Striated muscle dysfunction in Pulmonary Arterial Hypertension

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Conclusion and future research

7.1 CONCLUSION

In this thesis, evidence has been provided indicating that PAH is not limited to changes in the pulmonary circulation and the RV, but also involves alterations in LV and skeletal muscle function, which contribute to exercise intolerance. In figure 7.1 a schematic overview is provided to illustrate how PAH affects these striated muscles. The RV in PAH adapts to the increase in afterload and becomes hypertrophic. Despite this adaptation, the RV is not capable to sustain the long-term pressure overload and eventually dilates and fails. As a consequence of leftward septum bulging and reduced RV output, RV adaptation may lead to impaired LV filling. The reduction in LV filling leads to LV atrophy and contractile dysfunction (chapter 2). The reduction in both RV and LV function leads to a decrease in cardiac output, which results in impaired O_2 supply to the skeletal muscles. Furthermore, PAH and RV dysfunction leads to alterations in systemic factors [114]. For example, an increase inflammatory response and neurohormonal overstimulation is present in PAH-patients. Together with a reduction in O_2 supply this can affect skeletal muscle function. In addition, we propose that a change in skeletal muscle activity might be an extra trigger to induce skeletal muscle dysfunction. Inspiratory muscle activity may increase, eventually leading to a substantial reduction in inspiratory muscle strength and diaphragm weakness (chapter 3 and 4). However, peripheral muscle activity might decrease which leads to small but significant reductions

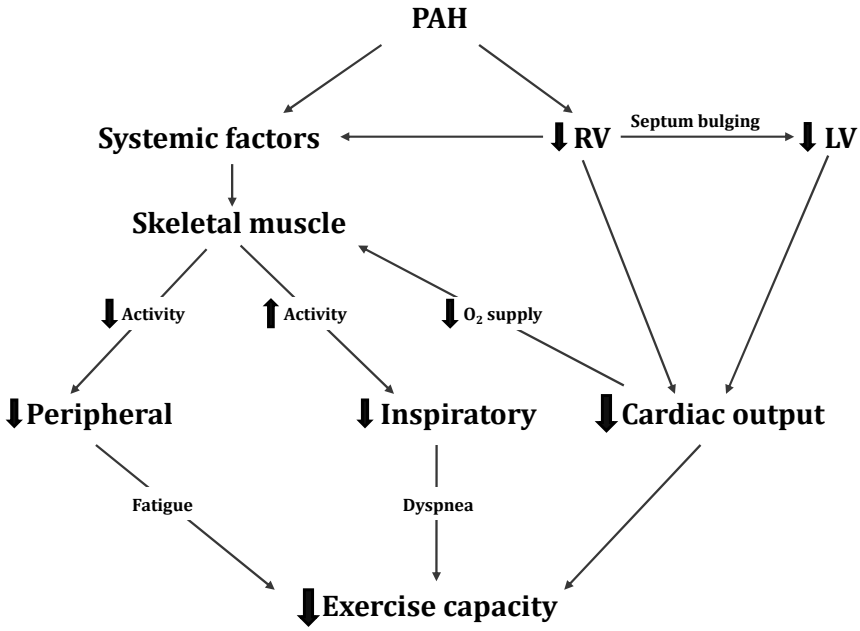

Figure 7.1: Schematically overview of the muscular adaptations involved in PAH contributing to exercise intolerance.

in peripheral muscle function (chapter 5). The reduction in peripheral and inspiratory muscle strength may contribute to the sensation of dyspnea and fatigue. Together with the reduction in cardiac output this may contribute to exercise intolerance in PAH-patients. Future therapeutic strategies targeting striated muscle function may lead to improvements in exercise capacity and quality of life of PAH-patients.

7.2 FUTURE RESEARCH

Clinical implications of LV dysfunction

Several studies have reported on impaired *in vivo* LV function in PAH-patients [35, 50, 51, 92, 129]. This has been attributed to left-ward septum bowing due to RV-to-LV dyssynchrony and reduced RV output in PAH-patients. We have shown in chapter 2 that cardiomyocyte atrophy and sarcomeric dysfunction contributes to the observed LV dysfunction. However, the clinical implications of these alterations is still unknown.

