CHAPTER 1

INTRODUCTION AND OUTLINE OF THE THESIS
PULMONARY CIRCULATION

The pulmonary circulation is a low-pressure circuit and is functionally coupled to the right ventricle (RV). Its main task is to facilitate gas exchange. Essentially, systemic venous return of deoxygenated blood is pumped into the pulmonary arteries by the RV where in the capillaries it is supplied with oxygen and where simultaneously carbon dioxide is eliminated. The oxygenated blood enters the left ventricle (LV) and is then ejected into the systemic circulation where it is transported to all the tissues of the body. The pulmonary circulation is suited to transport the same amount of blood (same cardiac output) as the systemic circulation but at much lower pressures, one-sixth of its systemic counterpart. Therefore, the pulmonary vascular bed and the RV have a different structure than the LV and systemic circulation.

There are several conditions that affect the pulmonary vasculature causing loss of vascular luminal cross-section (‘remodeling’) thereby increasing pulmonary vascular resistance (PVR). The increased resistance requires more energy by the RV to pump enough blood through the pulmonary vascular system resulting in increased pressure called pulmonary hypertension (PH). It has been estimated that when more than 50% of the pulmonary vascular bed is obstructed (resistance twice as high as normal; 300 dynes instead of 150), mean pulmonary artery pressure (PAP) is measurably increased from its normal value of 15 mmHg.\(^1\) With a greater resistance increase the rise in pressure may be up to six fold, i.e. mean PAP up to 90 mmHg.

Pulmonary hypertension is classified into five groups according to similar pathophysiological and therapeutic characteristics (Table 1).\(^2\) To determine PAP right heart catheterization is mandatory.\(^3\) By definition, when the mean PAP exceeds 25 mmHg at rest or >30 mmHg during exercise, pulmonary hypertension is diagnosed. When the pulmonary artery pressure is larger than 25 mmHg and pulmonary capillary wedge pressure is 15 mmHg or lower the arterial system is altered, and, in the absence of pulmonary or chronic thromboembolic disease, pulmonary arterial hypertension (PAH) is diagnosed. PAH is a devastating disease ultimately leading to RV failure and death if the pressure cannot be reversed sufficiently.\(^4\)

Two of the most distinctive categories of pulmonary hypertension are idiopathic pulmonary arterial hypertension (IPAH, category 1.1) and chronic thromboembolic pulmonary hypertension (CTEPH, category 4). In IPAH the cause of pulmonary vascular remodeling is still unknown, but lies in the distal small pulmonary arteries and arterioles. Abnormal proliferation of vascular smooth muscle cells leads to intimal hyperplasia, medial hypertrophy and adventitial proliferation, but, as yet, without an identifiable origin.\(^5\) Genetic causes may partly underlie
the disease. In CTEPH however, the vascular lesions are mainly present in the larger proximal pulmonary arteries. Incomplete thromboembolic resolution, after single or recurrent pulmonary emboli, results in fibrosis leading to mechanical obstruction of mainly large and to a lesser extent small pulmonary arteries. In the non-occluded areas distal small vessel vasculopathy, similar to lesions seen in IPAH, may develop over time aggravating the disease.\(^6\)

**THE ARTERIAL LOAD: RESISTANCE AND COMPLIANCE**

Patients with PH ultimately die from RV failure when arterial pressure overload continues. Therefore, it is important to understand the hemodynamics of the pulmonary circulation. A useful and easy way to characterize and quantify the functional state of the pulmonary arterial circulation is to assess the components of the arterial load on the RV. The two most important components are PVR and arterial compliance (C\(_A\)). Pulmonary vascular resistance is mainly determined by the small arteries and arterioles and can be calculated from the pressure-flow relationship
according to Ohm’s law as pressure drop divided by flow, i.e. mean PAP minus (mean) pulmonary capillary wedge or left atrial pressure, divided by cardiac output (CO). Arterial compliance is a quantitative measure of the arterial distensibility and reflects the storage capacity of all arteries. Several methods have been suggested to calculate \( C_a \), the simplest one being stroke volume divided by arterial pulse pressure. For the complete description of the arterial load, it is necessary to add the characteristic impedance of the proximal pulmonary artery (\( Z_c \)). Characteristic impedance is the ratio of blood mass to be accelerated and compliance of the proximal pulmonary artery. However, \( Z_c \) is of lesser importance compared with resistance and compliance and is therefore usually omitted.

