricular septal bowing, which results from a transeptal pressure gradient in diastole. The phenomenon by which the right ventricle directly influences left ventricular filling is known as direct ventricular interaction. The aim of the study presented in chapter 4 was to determine the effect of direct ventricular interaction on stroke volume. Forty-six PAH patients and 18 control subjects were studied. Magnetic resonance imaging measured stroke volume, right and left ventricular volumes, left ventricular filling rate and interventricular septum curvature. Transesophageal echocardiography measured left atrial filling. The results showed that compared to control subjects, patients had decreased stroke volume (28±13 vs. 41±10 ml/m², p<0.001), left ventricular end-diastolic volume (46±14 vs. 61±14 ml/m², p<0.001) and left ventricular peak filling rate (216±90 vs. 541±248 ml/s, p<0.001). Among patients stroke volume did not correlate to right ventricular end-diastolic volume or mean pulmonary artery pressure, but did correlate to left ventricular end-diastolic volume (r = 0.62, p<0.001). Leftward ventricular septal bowing was correlated to left ventricular filling rate (r = 0.64, p<0.001) and left ventricular end-diastolic volume (r = 0.65, p<0.001). From these data can be concluded that ventricular interaction mediated by the interventricular septum impairs left ventricular filling contributing to decreased stroke volume. The characteristic leftward ventricular septal bowing in pulmonary hypertension is the result of a transeptal pressure gradient during diastole as described earlier. The mechanism underlying this phenomenon is interventricular asynchrony. The mechanism was explored and described in Chapter 5. The aim of the study was to investigate whether the nature of the asynchrony lies in the difference in duration of shortening of the two ventricles; i.e. left-to-right delay in myocardial shortening, or in the onset of shortening. In addition, the functional impact of asynchrony was determined by assessing the association with left ventricular septal bowing and filling, and stroke volume. In 21 PAH patients, MRI myocardial tagging was applied. The onset time and peak time
of circumferential shortening were calculated, for the left ventricular free wall, septum and right ventricular free wall. The Laplace law estimated right ventricular wall tension. The results showed that myocardial shortening of both ventricles start simultaneously, and that the time to peak shortening was different for the left ventricular free wall, septum and right ventricular free wall respectively (293±58, 267±22 and 387±50 ms). Maximum leftward ventricular septal bowing was at 395±45 ms, coinciding with septal overstretch and peak time of the right ventricle. The left-to-right delay in peak time was not correlated with the QRS width, but was associated with right ventricular wall tension (r = 0.54, p = 0.01). The left-to-right delay in peak time correlated with leftward septal curvature, and correlated negatively with left ventricular end-diastolic volume (r = 0.50, p = 0.02) and stroke volume (r = 0.49, p = 0.02). Based on these findings we conclude that in PAH left to right asynchrony is caused by lengthening of right ventricular shortening and that right ventricular peak time coincides with septal overstretch and maximal leftward ventricular septal bowing. Furthermore, we observed that there is still myocardial shortening of the right ventricular free wall while the pulmonary valves are already closed, underscoring the ineffectiveness of right ventricular systolic function in end stage PAH.

The role of the right atrium in pulmonary arterial hypertension and especially the interaction with right ventricular function is largely unknown. Due to changes in right ventricular structure and function the right atrium has to adapt to compensate for diastolic and systolic function. Under physiological conditions the right atrium transfers large volumes at low pressures and can be quantified by, 1) The conduit volume; i.e. the amount of blood that flows directly from the veins into the right ventricle, 2) Reservoir volume: the blood being stored during ventricular systole. Conduit-to-reservoir volume quantifies right atrial function. In Chapter 6 the adaptive capacity of the right atrium in relation to right ventricular structure and function was studied. On average, the 14 patients had larger right atria than the 11 controls (42 [31-55] vs. 25 [17-30] ml/m\(^2\), p = 0.001), comparable reservoir volume (27 [20-30] vs. 25 [21-28] ml/m\(^2\), p=0.792), and decreased conduit volume (4 [2-9] vs. 13 [10-18] ml/m\(^2\), p = 0.003). In PH conduit-to-reservoir volume ratio is reduced (0.14 [0.08-0.92] vs. 0.61 [0.39-0.72], p = 0.002), and atrial contractile function is enhanced (43 [33-63] vs. 27 [18-29] %, p = 0.002). In patients, right atrial maximum volume was related to right ventricular end-diastolic volume index (r = 0.63, p = 0.022). Conduit-to-reservoir volume ratio was related to right ventricular ejection fraction (r = -0.71, p = 0.005), and inversely related to right ventricular isovolumic relaxation function (r = -0.63, p = 0.015. In pulmonary hypertension, the right atrium is larger, conduit-to reservoir volume ratio smaller and atrial contractile function is enhanced, probably as a result of a compensatory mechanism for impaired right ventricular diastolic and systolic function.

