CHAPTER 9

SUMMARY AND FUTURE PERSPECTIVES
SUMMARY

Pulmonary hypertension is a life-threatening disease characterized by progressive vascular remodeling resulting in increased pulmonary vascular resistance (PVR) and right ventricular (RV) pressure overload, eventually leading to RV failure. PH is classified into five subgroups of which PAH and CTEPH represent two key subgroups. Both disease entities have in common that the lesions are distributed in the arterial part of the pulmonary circulation. In CTEPH the lesions affect mainly the larger proximal pulmonary arteries, whereas in PAH lesions are mainly located in the distal small pulmonary arteries/arterioles. Therefore, the treatment approach of these two diseases is different. For PAH several specific medical therapies have been developed over the last decade to reverse or at least delay the disease progress. Before modern treatments were available the natural history, survival and prognostic factors have been determined. The prognosis was very poor, survival worse and determined by functional class and RV functional parameters. More contemporary studies have been performed to investigate the influence of modern specific-PAH therapy on pulmonary hemodynamics and survival, both are improved modestly and remain still poor. In addition, various prognostic factors have been identified in these studies consisting of functional class, exercise capacity (6-minute walk distance), gender and right heart sided hemodynamic parameters (right atrial pressure and cardiac output).

Pulmonary vascular resistance and $C_a$ are the two main components of arterial load. Studies by Lankhaar et al. in our institution have shown that PVR and $C_a$ are inversely related, which means that the RC-time $(PVR \times C_a)$ is constant under all circumstances studied so far, except in pulmonary hypertension secondary to left heart disease. Interestingly, this constancy holds also for CTEPH patients where the vascular lesions are unequally distributed between the two lungs. In chapter 2 we studied the relationship between PVR and $C_a$ in each lung and we showed that the RC-time is constant and the same for each lung individually. Based on this and the fact that similar relationships have been reported in other types of PH, this finding most likely implies that PVR and $C_a$ are equally distributed over the pulmonary vascular bed and that disease does not disrupt this relationship. Thus, if a segment, a lobe or a whole lung, is obstructed or removed the resistance increases and the compliance decreases, both in the same proportion. This is remarkable since in the systemic circulation resistance is mainly located distally in the peripheral arterioles whereas compliance is mainly located in the proximal aorta. Therefore, RC-time in the systemic circulation is not constant, and changes in hypertensive patients. Recent study by Tedford et al. confirmed the RC-time constancy in the pulmonary circulation in patients with various types of pulmonary vascular disease and also attributed this to the explanation that RC-time constancy is the consequence of the connected distribution of resistance and compliance over
the pulmonary arteries. However, these authors also showed that with increased pulmonary capillary wedge pressure, the inverse PVR and $C_a$ relationship changes.

In chapter 3 we introduced, tested and compared two non-invasive methods to assess local compliance of the aorta in healthy subjects in preparation for application in the derivation of (local) compliance in the pulmonary arterial system. We showed that the two methods can be used to derive segmental compliances of the arterial system. We also found that the majority of the aortic compliance is located in the proximal aorta and decreases from the ascending to the descending aorta. We therefore conclude that it is feasible to assess local and total compliance non-invasively.

In chapter 4 we studied the influence of pulmonary arterial load changes on RV power. It is known that total hydraulic power increases in PAH. Since compliance, which is related to oscillations, plays an important role in the pulmonary circulation, we studied the effect of load changes on mean and oscillatory power, and their sum total power, of the RV. We showed that oscillatory power as fraction of total power, i.e. the oscillatory power fraction, in healthy individuals is 23% and it remains the same in PAH. Compared with the systemic circulation, this oscillatory power fraction of 23% is high in health since the systemic fraction is 10%. In systemic hypertension the oscillatory power fraction increases, while it remains 23% in PAH. We discussed and showed in our analysis that this constant power fraction of the pulmonary load is the consequence of the proportional relationships of mean, systolic and diastolic pulmonary artery pressures, and thus the constant RC. This relation between pressure proportionality and RC-time constancy has recently been worked out in a simulation model of PH. Constancy of the fractional oscillatory power indicates that the oscillatory load of the RV, which is regarded as wasted energy, is relatively high and makes the RV work less efficient, but is not increased in pulmonary hypertension.

PVR is sometimes regarded as an important hemodynamic endpoint to measure therapeutic effectiveness in PAH. According to Poiseuille’s law however, it is to be expected that treatment with PAH-specific drugs, will have a larger effect on PVR in patients with high baseline PVR than low baseline PVR. In chapter 5 we investigated the relation between baseline PVR and PVR-response of approved PAH-specific drugs in patients with PAH. We showed convincingly that the degree of PVR decrease is indeed larger when PVR measured at baseline is higher. In other words, we showed that the PVR response should be quantified by simply calculating relative rather than absolute changes.

In contrast to PAH, CTEPH can be potentially cured by surgical removal of the obstructive lesions by pulmonary endarterectomy (PEA). This surgical technique was developed at the UCSD and practiced at several centers worldwide. PEA
is a technically demanding operation and requires excellent surgical skills and experience. Little is known about the long-term outcome and prognostic factors after PEA. In chapter 6 we investigated the long-term outcome and determined prognostic factors in patients with operable CTEPH after PEA. The results showed an overall in-hospital mortality of 6.9% since the start of the program and a 2.6% mortality in the last 3 years providing evidence for the learning curve. In the majority of patients a significant clinical improvement was observed. We concluded that long-term survival and operative mortality are satisfactory. Based on the learning curve we agree with recent guidelines recommending to limit PEA programs to experienced high volume centers.14 In addition, postoperative hemodynamic parameters (i.e. mPAP and PVR) were found to be of prognostic relevance. Indicating that residual PH determines outcome of the operation. A high PVR might indicate distal vasculopathy and thus residual PH after surgery. Therefore, the preoperative assessment of surgical accessibility of the vascular obstructions is crucial for the success of the operation. Until now there are no diagnostic tools which can visualize and/or quantify the extent of distal vasculopathy and its impact on hemodynamics.

