General Introduction and
Outline of the Thesis

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1.1 General Introduction

The diaphragm is the most important muscle of inspiration (1). It is a fascinating muscle with regard to structure, function and recovery after impairment. Treatment of diaphragm impairments like paralysis or herniation requires a multidisciplinary approach. In this line of thought we have formed such a team and the studies described in this thesis are the result of the aim to improve our understanding of the function and treatment of the paralyzed diaphragm.

The starting point of the research presented in this thesis was the treatment of symptomatic patients with hemidiaphragm paralysis by plication. These patients typically suffer from dyspnœa, which is treated by plication of the diaphragm in order to prevent its paradoxical movement on inspiration. A variety of open and minimally invasive plication techniques have been described, but all are hampered by postthoracotomy pain or limited vision. One of our patients made us change our approach: This patient with hemidiaphragm paralysis was found to have a hepatodiaphragmatic interposition of the large intestine, i.e. Chilaiditi’s sign. Because of this interposition, we choose a laparoscopic approach for plicating the diaphragm, to minimise the risk of intestine perforation or compression. In this patient, during surgery, visibility was excellent and, more important, the patient experienced minimal discomfort postoperatively. Minimally invasive techniques with their advantages such as decreased postoperative pain, improvement in patients’ functional status and pulmonary spirometry (2) have already found their way in the treatment of patients. However, the postoperative pain may be as severe as after open thoracotomy due to intercostals nerve damage by the trocars. Our new laparoscopic approach avoids this and may ease the decision-making process for the treatment of phrenic nerve palsy patients in the future.

Although the beneficial effect of plication has been proven, little is known about the underlying mechanisms of improvement, since pulmonary function typically improves minimally after such a procedure. Understanding these mechanisms in physiological terms might be important to obtain a better selection of patients who will benefit from such a procedure in the future.

Another important question for research was the proposed muscle
weakness during diaphragm inactivity. Several studies suggest that pulmonary complications after surgery are related to postoperative inspiratory muscle weakness (3,4). Pulmonary complications, such as atelectasis, pneumonia and respiratory failure are common after surgery and contribute to morbidity in patients who have undergone thoracic surgery. These pulmonary complications may, in part, be related to inspiratory muscle weakness. The nature of this postoperative inspiratory muscle weakness is unknown but might be the result of intrinsic muscle fiber weakness. Thoracic trauma due to thoracic surgery may cause intrinsic muscle weakness of the diaphragm as a result of impairment of the chest wall kinematics and respiratory muscle action. The benefit of a minimal invasive approach is its reduction of trauma. Another important question is the effect of diaphragm inactivity on its function during thoracic surgery. Although the detrimental effects of long-term mechanical ventilation on the ICU on diaphragm function have been well described, nothing is known about the short-term effects of mechanical ventilation during thoracic surgery on diaphragm function. In addition, the impact of the mode of inactivation (mechanical ventilation vs paralysis) on the diaphragm is unknown. Finally, although the beneficial effects of diaphragm plication have been described in patients with diaphragm paralysis, little is known about the underlying mechanisms of improvement, since pulmonary function typically improves minimal after such a procedure. Understanding these mechanisms in physiological terms might be important to make a better selection of patients who will benefit from such a procedure in the future.
1.2 Outline of the Thesis

To address the research questions raised above we divided this thesis in three parts: *First (part I)*, to describe diaphragmatic function and the changes occurring in eventration and paralysis. *Second (part II)*, to evaluate patients with a paralysed diaphragm in whom diaphragm plication was carried out to prevent its paradoxical movement on inspiration, and to evaluate the effects of surgical interventions on functional outcome. In order to diminish the complications after thoracic surgery, we describe a modified minimal invasive surgical technique in correcting diaphragm functional disorders. *Finally (part III)*, we evaluate diaphragm muscle fiber function after contractile inactivity during thoracic surgery, to study the effect of diaphragm inactivity on diaphragm muscle fiber function and structure. We also studied the molecular processes that might underlie diaphragm muscle fiber weakness by studying the changes in the gene expression profile in the diaphragm following contractile inactivity during thoracic surgery.