Prognosis in PAH has improved over the last years. This can be attributed to better insights in the pathobiology of the disease. However, monitoring disease and predicting prognosis remains challenging. Since decreased total compliance of the pulmonary vascular bed is associated with increased mortality in PAH, we hypothesized that proximal pulmonary artery stiffness, the relative area change (RAC), assessed non-invasively by MRI can predict prognosis. In Chapter 7 Eighty-six subjects were studied and underwent right heart catheterization and an MRI-scan to assess area
Summary and future perspective

distensibility (ΔA/ΔP·A) and RAC. Patients were followed up to 48 months. Kaplan-Meier plot and Cox proportional hazards regression analyses assessed the predictive value of area distensibility and RAC. In 70 patients, the diagnosis PAH was confirmed and 16 subjects served as controls. In comparison with controls, proximal pulmonary arteries of patients were distended (685±214 vs. 411±153 mm$^2$, $p<0.001$), less distensible (ΔA/ΔP·A: 0.46±0.38·10$^{-2}$ mmHg$^{-1}$ vs. 3.69±1.96·10$^{-2}$ mmHg$^{-1}$, $p<0.0001$), and RAC was smaller (20±10 vs. 58±21 %, $p<0.0001$). RAC showed an inverse curvilinear relation with mean pulmonary artery pressure ($R^2 = 0.47$). Eighteen patients (26%) died because of cardiopulmonary causes. Patients with a pulmonary artery RAC ≤ 6% had a worse prognosis than those with a value >16% (log-rank, $p<0.001$). The RAC predicted mortality better than area distensibility. From these data can be concluded that in PAH patients increased pulmonary artery pressure causes distension and possibly wall remodelling, both resulting in stiffening of the proximal pulmonary artery. In addition, our results showed that pulmonary artery relative area change is a good predictor of mortality.

In chapter 8 we summarize the pathophysiological mechanisms involved in right ventricular failure in end stage PAH and the clinical consequences of these insights on the management of these patients.

Future perspective

The studies described in this thesis view some of the mechanisms involved in right ventricular failure in PAH. Since the awareness that both morbidity and mortality are determined by right ventricular function, both basic and clinical investigators are encouraged to focus on the right ventricle(1). There is a field waiting to be explored. The study described in chapter 3 adds to our knowledge of NT-proBNP in pulmonary hypertension. Since this cardiac hormone is released under influence of myocardial stress, studies investigating NT-proBNP in relation to exercise are challenging. Furthermore, the diagnostic value of NT-proBNP in the diagnosis of early PAH in high-risk groups of patients for developing pulmonary hypertension, such as in scleroderma and BMPR-2 mutation carriers, should be evaluated in prospective studies. Finally, given the many treatment possibilities in pulmonary hypertension, there is a need of a single simple measure to guide therapy and support the decision to switch from oral to intravenous treatment. Based on the results of chapter 2 a goal oriented treatment approach seems to be justified, taking NT-proBNP level of 1685 pg/ml as a cut-off value (2). Multicenter prospective studies are currently designed to evaluate the feasibility and clinical value of such a goal.

The role of right ventricular diastolic function needs furthermore investigation in a larger study group. The predictive value should be compared to other known MRI parameters (3). In addition, the occurrence of right ventricular diastolic dysfunction in relation to the progression of pulmonary hypertension is of interest. Right ventricular diastolic dysfunction may precede systolic dysfunction. Therefore, isolated right ventricular diastolic dysfunction; i.e. in the absence of systolic dysfunction or compensated systolic function, may be an early sign of right ventricular failure. The clinical and prognostic role of non-invasive echocardiographic and MR measures of the diastolic right ventricular function in pulmonary hypertension should be further explored.
Interventricular mechanical asynchrony, the mechanism of leftward ventricular septal bowing, might potentially be eligible for myocardial pacing in those patients waiting for lung transplantation. Restoring synchronous ventricular function, may improve biventricular systolic and diastolic function. Preclinical studies are a requisite to explore the effects of biventricular pacing on cardiac function. Currently, the possible beneficial role of restoration of ventricular synchrony by pacemaker technology is under investigation in our institute.

