Summary

Chapter 1 introduces the objective of this thesis, the role of the functional status in patients scheduled for major surgery. The focus of perioperative hospital care is increasingly on preventive care. The studies described in this thesis reflect this development, with emphasis on the preoperative functional status of older patients (>60 years) scheduled for abdominal or thoracic surgery. The current outpatient preoperative evaluation aims to identify patients at risk of postoperative complications, by evaluating the presence of well-known demographic and/or medical factors such as age, sex, and comorbidities. This preoperative evaluation, however, pays little attention to the possible impact of the patients' preoperative functional status on postoperative outcomes even though the literature provides several reasons to do so. Physical fitness as part of patients' preoperative functional status could reflect the capacity to cope with surgical stress. This thesis will consider physical fitness in relation to postoperative recovery and surgery-related side effects, such as postoperative complications, functional decline, and mortality. A distinction is made between patients' ability to execute a task or action (capacity) and what a patient really does in his or her current environment (performance). Furthermore, this thesis will investigate the functional status as a modifiable determinant for the postoperative course in order to improve the preoperative status and postoperative course of the patient. In conclusion, this thesis will investigate the following two research questions: (1) what is the relationship between physical fitness and the postoperative recovery (such as mortality, respiratory function, incidence of postoperative pulmonary complications, length of hospital stay, and discharge destination) and (2) what is the effect of a short course of physical training given preoperatively on preoperative physical fitness and on the postoperative recovery from elective abdominal and thoracic surgery in older patients

Chapter 2 of this thesis reviewed the literature including a meta-analysis about the predictive value of preoperative physical fitness for the risk of postoperative cardiopulmonary complications after abdominal and non-cardiac thoracic surgery. The meta-analysis summarised the risk estimates of postoperative cardiopulmonary complications for the various components of preoperative physical fitness. After a systematic search of medical databases, 14 prospective cohort studies were included. Maximal aerobic capacity (VO_{2max}) was the most frequently studied component (10 studies) besides stair climb test (3 studies) and a two-minutes-walk-test (one study). Twelve studies reported on lung surgery, one on abdominal surgery and one on both types of surgery. Eight studies reported on postoperative cardiopulmonary complications, three on

postoperative pulmonary complications and three on both complications. The pooled odds ratios for the risk of postoperative cardiopulmonary complications were 4.9 (95% CI 1.8–13.7) and 2.5 (95% CI 0.6–9.9) for VO_{2max} <15 ml/kg/min and VO_{2max} <20 ml/kg/min, respectively. Heterogeneity of results for the cut-off point of 15 ml/kg/min were explained by methodological quality and degree of fitness of the study population. The pooled odds ratios for the risk of postoperative pulmonary complications were 2.7 (95% CI 0.4–18.0) and 2.0 (95% CI 0.9–4.6) for VO_{2max} <15 ml/kg/min and VO_{2max} <20 ml/kg/min, respectively. The pooled odds ratio on postoperative cardiopulmonary complications for inability of climbing three flight of stairs was 2.1 (95% CI 1.2–3.7). In this chapter we concluded that physical fitness, expressed as VO_{2max}, is predictive for the development of postoperative cardiopulmonary complications in patients after lung surgery. There is a serious lack of studies investigating other components than maximal aerobic capacity and of studies including patients who had to undergo abdominal surgery.

Logically from the preceding chapter, in **chapter 3** we studied components of physical fitness other than the aerobic capacity in patients scheduled for major abdominal surgery. A prospective cohort study of 175 patients (>60 years) investigated whether physical activity and indices of physical fitness are of additional value to known risk factors (age, metastatic cancer, diabetes, COPD, heart diseases, smoking, productive cough) in predicting the postoperative recovery. Multivariate analysis of both physical and known, conventional risk factors identified adequate activity level (OR 5.5, 95% CI 1.4–21.9) and endurance of the inspiratory muscles (OR 5.2, 95% CI 1.4–19.1) as independent predictors for short-term mortality. The C-index for the model including the physical fitness and activity factors was 0.82 versus 0.67 for the model with conventional factors (p<0.001). The C-index for the prediction model of discharge destination (home or nursing home) including physical activity and fitness factors improved from 0.66 to 0.80 (p<0.001). For length of stay, multivariate analysis revealed adequate activity level (HR 0.6, 95% CI 0.4–0.8) and inspiratory muscle strength (HR 0.6, 95% CI 0.5–0.9) as independent predictors. We conclude that preoperative physical activity and physical fitness were prognostic of postoperative recovery, additional to conventional predictors. This result emphasizes the role of physical activity and physical fitness in the pre-operative evaluation of elderly patients.

