SUMMARY AND CONCLUSIONS

When a patient is under general anaesthesia and muscle relaxation is required, the anaesthesiologist must assess whether the degree of muscle relaxation is sufficient for endotracheal intubation and the surgical procedure. After completion of the procedure, he must know whether the muscle relaxation has disappeared and the patient has regained adequate airway reflexes and ventilatory control. The 'gold standard' for measuring the neuromuscular function is mechanomyography of the adductor pollicis muscle, i.e. measurement of the contraction forces of the adductor pollicis muscle after stimulation of the ulnar nerve. The aim of this thesis was to study the effect of the measurement technique itself, i.e. the nerve stimulation and force measurement, on the results when mechanomyography of the adductor pollicis muscle is employed in pharmacodynamic studies of muscle relaxants. After the evaluation of the Relaxometer, which was the measurement device used for the mechanomyography of the adductor pollicis muscle in this investigation, the effect of the measurement technique on the results was studied first in the absence, and later in the presence of muscle relaxation.

The tests performed to evaluate the nerve stimulation and force measurement of the Relaxometer (Chapter 3) show that the Relaxometer is an accurate measurement device, suitable for monitoring neuromuscular function for clinical research.

Both single twitch (ST; 0.1 Hz) and train-of-four (TOF; 4 stimuli at 2 Hz, followed by a 10.5 s stimulus interval, i.e. the time between two consecutive TOF stimuli) are stimulation patterns of the ulnar nerve which are commonly employed in pharmacodynamic studies. When ST or TOF stimulation is started in the absence of muscle relaxation twitch forces of the adductor pollicis increase progressively and then stabilize. Stabilized twitch forces are greater in response to TOF than to ST stimulation (Chapter 4).

An increase in twitch force can be related either to an increase in thumb abduction (adjusted in order to correct the progressive decrease in thumb preload and thus maintain the preload constant, as employed in Chapter 4 and recommended in the Good Clinical Research Practice guidelines for mechanomyography) or to a progressive decrease of thumb preload towards its resting tension (at a constant degree of abduction; Chapter 5). In the presence of a constant preload a larger increase in twitch force is seen than when thumb abduction is held constant. Changes in length of the contracting muscle fibres and creep phenomena in the connective tissue of the muscles, both leading to changes in the sarcomere length of the muscle fibres, may explain these observations. In general, a stabilized preload at a constant degree of abduction is required in order to obtain a stable twitch force.

However, twitch forces do increase when ST stimulation is started after stabilization of the thumb preload at a constant degree of thumb abduction (Chapter 6). In addition, it is shown in Chapter 6 that twitch forces can increase following the administration of muscle relaxants. In some patients the twitch forces increased before the onset of neuromuscular block after the administration of vecuronium or d-tubocurarine, while in all patients the twitch forces appeared to increase after recovery from suxamethonium.
In Chapter 7 it is shown that prolonged ST stimulation of the adductor pollicis muscle contributes to the increase in twitch force. The increase in twitch force in response to ST stimulation is probably related to the stimulation frequency, as discussed in Chapter 8. When ST or TOF stimulation with a 10 s stimulus interval was employed, twitch forces of the tibialis anterior muscle in the cat showed the so-called staircase effect. The staircase effect is an increase in twitch force accompanying an increase in stimulation frequency. As TOF stimulation with 10 s between consecutive trains has a higher average frequency than 0.1 Hz ST stimulation, twitch forces may be expected to increase more during TOF than during ST stimulation. This is consistent with our observations.
In Chapters 9 and 10, the effect of the measurement technique on the results was studied in the presence of muscle relaxation. As shown in Chapter 9, ST and TOF stimulation may yield different apparent time courses for a muscle relaxant after the administration of a bolus. However, ST and T1 (first twitch of a train-of-four) forces do not differ in the presence of a stable 50% neuromuscular block (Chapter 10). The latter observation was made in the tibialis anterior muscle of the cat. In Chapter 10 it is also demonstrated that the ST or T1 forces during ST or TOF stimulation with a stimulus interval of 10 s or more are not affected by the preceding stimulus during a stable 50% neuromuscular block. These results indicate that there are no significant differences in acetylcholine release during ST or T1 stimulation in these circumstances when the stimulus interval is 10 s or more. Differences in blood flow and consequent drug delivery may be solely responsible for the observed differences in time course after a single bolus injection of a muscle relaxant when either ST or TOF stimulation with a stimulus interval of 10 s or more is used.
On the basis of the studies performed in absence of muscle relaxation, two recommendations concerning twitch stabilization and thumb preload can be made. Firstly, routine prior stabilization of twitch force is not recommended when measuring the time course of action of a muscle relaxant in the clinical research setting. Stabilization of twitch forces takes too long for many clinically relevant studies of neuromuscular function (Chapter 4). Secondly, it is suggested that the degree of thumb abduction should be held constant after the preload is set initially at between 250 and 300 g. A constant thumb abduction with a preload drifting to its resting tension is accompanied by a smaller increase in twitch force than is an increasing thumb abduction with a constant preload (Chapter 5).

The effect of the measurement technique on the results observed in the absence of muscle relaxation may also influence the results in the presence of muscle relaxation. As shown in Chapter 6, the resting tension of the preload is not affected by muscle relaxation. Thus, after the administration of a muscle relaxant the increase in twitch force associated with the drifting of preload to its resting tension is relatively constant once preload has stabilized. On the other hand, the increase in twitch force related to the stimulation frequency of the adductor pollicis muscle is probably not constant after the administration of a muscle relaxant. As the stimulation of the muscle is diminished in the presence of muscle relaxation, this staircase effect of muscle stimulation on the twitch force may depend on the degree of relaxation. It may also differ for ST and TOF stimulation, since the increase in twitch force in the absence of muscle relaxation is smaller during ST than during TOF stimulation. When ST or TOF stimulation is started at the moment of administration of the bolus and thumb abduction is maintained constant throughout the measurement, twitch forces are greater than the initial value after recovery from neuromuscular block is complete, due to the drifting of preload to its resting tension and the frequency of stimulation of the adductor pollicis.

In conclusion, it is shown in this thesis that, when mechanomyography of the adductor pollicis muscle is performed, changes in either thumb preload or in thumb abduction may be accompanied by changes in twitch force and that ST and TOF stimulation may affect the twitch forces in a frequency dependent way in the absence of muscle relaxation as well as after a single bolus of a muscle relaxant. Routine prior stabilization of the twitch force is not recommended when the time course of action of a muscle relaxant is measured in the clinical research setting and it is suggested that thumb abduction should be held constant after the preload is set initially at between 250 and 300 g. These recommendations imply that the increase in twitch force that accompanies the consequent drifting of preload to its resting tension after the start of the measurement cannot be avoided. The effects of ST and TOF stimulation on twitch force may only be reduced by decreasing the stimulation frequency. However, decreasing the stimulation frequency will limit time resolution when monitoring rapid changes in neuromuscular transmission, e.g. the onset of neuromuscular blockade.