There is still a need for new end-points in clinical trials. Although expensive, MRI is potentially, the tool to monitor and evaluate therapy in clinical trials. Measures of right ventricular structure, function, pulmonary artery stiffness, can be obtained in a single MRI session. In addition, techniques to measure pulmonary perfusion are currently under investigation and the first results are encouraging (4).

The complex coupling between the right ventricle and the pulmonary vascular tree is still not well understood. Mathematical modelling of this interaction is a promising way to extend our knowledge of right ventricular failure. Current research performed at our institute is underway to develop these models.

Finally, to understand the molecular basis of the transition of right ventricular adaptation to failure, and find adequate treatments to prevent such a transition, animal studies are a requisite. There are strong arguments that hypoxia of the cardiomyocyte might play a key role in the process of right ventricular adaptation to failure. This hypothesis is currently under investigation in several pulmonary hypertension animal models and will be tested in patients by means of PET measurements. Based on the findings of these studies, future studies will focus medical therapies able to prevent the transition of right ventricular adaptation to failure.
References


Nederlandse samenvatting
Pulmonale arteriële hypertensie (PAH) is een aandoening van de kleine pulmonale vaten. In de afgelopen jaren is er veel onderzoek verricht naar de pathobiologie. Dit heeft geleid tot een beter inzicht in de ziekte met als gevolg een verbetering van de behandeling daarmee samenhangend de overleving van deze groep patiënten. Desondanks is de prognose van PAH patiënten op dit moment nog steeds slecht. In het algemeen is het inzicht dat de mortaliteit direct geassocieerd is met de functie van de rechterkamer.

In het beloop van de ziekte is er een transitie van een geadapteerde rechterkamer, die instaat is zijn functie te behouden bij hoge druk overbelasting, naar een falende rechterkamer. Inzichten in dit proces en de rol van de linkerkamer, atria en de grote pulmonale vaten is nihil. De studies die in dit proefschrift, getiteld ‘De effecten van pulmonale hypertensie op de cardiale functie’, beschreven staan hadden globaal twee doelen: 1) Inzicht verkrijgen in het proces van rechterkamer falen, 2) Metingen die bijdragen aan het vroeg detecteren van rechterkamer falen. **Hoofdstuk 1** van dit proefschrift geeft een overzicht van de pathobiologie, pathogenese en genen in PAH. Veder worden de classificatie, diagnostiek en behandeling besproken.

Pulmonale hypertensie leidt tot drukoverbelasting van de rechterkamer. Daardoor neemt de wandspanning van het myocard van de rechterkamer toe. Brain natriuretic peptide en het biologisch inactief equivalent N-terminal pro brain natriuretic peptide (NT-proBNP) worden vrij gemaakt door de cardiomyocyten onder invloed van verhoogde wandspanning. Zowel brain natriuretic peptide als NT-proBNP kunnen worden gebruikt om de ziekte en behandelingseffecten te monitoren. Bovendien fungeren beide hormonen als prognostische markers in patiënten met pulmonale arteriële hypertensie. Echter, inzicht in structurele en functionele veranderingen van de rechterkamer in relatie tot veranderingen in NT-proBNP zijn onbekend. In **Hoofdstuk 2** wordt de relatie van de verandering in NT-proBNP gerelateerd aan de structurele en functionele veranderingen van de rechterkamer in 30 pulmonale hypertensie patiënten. De relatieve verandering in NT-proBNP van patiënten onderbehandeling is gecorreleerd met de relatieve verandering in rechterkamer eind-diastolisch volume index ($r = 0.59, p < 0.001$), rechterkamer massa index ($r = 0.62, p < 0.001$) en rechterkamer ejectie fractie ($r = -0.81, p < 0.001$). Een relatieve toename van NT-proBNP weerspiegelt rechterkamer dilatatie, hypertrofie en een verslechtering van systolische functie, en moet worden geïnterpreteerd al seen teken van rechterkamer falen.