It was found by Lankhaar et al.\(^8\),\(^9\) and others\(^10\),\(^11\) that the pulmonary circulation has the unique characteristic that PVR and \( C_a \) are inversely related, i.e. the product of these two parameters (PVR\( \times C_a \), units seconds), the so-called time constant of the pulmonary arterial system, or RC-time, remains constant at approximately 0.7 s under all circumstances, studied up till now. Interestingly, this relationship holds also for CTEPH patients where the obstructions are heterogeneously distributed over the two lungs.\(^8\),\(^9\) It is the question, however, how resistance and compliance are distributed over the individual lungs, and consequently if RC-time constancy holds for both lungs together as well as for individual lungs. Therefore, in chapter 2, we will investigate whether RC-time remains the same for single lungs and both lungs. Furthermore, since several compliance estimations exist, it is still unclear what is the best method of determination. Therefore, we will introduce and test two non-invasive methods to determine \( C_a \) and apply them to the systemic tree, as a preparation for application to the pulmonary arterial load in chapter 3.

**THE ARTERIAL LOAD AND RIGHT VENTRICULAR POWER**

The increased load on the heart in PAH requires more power to be delivered by the right heart. Power is the product of pressure and flow and with the increased pressure and (initially) small decrease in flow, power is strongly increased. Total hydraulic power consists of mean power (mean pressure times mean flow) which is related to resistance and oscillatory power (pulsatile pressure times pulsatile flow) which is related to compliance. Because oscillatory power does not add to the production of net forward flow, it is regarded as ‘wasted’ energy. The amount of oscillatory power in the pulmonary circulation is a larger part of total power than it is the case in the systemic circulation.\(^12\),\(^13\) How arterial load changes affect RV hydraulic power in PAH is largely unknown and will be studied in chapter 4.
TREATMENT EFFECT ASSESSMENT AND RESISTANCE CHANGE

Currently, several approved PAH-specific therapies are in use to reverse or at least delay disease progression in PAH. All types of drugs have vasodilatory properties and probably to some extent antiproliferative effects as well, both effects lower PVR and consequently lower PAP, and/or increase CO. Therefore, PVR is often taken as an important hemodynamic measure in clinical studies and absolute changes in PVR are commonly used to compare different treatments. According to Poiseuille’s law however, a similar dilatation in small arteries will lead to more reduction in PVR in arteries with a small radius at baseline than arteries with a large radius. For this reason, it is conceivable that a similar therapeutic effect of drugs will lower PVR more if baseline PVR is high (small radius) than when PVR is low. Therefore, we investigate in chapter 5 the hypothesis that the initial PVR predicts the PVR response on treatment and that the relative rather than the absolute treatment response in PVR gives a systematic result.

SURVIVAL IN CTEPH VS. IPAH

For CTEPH the natural history and treatment are completely different from IPAH. This disease can be, if not too distally located, cured with surgical disobliteration by pulmonary endarterectomy (PEA), which is therefore the standard treatment in most patients. This very demanding operation, performed through median sternotomy during circulatory arrest under deep hypothermia, was first developed and established at the University of California, San Diego (UCSD), and is now practiced at several centers worldwide. At experienced centers, the outcome is satisfactory with restoration of pulmonary hemodynamics to normal or near normal values. In 1999 St Antonius hospital started a PEA program based on the program performed at the UCSD, and in chapter 6 we will evaluate the outcomes of our institutional PEA program. We will also try to identify prognostic factors and ways to improve outcomes.

Not all CTEPH patients are operable and those patients are treated medically. Before modern treatment with PAH-specific drugs became available, small studies showed poor survival. In one study it was reported that the 5-year survival rate was only 10% when mean PAP exceeded 50 mmHg. Another study reported a 3-year survival of 10% with a mean PAP of greater than 30 mmHg. However, these studies were limited by selection and lead time bias and no conclusion could be drawn about the actual survival of these inoperable CTEPH patients without modern medical treatment. Therefore, in chapter 7 we will study the results of inoperable CTEPH patients treated with PAH-specific medical therapy, regarding treatment outcome and survival.
In chapter 8 we merge our current findings and give an integral approach to describe pulmonary hemodynamics.

In chapter 9 we summarize our findings and discuss future perspectives.

REFERENCE LIST