Not all patients with CTEPH are eligible for PEA. It has been shown that inoperable patients without medical treatment have a poor prognosis related to hemodynamic severity.15,16 Although PAH-specific therapy is not approved for CTEPH, we have been treating these inoperable patients with PAH-specific therapy on a compassionate use basis since 2004. The influence of this therapy on survival and prognostic factors was studied in chapter 7. We showed an improved overall survival with PAH-specific therapy compared with survival rates observed in the pre-modern treatment era. However, in contrast to the study by Condliffe et al.17 published at the same time as ours, we could show a survival benefit between survivors and non-survivors who were treated with PAH-specific therapy. In addition, we identified prognostic factors which appeared to be similar to well known prognostic factors in PAH studies.5

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In chapter 2 we have shown that the inverse relationship between PVR and compliance holds for a single lung. What remains unknown is whether indeed resistance and compliance are uniformly distributed along the pulmonary arterial tree, although the uniformity between different types of PH is highly suggestive for that. To validate this we suggest to measure pulmonary artery pressure and blood flow velocity (e.g., with an electromagnetic catheter-tip velocity transducer), combined with an intravascular ultrasound, at several locations in the pulmonary artery tree. By using this approach, local compliance along the pulmonary circulation from proximal to distal might be assessed (methods as proposed in chapter 3).
In chapter 3 we introduced a new method to assess local arterial compliance. While we developed this method with the goal to apply it on the pulmonary arterial tree, this method makes it possible to study local (aortic) compliance and cardiovascular diseases in the systemic circulation in several diseases. For instance, the relation between local changes in (proximal) aortic compliance in hypertension and ageing, also arterial compliance in Marfan, atherosclerosis, diabetes, etc. are of interest. Another advantage of this method is that it allows studying the influence of surgically placed aortic conduits on arterial compliance. The method can be and should be used to study local and global compliance (changes) in the pulmonary arterial tree.

From the study about the RV oscillatory power from chapter 4 we now understand that during development of pulmonary hypertension the oscillatory power fraction remains constant (at a high level of 23%). This oscillatory power as explained in chapter 4 is regarded as ‘wasted energy’ in the sense that it does not add to net forward flow and makes the RV function inefficient, thus a reduction could be beneficial for the RV. Since the constant power fraction results from the constancy of RxC_a, simple reduction of resistance cannot reduce the power fraction. Thus it seems beneficial to lower this oscillatory power by enhancing arterial compliance over and above the increase in compliance provoked by resistance reduction alone. Experimental animal studies have been performed to show that reduction of arterial stiffness by increasing the elastin content in the pulmonary arterial wall,^{18,19} and possibly by breakage of advanced glycation end products^{20,21} (the latter treatment option comes from the systemic circulation). Further research will be necessary to investigate whether compliance enhancing therapeutics can be of help to reduce the pulsatile load. Another approach to reduce the power output of the right ventricle without changing the properties of the pulmonary vasculature is by placing a right ventricular assist device (RVAD). This unloads the RV while CO is maintained. Recent developments have shown that this type of device can be implanted percutaneously.^{22} Before applying an RVAD it will be important to investigate the influence of various flow rates on the pulmonary vasculature in PAH in order to assess the adequate amount of flow without causing detrimental effects on the diseased vasculature.

From chapter 5 we learnt that relative rather than absolute changes in PVR better reflects treatment response. The advantage of this approach is that a comparison between PAH specific drugs based on changes in PVR can be made. In addition, our results showed that at a high PVR at baseline, a larger drop in PVR is required to achieve a similar relative drop in PVR. However, recent results from our group showed that a decrease in PVR with PAH-specific therapies can still lead to progression of right ventricular failure and a poor survival.^{23} This may be because the achieved PVR is usually not nearly close to normal values. We do know, namely, from lung transplants and PEA that normalization of PVR will
lead to normalization of RV function. The question that needs to be addressed in the future is: ‘what is the relative PVR change that will preserve/improve right ventricular function and improve survival’.

In chapter 6 and chapter 7 we determined prognostic factors in operable CTEPH patients after PEA, and in inoperable CTEPH patients in the modern treatment era. For the operable CTEPH patients it would be very useful to be able to predict which patients will and will not benefit from surgery. It is known that patients with severe small vessel disease are very likely not to benefit from PEA because of the surgical inaccessibility of small vessel disease. However, no accurate measures or diagnostic tools are yet available to assess the severity of small vessel disease, except the suspicion that patients with out of proportion PH in relation to the angiographic obstructions are likely to have small vessel disease. These patients are difficult to distinguish from PAH. Therefore, it is very important to find a tool or measure(s) to assess the extent of distal obstruction in patients with CTEPH for evaluation of operability. Novel progresses made in CT imaging and MR perfusion imaging of the lungs might make it possible to get information on the localization of the lesions in the pulmonary vascular bed. Another recent development which needs further validation before applying it in clinical practice is the partitioning of resistance with the occlusion technique to distinguish CTEPH patients with proximal and distal disease. However, because of its invasiveness and technical difficulty, imaging techniques are probably more promising. For the inoperable CTEPH patients only one randomized clinical trial has been performed. Therefore, more research is necessary to assess the effectiveness of PAH-specific drugs in inoperable CTEPH.

REFERENCE LIST

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