De systolische functie van de rechterkamer speelt een belangrijke rol bij toegenomen drukoverbelasting. Over de diastolische functie van de rechterkamer is weinig bekend. Er zijn echter indirecte aanwijzingen dat de diastolische functie van de rechterkamer ook z'n rol speelt. Door de drukoverbelasting kan het proces van myocard relaxatie en vulling van de rechterkamer verstoord zijn. Bovendien kan de compensatoire hypertrofie van het myocard leiden tot een afname van de compliantie van de kamer en dus resulteren in diastolische dysfunctie. Het doel van de studie beschreven in **Hoofdstuk 3** is te onderzoeken of in patiënten met pulmonale hypertensie rechterkamer diastolische dysfunctie aanwezig is, en of de mate van diastolische dysfunctie gerelateerd is aan de mate van rechterkamer hypertrofie of drukoverbelasting. Met behulp van een phosphodiesterase-5-remmer, Sildenafil, is onderzocht of een verlaging van de drukoverbelasting leidt tot een verbetering van de diastolische functie. Als laatste is de rechterkamer diastolische dysfunctie gerelateerd aan cardiale parameters die ziekte ernst reflecteren.
Nederlandse samenvatting

en-twintig patients en elf controles zijn onderzocht. Isovolumetrische relaxatie tijd (IVRT), rechterkamer vullingsnzelheid (E), atrium geïnduceerde vullingsnzelheid (A) en E/A kwantificeren diastolische functie. Invergelijking tot de controles is er bij patienten sprake van verlengde IVRT (133,5±53,2 ms vs. 29,3±20,8 ms, p<0,001), afgenomen vullingsnzelheid (E) (3,0±1,6 s⁻¹ vs. 6,4±2,5 s⁻¹, p<0,001), en E/A (1,1±0,7 vs. 5,3±4,9, p<0,001). De atrium geïnduceerde vullingsnzelheid is toegenomen (A) (3,0±1,4 s⁻¹ vs. 1,5±0,9 s⁻¹, p = 0,001). IVRT is gerelateerd aan de massa van de rechterkamer (r = 0,56, p = 0,005) en pulmonale vaatweerstand (r = 0,74, p<0,0001). Sildenafil verbetert de diastolische en systolische fuuctie de rechterkamer. Het effect van sildenafil op de diastolische functie zou kunnen komen door het effect op de drukoverbelasting van de rechterkamer of door een direct effect op de cardiomyocyt. Verder onderzoek is nodig om deze vraag te beantwoorden. IVRT is gerelateerd aan NT-proBNP (r = 0,70, p<0,001), en er is een omgekeerde relatie met cardiac index (r = -0,70, p<0,001) en de rechterkamer ejection fraction (r = -0,69, p<0,001). De correlaties van diastolische functie en prognostische parameters laat zien dat de diastolische het een belangrijke rol speelt in rechterkamer falen.

De rechterkamer is zeer belangrijk bij patienten met pulmonale hypertensie. De rol van de linkerkamer wordt in het algemeen onderschat. In patienten met pulmonale hypertensie wordt er bij echocardiografie het karakteristieke paradoxe septum bewegen gezien, ook wel linker ventrikel septum buiging genoemd. Het buigen van het septum ontstaat door een transseptaal drukgradient van rechts naar links in diastole. Het fenomeen waarbij de rechterkamer de vulling van de linkerkamer beinvloed staat bekend als directe ventriculaire interactie. Het doel van de studie beschreven in hoofdstuk 4 was het effect van directe ventriculaire interactie bepalen op het slagvolume. Vier-en-zestig patienten met pulmonale arteriële hypertensie en achttien controles zijn onderzocht. Slagvolume, rechter- en linkerkamer volumes, linkerkamer vullingsnzelheid en de curvatuur van het interventriculaire septum is middels MRI gemeten. Transoesofageale echocardiografie is gebruikt om de vullingsnzelheid van het linker atrium te bepalen. Invergelijking tot de controles is er bij patienten sprake van een afname van het slagvolume, (28±13 vs. 41±10 ml/m², p<0,001), linkkamer einddiastolisch volume (46±14 vs. 61±14 ml/m², p<0,001) en linkkamer piek vullingsnzelheid (216±90 vs. 541±248 ml/s, p<0,001). Het slagvolume is niet gerelateerd aan de rechterkamer eind-diastolisch volume of gemiddelde pulmonaal arterie druk. Er is wel een relatie met de linkerkamer eind-diastolisch volume (r = 0,62, p<0,001). De mate van septum kromming is gerelateerd aan de piek vullingsnzelheid van de linkerkamer (r = 0,64, p<0,001) en linkerkamer eind-diastolisch volume (r = 0,65, p<0,001). Directe ventriculaire interactie, gemedieerd door het interventriculaire septum, hindert de vulling van de linkerkamer en draagt bij aan het lage slagvolume.