Chapter 4 introduced an alternative way to assess the function of the respiratory system. Besides a deterioration of muscle function due to anaesthesia, surgery close to the diaphragm can cause reflex inhibition of phrenic nerve output, further exacerbating the

decline in diaphragm function. In an exploratory feasibility study we investigated the discriminatory properties of linear (variability) and nonlinear (entropy) analyses of the respiratory pattern in the assessment of the adaptive capacity of the respiratory system. Use in the preoperative stratification provides merely a short-term sample time (3–5 minutes). Six young healthy volunteers (control group) and 10 older persons indicated as high-risk for postoperative pulmonary complications participated in this study. All subjects performed a respiratory test covering 70 eupneic breathing cycles. Variability of the pressure curve was quantified by the coefficient of variation of the inter-breath intervals and the amplitudes. Non-linear properties were determined as sample entropy. No significant difference was found between the coefficient of variation of the inter-breath intervals for controls (median 0.11; IQR 0.09–0.15) and patients (median 0.10; IQR 0.07–0.13). The difference between the coefficient of variation of the amplitudes of the inspiratory curves for controls (median 0.19; IQR 0.13–0.22) and patients (median 0.13; IQR 0.09–0.20) did not reach significance either (p=0.19). The same was true for the difference in expiratory curves between controls (median 0.22; IQR 0.13–0.31) and patients (median 0.12; IQR 0.07–0.22) (p=0.16). By contrast, the sample entropy distinguished significantly controls (median 0.29; IQR 0.22–0.43) from patients at high risk for postoperative pulmonary complications (median 0.19; IQR 0.14–0.24) (p=0.03). We concluded that short-term complexity-related measures of the respiratory system seem to be valid parameters for use in the risk stratification in the preoperative care of patients scheduled for major surgery affecting the postoperative respiratory function.

Following on from the observational research in the previous chapters, chapter 5 and 6 provided two experimental pilot studies that investigated the trainability of the preoperative physical fitness aiming to improve the postoperative recovery.

Chapter 5 investigated the feasibility and effects of preoperative inspiratory muscle training on the incidence of atelectasis in patients at high risk of postoperative pulmonary complications scheduled for elective abdominal aortic aneurysm surgery. Twenty high-risk patients were randomly assigned to receive preoperative inspiratory muscle training or usual care in a single-blind randomized controlled pilot study. Effectiveness outcome variables were atelectasis, inspiratory muscle strength and vital capacity. Feasibility outcome variables were adverse effects and patient satisfaction with inspiratory muscle training. Despite randomization, patients in the intervention group were significantly older than the patients in the control group, 70 ± 6 years versus 59 ± 6 years, respectively (p=0.001). Yet, eight patients in the control group and three in the intervention group

developed atelectasis (p=0.07). No adverse effects of preoperative inspiratory muscle training were observed and patients considered that inspiratory muscle training was a good preparation for surgery. In this chapter we concluded that preoperative inspiratory muscle training is well tolerated and appreciated and seems to reduce the incidence of atelectasis in patients scheduled for elective abdominal aortic aneurysm surgery.

In **chapter 6** we investigated the feasibility and preliminary effect of a short-term intensive preoperative exercise programme for elderly patients scheduled for elective abdominal oncological surgery. Forty-two elderly patients (>60 years) were included in a single-blind randomized controlled pilot study. The patients were randomly assigned, twenty-two to receive a short-term intensive therapeutic exercise programme to improve muscle strength, aerobic capacity, and functional activities, given in the outpatient department and twenty patients to a home-based exercise advice. The main outcome measures were parameters of feasibility, preoperative functional capacity and postoperative course. The intensive training programme was feasible, with a high compliance and no adverse events. Respiratory muscle endurance increased in the preoperative period from 259 ± 273 J to 404 ± 349 J in the intervention group and differed significantly from that in the control group (350 ± 299 to 305 ± 323 J) (p<0.01). Timed-Up-and-Go, chair rise time, LASA Physical Activity Questionnaire, Physical Work Capacity and Quality of Life (EORTC-C30) did not reveal significant preoperative differences between the two groups. There was no significant difference in postoperative complications and length of hospital stay between the two groups. The slight differences in the outcome of both groups could possibly be explained by the low contrast between the groups. A *post hoc* analysis revealed an association between the moderate activity of both groups and the incidence of postoperative complications. We concluded that an intensive therapeutic exercise programme was feasible and improved the respiratory function of patients due to undergo elective abdominal surgery compared with home-based exercise advice. Further research is needed to determine the effect of a preoperative exercise program aimed at increasing general physical fitness.

The concluding **chapter 7** summarizes and discusses the results of the PhD thesis research. The studies described in this PhD thesis highlight the role of functional status in older patients scheduled for abdominal and thoracic surgery which is increasingly common in older patients.

In the first part of this thesis, observational research provided convincing evidence that preoperative physical fitness and in particular physical activity are associated with

postoperative recovery after elective abdominal and thoracic surgery in older patients. In the second part, pilot experimental studies showed feasibility of preoperative high intensive physical training programmes and revealed a borderline effect on the incidence of postoperative complications in abdominal surgery.

The research studies were conceived and carried out in the real-life healthcare addressing clinical questions and using of usual care measurements, so results can readily be applied to day-to-day clinical practice. Limitations were the number of available patients in the randomized clinical trials and the lack of equipment for more fundamental measurements.

The results reported in this thesis and in the literature support the recommendation to incorporate physical activity and physical fitness factors into the risk stratification of the preoperative work-up. Observational research should focus on the use of non-linear analyses of the respiratory pattern in the preoperative evaluation. Furthermore it should be extended to the rationale behind the association of physical fitness and activity with the postoperative course. This research is needed to address the optimization of training parameters of the general physical fitness training programme and the training effect on postoperative complications by well-powered RCTs.

We hope that our findings contribute to a more functional health-based approach to hospital and surgical care. The results of these and future studies will contribute to the current transition of medical oriented hospital care to care including patients' functional health.