Future Perspectives

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More and more is known about the function of the diaphragm, our most important respiratory muscle. But until today, possibilities to correct impairments are limited. In this chapter we briefly comment on points requiring further study

10.1 Surgical technique

Surgical treatment of diaphragm paralysis or eventration by plication of the diaphragm has been described since many years but the main achievement is the way we approach the diaphragm, thoracopically or laparoscopically. While the minimally invasive approach undoubtly has benefits, some questions remain unanswered:
1. Is muscle-wasting after denervation really irreversible?
2. Should only the fibrous dome be plicated?
3. How tight should the plication be, as a very tight plication interferes with the outward movement of the lower ribs during inspiration.

Until 2006 only a few reports with very limited numbers of patients have been published using a laparoscopic or thoracoscopic technique for surgical plication (1). For years the classic thoracotomy was the technique of choice. The main disadvantage of this technique was the so-called post-thoracotomy pain. Currently the most common used video assisted technique to plicate the diaphragm is thoracoscopy. First, the advantages of a thoracoscopic technique above a thoracotomy are obvious: less tissue trauma and an excellent field of vision. However, this technique has also its drawbacks. First, although the incisions are smaller, the incidence and intensity of post-thoracotomy pain does however not seem to be very different to that in the open approach (2). Second, a paralyzed diaphragm can be very thin and extreme care has to be taken not to puncture the abdominal organs. Third, it is questionable whether this procedure can be performed safely for the patients with bilateral surgery (3). Finally, it is difficult to achieve the same tightness of the plication by thoracoscopy in comparison to open thoracotomy (3).

But, doing the same operations in a minimal invasive way is part of today’s challenge and will not likely replaced by the open procedure. There is no discussion that all video assisted techniques have their own learning curve to optimize the result with minimal complications and beneficial effect of surgery. The described modified laparoscopic technique might offer a better alternative than the classic thoracoscopic
approach for the arguments given in this thesis (4), as described in chapter 5.

For the final answer which technique to use, either thoracoscopic, laparoscopic or even open thoracotomy, a randomized trial is required. This type of study will be difficult to perform given the rarity of the disease and requires participation of large international surgical centers. In addition, given the popularity of video assisted surgery it is questionable whether open thoracotomy should be a separate arm in such a trial.

A comparison between the techniques should be made based on functional outcomes (exercise tolerance) and complication rates. Other points which need to be studied are the long-term benefits and health-related quality of life in patients after diaphragmatic plication.

10.2 Effect of artificial ventilation

During the past decade, several studies have used diaphragm biopsies obtained during thoracotomy to investigate the effect of, for instance, COPD (5-15) and heart failure (16,17), on the diaphragm. Marked muscle fiber weakness was seen in the diaphragm already after two hours of surgery but not in other respiratory muscles. Apparently diaphragm function decreases quickly and this may explain the high rate of respiratory complications following surgery. Diaphragm weakness might be even more exaggerated after operations of longer (>2 hours) duration. If such time-dependency of diaphragm muscle weakness is confirmed in future studies by studying biopsies obtained at multiple time-points during longer-term thoracic surgery, it opens the way for new methods to prevent pulmonary complications, for example, by gentle diaphragmatic muscle pacing during long-lasting operations. In ventilated patients on an intensive care unit such pacing could also be considered, either by phrenic nerve stimulation or by electrodes placed in a nasogastric tube. These tubes already exist: The so-called NAVA (Neurally Adjusted Ventilator Assist) ventilation uses diaphragmatic phrenic nerve activity to trigger the ventilator.

Future studies on high-risk patients should evaluate whether the magnitude of diaphragm muscle fiber weakness correlates with the incidence of pulmonary complications.

10.3 Diaphragm atrophy
Postoperative pulmonary complications after thoracic surgery are common and contribute to morbidity in patients who have undergone thoracic surgery. Possible solutions may result from molecular research: The inhibition of E3-ligases, such as MAFbx and MuRF-1, which are considered key markers of proteolytic activity in muscle, may also become part of a solution to prevent the development of inspiratory muscle weakness and so reduce postoperative pulmonary complications and weaning problems.

The mechanism(s) that prevent the initial development of diaphragm weakness in patients with diaphragm paralysis is still unclear (chapter 9). In contrast to the cyclic passive shortening of the diaphragm during mechanical ventilation, the paralyzed hemidiaphragm undergoes cyclic stretch due to the persistent contractions of the normally innervated contra lateral hemidiaphragm. This paradoxical, cranial, movement of the paralyzed diaphragm during inspiration is a hallmark feature of patients with hemi-diaphragm paralysis. Passive stretch is a known stimulus for muscle protein synthesis and growth (18), and might play an important role in the maintenance of muscle mass. Within the muscle’s sarcomere, the giant protein titin is considered to play an important role in the stress-response machinery (19) by acting as a mechano-sensor that regulates muscle protein expression in a sarcomere strain-dependent fashion (20,21). Titin is an attractive candidate for sensing the passive stretch imposed on paralyzed diaphragm muscle fibers, and might be involved in the initial preservation of muscle fiber size and contractile function.

Future studies are needed to identify the mechanical and molecular mechanisms that underlie the human diaphragm’s resistance to weakness and atrophy following paralysis.

10.4 Pulmonary volume
Another focus in our research is the function of the paralysed hemi-diaphragm and the effect on the ipsilateral and contra lateral pulmonary volume and cardiac volumes. Physiological studies of the respiratory system classically include volume and pressure variations. But as the diaphragm is neither visible nor easily accessible from the outside of the body, studying the diaphragm deformation requires the use of three-dimensional medical images, either CT scan or (dynamic) MRI.
Therefore we designed, and are currently performing, a study to measure the volume of both the ipsi- and contra lateral thoracic cavities, as well as the heart-function during breathing sequels using dynamic MRI-techniques.

In this study design we focus on intra-cardiac volumes, to see if the filling of the right atrium and right ventricle deteriorate during the paradoxical movement of the paralysed hemidiaphragm. Our hypothesis is that the cardiac function will be preserved.

All these exciting topics seem worth to be explored further and we are much interested to see what will be the results. But only time will tell... or, as an old Chinese proverb states: “Only when the dust settles you will see...whether you are riding a horse...or a donkey”.

References