Het karakteristieke buigen van het septum in patienten met pulmonale hypertensie wordt veroorzaakt door een drukgradient over het septum van rechts naar links in diastole. Het mechanisme dat ten grondslag ligt aan dit fenomeen is interventriculaire asynchronie. In hoofdstuk 5 is de interventriculaire asynchronie beschreven. Het doel van de studie is te onderzoeken of de oorsprong van de asynchronie gelegen is een verschil in duur van verkorting of dat er een verschil is in het moment van myocard verkorting. Door de mate van asynchronie te relateren aan de curvatuur van het interventriculaire septum, de vulling van de linkerkamer en het slagvolume is de functionele betekenis bepaald. Er is in een-en-twintig patienten met pulmonale arteriële hypertensie MRI tagging verricht. De begin tijd en
de tijd tot piek circumferentiele verkorting zijn berekend voor de linkerkamer vrije wand, het septum en de rechterkamer vrije wand. Middels de wet van Laplace is de wandspanning van de rechterkamer geschat. In patiënten met pulmonale arteriële hypertensie straten de beide hartkamers simultaan met verkorten, de tijd tot piek verkorting van de linkerkamer vrije wand, het septum en de rechterkamer vrije wand is verschillend (293±58, 267±22 and 387±50 ms). Maximale septum curvatuur is op 395±45 ms envalt samen met overstretch van het septum en de tijd tot piek verkorting van de rechterkamer. Het links-rechts verschil in tijd tot piek verkorting is niet gerelateerd aan de duur van het QRS-complex. Er is wel een relatie met de wandspanning van de rechterkamer \( r = 0.54, p = 0.01 \). Het links-rechts verschil in tijd tot piek verkorting is gerelateerd aan de mate van septum curvatuur, en er is een negatieve relatie met het linkerkamer eind-dia-stolisch volume \( r = 0.50, p = 0.02 \) en slagvolume \( r = 0.49, p = 0.02 \). In patiënten met pulmonale arteriële hypertensie wordt de links-rechts asynchronie veroorzaakt doordat de rechterkamer langer bezig is met verkorten dan de linkerkamer. De piek verkorting van de rechterkamer valt samen met het moment waarop de curvatuur maximaal is. De rechterkamer is nog bezig met verkorten terwijl de pulmonales klep al gesloten is. Deze observatie bevestigt dat de rechterkamer functie in patiënten in het eind-stadium van de ziekte inefficiënt is.