It has been proposed that mechanical inactivity of the diaphragm during mechanical ventilation rapidly causes diaphragm atrophy and weakness (5). However, conclusive evidence for the notion that diaphragm weakness is a direct consequence of mechanical inactivity is lacking. Studying hemidiaphragm paralysis allowed us to investigate the effect of contractile inactivity on diaphragm muscle fiber function and structure.

Part I

**Chapter 2** describes the embryology, the anatomy and physiology of the diaphragm and also the functional assessment and imaging.

In **chapter 3** we will evaluate functional disorders of the diaphragm: paralysis and eventration. Although these conditions are considered to be two separate entities, they are discussed together, because symptoms and treatment are similar. In symptomatic patients with unilateral disease, surgical correction may be indicated.

Part II
Diaphragm muscle weakness may cause severe dyspnoea. In symptomatic patients with unilateral diaphragm paralysis, diaphragm plication is the treatment of choice. In **Chapter 4** we evaluated patients with a paralysed diaphragm in whom diaphragm plication was carried out to prevent its paradoxical movement on inspiration. This time-honoured approach often brings relief, but the mechanism for this improvement is not well understood. Furthermore, it remains unknown whether subjective relief of symptoms also translates into an improvement of exercise tolerance. Cardiopulmonary exercise testing might provide a means to unravel the mechanisms that underlie the relief of exercise induced dyspnoea since this test enables to study the effects of surgery on ventilatory, circulatory and gas exchange parameters at exercise. For this reason, we performed cardiopulmonary exercise tests in a group of patients diagnosed with hemidiaphragm paralysis before and after plication of the diaphragm in order to explain the symptomatic relief. **Chapter 5** describes a modified laparoscopic diaphragmatic plication technique in patients with unilateral diaphragm paralysis. The laparoscopic technique has the advantage of excellent field of vision during surgery, postoperative recovery with minimal pain and early discharge from the hospital. At the end of this part, in **chapter 6** we will describe an unusual treatment of patent foramen ovale after pneumonectomy in three patients. After a pneumonectomy, anatomical adaptations occur with repositioning of intrathoracic structures (6,7). We postulated that plication of the diaphragm would correct the cause and would obviate the need for cardiac surgery because the right ventricular compression by the elevated right hemidiaphragm is the main cause of PFO and surgical plication of the right hemidiaphragm is possible sufficient to close the PFO again.

**Part III**

Little is known on how diaphragm inactivity or paralysis affects diaphragm fiber function and structure and investigations to answer this question are described in **chapters 7, 8, and 9**. In **chapter 7** we aimed to evaluate diaphragm muscle fiber function after contractile inactivity during thoracic surgery. The objective of this chapter was to investigate
whether a short-term interruption of normal inspiratory muscle activity during surgery caused weakness of the diaphragm. We determined the contractile performance of single diaphragm muscle fibers from biopsies taken at the beginning and at the end of a thoracic operation. These tests should reveal whether intrinsic diaphragm muscle fiber weakness develops during thoracic surgery, independent of patient motivation or effects on neural input. To test whether changes in diaphragm contractile performance were part of a generalized muscle weakness, we evaluated also muscle fibers from the non-respiratory latissimus dorsi muscle.

The study described in chapter 8 evaluated the gene expression profile in the diaphragm following contractile inactivity during thoracic surgery. In chapter 7 we found the development of marked diaphragm muscle fiber weakness during two hours of thoracic surgery. This loss of muscle fiber function was not part of a generalized muscle weakness as function of the non-respiratory latissimus dorsi muscle was preserved. To disentangle the molecular processes that might underlie the development of diaphragm muscle fiber weakness during thoracic surgery we studied changes in the gene expression profile.

In chapter 9 we investigated diaphragm muscle fiber function and structure in humans with hemidiaphragm paralysis. The contractile performance of demembranated muscle fibers was determined, as well as fiber ultrastructure and morphology. Finally, expression of E3 ligases and proteasome activity was determined to evaluate activation of the ubiquitin-proteasome pathway. The human diaphragm might be relatively resistant to contractile inactivity.

References

