SUMMARY AND CONCLUSIONS

Neuromuscular blocking agents are being used for over half a century in clinical anesthesia. They have played an important role in the development of modern anesthesia and surgery, and in the understanding of physiological processes that take place at the neuromuscular junction. These drugs are administered to patients to provide tracheal intubation, to facilitate artificial ventilation, to create optimal surgical conditions and to enable ventilatory treatment for specific diseases, e.g. tetanus. In order to optimize safety in administration of the muscle relaxants, the individual drug response should be assessed by monitoring the characteristics of muscle relaxant induced neuromuscular block.

A goal of this thesis is to evaluate the different techniques that are used at present to monitor the neuromuscular effects of muscle relaxants, e.g. by mechano-myographic, electromyographic or accelographic equipment.

Relaxation of the intrinsic laryngeal muscles is mandatory in the development of optimal intubating conditions in order to prevent traumatic injury of the vocal cords during tracheal intubation. Due to the absence of suitable monitoring techniques, knowledge of the response of laryngeal muscles to neuromuscular blocking agents is fragmentary and is based on empiricism and extrapolation from other muscles. Therefore, development of an *in vivo* model for measuring the effects of muscle relaxants on the vocal cords and definition of more objective criteria to assess the quality of intubating conditions were other goals of this thesis.

Chapters 1 to 5 review the methods currently used to monitor neuromuscular transmission and summarize the existing differences in evaluation criteria as well as the controversies regarding the suitability of the various monitoring techniques for the clinical setting.

Chapter 1 presents the history of tracheotomy, tracheal intubation and the development of endotracheal tubes.

Chapter 2 is on monitoring of neuromuscular transmission. The relevant anatomy and physiology of neuromuscular transmission and muscle contraction are reviewed and the pharmacological action of neuromuscular blocking agents is described. Also, the features of peripheral nerve stimulators and of neuromuscular transmission analyzers are summarized, and the clinically used nerve stimulation patterns are discussed in greater detail. Based on the available information summarized in this chapter, the main characteristics and technical requirements for the future monitoring equipment is defined and the need for standardized nerve stimulation patterns is emphasized.

Chapter 3 is a review of the literature data on differences in muscular respo neuromuscular blocking agents. Based on this review, simple extrapolations data observed in one single skeletal muscle to other skeletal muscles, as uncritical generalization in the interpretation of these data should be ques Also, a number of possible mechanisms by which the different effects of relaxants can be explained at the various muscles are described and discussed.

Chapter 4 focuses on the current clinical scoring systems used to assess intu conditions and shows also their limitations. Two alternative methods to intubating conditions with greater accuracy and presumably with greater c impact are also briefly discussed.

Chapter 5 summarizes the present state of the clinical practice regarding tracheal intubation with emphasis on the position, advantages and disadvanta the muscle relaxants. It provides also justification for the future search f optimal agent that will be most probably a nondepolarizing compound with the course profile of succinylcholine, however, free of its unwanted effects.

Chapter 6 justifies the supplements. The various studies in supplements I were undertaken with the following aims:

- to present a neuromuscular transmission analyzer that meets the requiremer modern standards of monitoring of neuromuscular transmission,
- to develop experimental methods to quantify the neuromuscular blocking ef of muscle relaxants on the vocal cords in animal and man, in order
- to investigate the effects of muscle relaxants in animal and man at the cords and skeletal muscle simultaneously,
- and to demonstrate the importance of standardization of criteria to a neuromuscular block with particular emphasis on the nerve stimulation patte

The supplements are papers published or submitted for publication. They reports on experimental work focused on monitoring of neuromuscular transmis with special interest in the quantitation of neuromuscular block at the vocal cord

Supplement I describes a new computerized mechanomyographic neuromusc transmission analyzer. It was specially developed to meet the modern demands are imposed on such monitors. The analyzer consists of a master computer un combination with a microprocessor-driven constant-current nerve stimulator monitoring unit. Various nerve stimulation patterns can be selected and all rele data are continuously presented on screen.

Supplement II presents an *in vivo* model in the cat which enables to study neuromuscular blocking effects of muscle relaxants simultaneously on the cords and on the tibialis anterior muscle. Following recurrent nerve stimulation force of the evoked vocal cord movements is measured mechanomyographic The main finding of this study shows that the vocal cords react with diff

sensitivities to the muscle relaxants when compared to the tibialis anterior muscle.

In **Supplement III**, the effects of single twitch and train-of-four stimulation were studied on neuromuscular block characteristics following a slow bolus dose of rocuronium at the vocal cords and at the tibialis anterior muscle in pigs. It was shown that train-of-four stimulation resulted in an increased sensitivity of both muscles for rocuronium resulting in a shorter lag time, a more intense and longer lasting neuromuscular block when compared with single twitch stimulation. This increased sensitivity is probably caused by a diminished release of acetylcholine following the nerve stimulation at higher frequency.

Supplement IV describes a dose response study of vecuronium on the vocal cords in man. Log-logit analysis of the dose response relationship following a two-step administration of vecuronium was performed. The derived ED50 and ED90 values were 33 and 40 μg/kg, respectively, with a 95% confidence interval of 30-36 and 35-46 μg/kg, respectively.

Supplement V presents the results of a clinical study in which intubating conditions were assessed 60 or 90 seconds following administration of 600 μg/kg rocuronium or 1.5 mg/kg suxamethonium preceded by 10 mg gallamine. A control group of patients who did not receive a muscle relaxant was also included. It was concluded that this dose of rocuronium produces, like suxamethonium, excellent intubating conditions in all patients 60 seconds after its administration. These results, when combined with others in a greater number of patients, will challenge the supremacy of suxamethonium, which is still the "golden standard" drug for endotracheal intubation.

The experimental work described in this thesis resulted in completion of the development of a mechanomyographic-based neuromuscular transmission analyzer which, in clinical practice in different centers, has been proved to be a sophisticated and reliable piece of equipment. Also a new *in vivo* experimental method has been developed, allowing simultaneous study of the pharmacodynamic profile of neuromuscular blocking agents at the skeletal muscle and the vocal cords. The results generated by the vocal cord - tibialis anterior muscle preparation have confirmed or demonstrated:

- difference in the sensitivity of these muscles to the effects of neuromuscular blocking drugs.
- important stimulation frequency dependent alterations of the block characteristics on the vocal cords similar to those observed earlier on the peripheral skeletal muscles. Therefore, in studies focused on the relationship between the onset time and the rate of development of intubating conditions the single twitch stimulation should be used. The train-of-four stimulation will produce faster onset time, but this is confined to the stimulated muscle only which, in turn, will prompt intubation attempts before adequate intubating conditions could have developed.

Further clinical experiments demonstrate that intubating conditions cannot assessed by direct measurements from the skeletal muscle, or from the vocal co Consequently, the validity of the qualitative methods for the assessment intubating conditions remains unchallenged, however, they could and should further refined.