De rol van het rechter atrium in pulmonale hypertensie en de interactie met de functie van de rechterkamer is grotendeels onbekend. Door de veranderingen in structuur en functie van de rechterkamer is het rechter atrium genoodzaakt te adapteren om te compenseren voor de veranderingen in functie van de kamer. Onder fysiologische omstandigheden gaat er een grote hoeveelheid aan bloed van het atrium naar de kamer. Dit volume kan worden gekwantificeerd door, 1) het conduit volume; dit is het bloed dat direct vanuit het veneuze systeem het rechteratrium passeert en de kamer instroomt, 2) het reservoir volume; het bloed dat tijdens de systole van de kamer in het rechter atrium opgeslagen wordt. De verhouding van conduit-reservoir volume is een maat voor rechter atrium functie. In hoofdstuk 6 is onderzocht hoe het rechter atrium zich adapteert aan veranderingen in rechterkamer geometrie en functie. In veertien patiënten met pulmonale hypertensie en elf controles zijn volumes en functie van het rechter atrium bepaald. Van de rechterkamer is naast de volumes, myocard massa, en systolische en dia-stolische functie bepaald. Gemiddeld hebben patiënten grotere atria dan de controles (42 [31-55] vs. 25 [17-30] ml/m², \( p = 0.001 \)), het reservoir volume is vergelijkbaar (27 [20-30] vs. 25 [21-28] ml/m², \( p = 0.792 \)), en het conduit volume is kleiner (4 [2-9] vs. 13 [10-18] ml/m², \( p = 0.003 \)). In patiënten is de functie van het atrium kleiner (0.14 [0.08-0.92] vs. 0.61 [0.39-0.72], \( p = 0.002 \)), en afhankelijk van de contractie van het atrium (43 [33-63] vs. 27 [18-29] %, \( p = 0.002 \)). In patiënten is het maximale atrium volume gerelateerd aan het rechterkamer eind-dia-stolisch volume \( r = 0.63, p = 0.022 \). Rechter atrium functie is gerelateerd aan de systolische functie van de rechterkamer \( r = -0.71, p = 0.005 \), en er is een negatieve relatie met de dia-stolische functie van de rechterkamer \( r = -0.63, p = 0.015 \). In patiënten met pulmonale hypertensie speelt het reservoir volume een belangrijke rol in de functie van het rechter atrium en de vulling van de rechterkamer. Dit komt mogelijk doordat het rechter atrium moet compenseren voor de verslechtering van dia-stolische en systolische functie van de rechterkamer. De prognose van patiënten met pulmonale arteriële hypertensie is sterk verbeterd de laatste jaren. Dit komt door de verbeteringen van de inzichten in de ziekte. Het blijft echter een uitdaging om de ziekte te monitoren en de prognose bepalen. In patiënten met pulmonale arteriële hypertensie is de afname
van de totale compliantie van het pulmonale vaatbed geassocieerd met een verhoogde mortaliteit. In hoofdstuk 7 is onderzocht of non-invasief gemeten stijfheid van de proximale pulmonaal arterie, de relatieve oppervlakte verandering (RAC), de prognose kan voorspellen in patienten met pulmoanle arteriele hypertensie. Bij 86 mensen is een rechter hartcatheterisatie en een MRI-scan gedaan om oppervlakte distensibiliteit en RAC te bepalen. De patienten zijn voor 48 maanden gevolgd. Kaplan-Meier plot en Cox proportional hazards regressie analyse zijn gedaan om de voorspellende waarden van oppervlakte distensibiliteit en RAC te bepalen. In 70 patienten, is de diagnose pulmonale arteriele hypertensie bevestigd. De overige 16 mensen dienden als controle groep. In vergelijking tot de controles is de proximale pulmonaal arterie in patienten gedilateerd. ($685\pm214$ vs. $411\pm153$ mm$^2$, $p<0.001$), minder distensibel ($\Delta A/\Delta P\cdot A: 0.46\pm0.38\cdot10^{-2}$ mmHg$^{-1}$ vs. $3.69\pm1.96\cdot10^{-2}$ mmHg$^{-1}$, $p<0.0001$), en RAC is kleiner ($20\pm10$ vs. $58\pm11\%$, $p<0.0001$).

De relatie tussen RAC en de gemiddelde druk in de arterie pulmonalis is een hyperbool ($R^2 = 0.47$). Achtien patients (26%) zijn overleden aan rechterkamer falen. Patienten met een RAC $\leq 16\%$ hebben een slechtere prognose dan patienten met een RAC $>16\%$ (log-rank, $p<0.001$). RAC is een betere voorspeller van mortaliteit dan oppervlakte distensibiliteit. In patienten met pulmonale arteriele hypertensie zorgt de druk verhoging voor het dilateren van de pulmonaal arterie en mogelijk wand remodelering. Beiden leiden tot het stijver worden van de proximale pulmonaal arterie. De non-invasief gemeten RAC is een goede voorspeller van mortaliteit.

In hoofdstuk 8 zijn de pathofysiologische mechanismen betrokken bij rechterkamer falen samen met de klinische consequenties opgesomd.