PAH-patients eventually die from right heart failure, which may suggest that LV function is inferior in PAH. However, it has been suggested that the LV contributes for 20% - 40% to RV work. Furthermore, RV dyssynchrony is associated with LV dyssynchrony and LV dysfunction in PAH [46]. Therefore, improving LV function in PAH-patients may lead to improvements in RV function. This may be achieved by cardiac resynchronization therapy, thereby reducing RV-to-LV delay in peak myocardial shortening and consequently reduce leftward septum bowing. In a recent pilot study, RV pacing improved LV stroke volume, diastolic filling and RV contractility in patients with CTEPH [53].

In addition, LV dysfunction might play a large role in the post-operative complications observed in PAH-patients after a lung-transplant. The hypertrophic and hypercontractile RV vigorously pumps blood into the now low resistance pulmonary vasculature after a lung-transplant. The LV may not be able to cope with the sudden increase in LV filling and fails. Several case reports on PAH-patients undergoing a lung-transplant describe the presence of LV failure or dysfunction [4, 9, 67, 144, 153]. It would be of interest to study LV function before and shortly after lung-transplantation to examine which patients are at risk for post-operative complications. This could give directions to improve LV function shortly before lung-transplantation or to gradually increase LV filling after the lung-transplant.

Partitioning the contributors of muscle weakness and fatigue

In chapters 4 and 5 we have shown that sarcomeric function in the diaphragm and quadriceps muscle of PAH-patients is impaired. This may contribute to the observed reduction in *in vivo* muscle strength and fatigue. However, impaired O_2 supply or extraction of the muscles could also be an important contributor to impaired exercise capacity. Due to the lowered cardiac output, O_2 supply to the muscles might be limited.

In addition, skeletal muscle capillary density might also be reduced, thereby further reducing O_2 supply to the muscle fibers.

Further experiments to discriminate between intrinsic muscle weakness and limitations in O_2 supply and extraction of the muscles are necessary. This may be accomplished by measuring exercise capacity and muscle strength under normoxic and hyperoxic (100% O_2) conditions. With standard cycle ergometry, impaired cardiac function is possibly the major factor limiting exercise capacity in PAH-patients. However, with single leg strength measurements, it can be assumed that cardiac output is not limited. These measurements could identify the role of centrally limited O_2 supply versus compromised peripheral O_2 use. With the addition of O_2 supplementation it might be possible to study the contribution of intrinsic muscle weakness. Combined with measurements on muscle perfusion and metabolism more insight in the different contributors of exercise impairment in PAH-patients can be studied.

Treating skeletal muscle dysfunction

Improving sarcomeric function in PAH-patients is of interest as it at least partly contributes to skeletal muscle weakness. As described in the discussion, the fast-skeletal troponin activator Tirasemtiv, is of interest as it specifically targets skeletal muscles and has no effect on cardiac or smooth muscle cells [118]. It increases the Ca^{2+} sensitivity of muscle fibers and thus submaximal force generation.

To investigate the effect of this calcium sensitizer in PAH, the monocrotaline or sugen hypoxia rat model can be used. The response to Tirasemtiv can be studied in *ex vivo* preparation but it might be more valuable to study the response *in vivo*. The effect on inspiratory muscle function can then be studied with whole body plethysmography. With this technique, tidal volume, breathing frequency and minute ventilation, can be studied in conscious rats. In addition, calcium sensitizers might be more energetically beneficial, as less calcium is needed for a certain force response. Reuptake of calcium into the sarcoplasmic reticulum is a high energy consuming process. Previous studies with an other calcium sensitizer showed that neuromechanical efficiency improved by ∼20% in healthy controls [24]. Therefore, it would be of interest to study endurance capacity and muscle fatigue in these rats.

Tirasemtiv is currently in clinical trials for amyotrophic lateral sclerosis patients. In future, this may potentially be an additional treatment for PAH-patients. This would also give more insight in the contribution of sarcomeric dysfunction to muscle weakness and exercise intolerance.