**Toekomst perspectief**

De studies die in dit proefschrift staan beschrijven enkele mechanismen die betrokken zijn rechter hartfalen in PAH patienten. Sinds men zich bewust is dat zowel morbiditeit als mortaliteit bepaald wordt door de functie van de rechterkamer, wordt basaal en klinisch onderzoek gestimuleerd om zich op de rechterkamer te concentreren (1).

De studie beschreven in hoofdstuk 2 draagt bij aan de kennis van NT-proBNP in pulmonale hyeprtensie. Daar dit hormoon vrijkomt onder invloed van verhoogde wandspanning van het myocard, zijn toekomstige studies die NT-proBNP onderzoeken in relatie tot inspanning interressant. Verder zou de waarde van NT-proBNP in de vroege diagnostiek van PAH in hoog risico groepen, zoals scleroderemie patienten en dragers van een BMPR-2 mutatie, in een prospectieve studie moeten worden onderzocht. De rol van NT-proBNP bij de behandelingsopties in patienten met PAH zal verder moeten worden geëxploreerd. Er is vraag naar een simpele maat om therapie bij te stellen, op te hogen of te veranderen van oraal naar intraveneuze therapie. Op grond van de resultaten uit hoofdstuk 2 en eerder onderzoek lijkt een doelgerichte behandeling met aan NT-proBNP afkapwaarde van 1685 pg/ml gerechtvaardigd (2). Prospectief multi-center onderzoek is opgezet om de haalbaarheid en de klinische waarde van een doelgerichte behandeling in relatie tot NT-proBNP te bepalen.

De diastolische functie van de rechterkamer zal in een grotere studie groep moeten worden onderzocht en de voorspellende waarde zal vergeleken moeten worden met bestaande MRI parameters (3). Hiernaast is het ontstaan van diastolische dysfunctie in relatie tot progressie van de ziekte interessant.
Rechterkamer diastolische dysfunctie kan voorafgaan aan systolische dysfunctie. Wanneer rechterkamer diastolische dysfunctie voorkomt in afwezigheid van systolische dysfunctie, zou dit kunnen duiden op het ontstaan van rechterkamer falen. Het zou in theorie mogelijk moeten zijn om met behulp van pacemaker techniek de mechanische interventriculaire asynchronie, het mechanisme van de paradoxe septum beweging, te herstellen in ernstig zieke patienten die in afwachting zijn van longtransplantatie. Door de resynchronisatie wordt de biventriculaire systolische en diastolische functie verbeterd. Preklinisch onderzoek is nodig om het effect van pacen op de cardiale functie vast te stellen.

De zoektocht naar nieuwe objectieve uitkomstmaten in klinisch onderzoek gaat voort. Hoewel de MRI een kostbare onderzoeks ‘tool’ is, heeft het de potentie om een belangrijke rol te spelen als het gaat om monitoren en evalueren van therapie in klinisch onderzoek. Parameters zoals rechterkamer volumes, massa, functie, stijfheid van de pulmonaal arterie kunnen worden verkregen in een MRI sessie. Technieken die de perfusie van de longen kunnen quantificeren worden onderzocht. De eerste resultaten zijn zeer bemoedigend (4). De koppeling tussen de rechterkamer en het pulmonale vaatbed is een moeilijk begrip en er zijn nog onduidelijkheden. Wiskundige modellen van de interactie van het hart en het vaatbed is een veelbelovende methode om onze kennis te verbreden. Binnen de onderzoeksgroep van het Vumc wordt hieraan gewerkt.

Om te begrijpen wat er gebeurt in patienten waarbij rechterkamer falen optreedt, is het noodzakelijk de moleculaire basis te bergijpen. Het is van belang om inzicht te krijgen in de transitie van de geadapteerde naar een falende rechterkamer speelt. Dierstudies zijn hiervoor noodzakelijk. Er aanwijzingen dat hypxie van de cardiomyocyt een belangrijke rol speelt in dit proces. Dit wordt onderzocht momenteel onderzocht in een diermodel en zal in patienten worden onderzocht middels PET. De bevindingen van deze studies vormen het fundament voor toekomstige studies die zich zullen focussen op therapien, die de transitie van een geadapteerde naar een falende rechterkamer kan voorkomen.
Referenties


Dankwoord
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Curriculum vitae
List of publications
List of publications


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