Preoperative **Physical fitness** in older patients

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VRIJE UNIVERSITEIT

Preoperative physical fitness in older patients

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op dinsdag 14 mei 2013 om 15.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

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geboren te Vlissingen

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1

Introduction

The focus of healthcare is increasingly on preventive care,[1] and this is also true for perioperative hospital care. Several aspects of preventive care are already being implemented during the preoperative phase, such as assessment of the patient's health, evaluation of the operative risk, and, where necessary, optimization of the patient's mental and physical condition. Perioperative hospital care is mainly focused on frail patients, who are typically aged 60 years or older and suffer from multiple medical conditions. In an increasing number of Dutch hospitals, the preoperative consultation is now common practice,[2] with anaesthetists having a coordinating role in the interdisciplinary management strategy for individual patients.

Role of preoperative functional status

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, which are major surgical procedures.[3] Patients' preoperative functional status is considered in relation to surgery-related side effects, such as postoperative complications, functional decline, and mortality. 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, diabetes, chronic obstructive pulmonary disease (COPD), and heart failure.[4-9] 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.[10-12] For this reason, functional status should be further investigated as part of the preoperative work-up in the future.

In the studies described here, functional status is investigated both as a predictor and as a prominent determinant of change (preferably improvement) during recovery from elective major surgery.

Relevance

It is essential to prevent a complicated postoperative course and to ensure that patients can perform activities of daily living (ADL) and instrumental activities of daily living (IADL) adequately after discharge from hospital, and this is especially true for older patients, in order to maintain quality of life and independent functioning and to limit the direct costs of care and additional costs, especially if home care or admission to a nursing home is necessary. In 2011, 15.6% of the Dutch population was older than 65 years (CBS, Statistics Netherlands, 2011), but this proportion will increase the coming decades by about 2% every 5 years. In 2040 more than a quarter of the population will be older than 65 years (CBS, Statistics Netherlands, 2011), and these individuals will account for a sizable part of healthcare costs. Although the level of physical activity of the Dutch population has increased over the last decade, in 2009, 52.8% (95% CI 49.5–56.1%) of people older than 65 years met the requirements for the Dutch Standard for Healthy Exercise.[13] This affects the functional status of patients, putting older patients at a disadvantage when hospitalization is necessary.

Effects of hospitalization and surgery in older patients

Functional decline is a common side effect during and after hospitalization and major abdominal and thoracic surgery.[14,15] It is mainly due to a low level of physical activity after surgery, which leads to loss of physical condition, and to the physiological side effects of surgery and medication. Decreased physical activity is common during the perioperative period and can only in part be explained by mandatory bed rest as a result of manifest pathology and the type of surgery scheduled.[16] During hospitalization, patients stay in bed most of the day, even though there is usually no medical reason for this.[16] Bed rest leads to a loss of lower extremity strength, power, and aerobic capacity. Even young and healthy people lose about 100–200 g lean body mass per week when hospitalized, and older people have a 3-to 6-fold greater rate of muscle loss.[17] Kortebein reported that healthy older people lost 1 kg of lean body mass after 10 days' bed rest, mainly from the ambulatory and postural muscles of the lower extremities, which are important for mobility.[18] In addition, older patients do not usually return to their previous level of physical activity after a period of inactivity, leading to a protracted functional decline.[18]

Functional decline is also caused by major surgery which is a challenge to the physiological system. The surgical stress response encompasses a wide range of physiological effects which seriously and directly impair cardiopulmonary and muscle function.[19] Hormonal dysregulation and an inflammatory response to surgery contribute to an accelerated loss of lean tissue.[20] Muscle mass is lost at a 3-fold higher rate during hospitalization secondary to surgery and medical treatment than during bed rest at home.[21]

Special attention should be paid to the perioperative decline in respiratory muscle function, and in particular diaphragm function, in patients scheduled for abdominal and thoracic surgery. Besides a deterioration of muscle function due to anaesthesia (even during surgery), surgery close to the diaphragm can cause reflex inhibition of phrenic nerve output, further exacerbating the decline in diaphragm function.[22] Mechanical ventilation can also result in a further decline in respiratory muscle function in this patient group.[23]

The above-mentioned consequences of surgery could lead to functional decline, which can be considered an iatrogenic event in old (>60 year) patients as it leads to a higher risk of postoperative complications and mortality, a longer hospital stay, and a protracted and sometimes permanent loss of mobility and ADL.[4,24,25] Theoretically, a good preoperative functional status could positively influence these outcomes. Recently, Malani and Covinsky emphasized the importance of the functional status in surgery.[26,27] Figure 1.1 summarizes the described phenomena and serves as the central model in this thesis.

Conceptual frame

Functional status is not a well-defined concept, which hampers its use in research.28 In this thesis, functional status is operationalized as part of patients' health, as stated by Huber et al.,[29] who consider health as a dynamic property. Thus a physically healthy person has the capacity to cope with physiological stress (among which surgical stress) and to restore the physiological balance, a process called allostasis.[30] This is consistent with the WHO International Classification of Functioning, Disability, and Health (ICF),[31] which distinguishes between performance and capacity as qualifiers of reality and potential

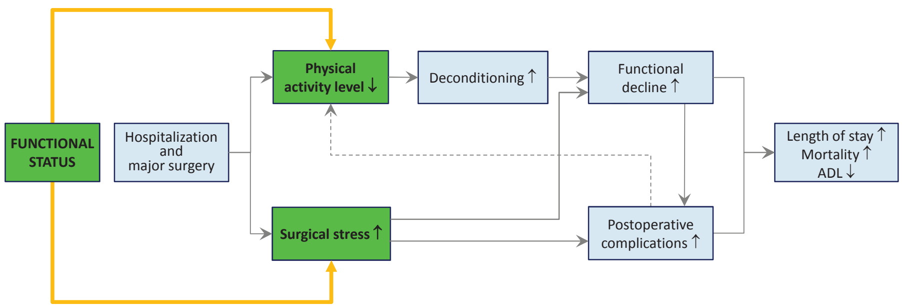

Figure 1.1 Visualization of possible effects of surgery and hospitalization in older patients and the role of preoperative functional status.

in daily life, respectively. A combination of specific performance- and capacity-based measures might provide prognostic information[32] to predict the postoperative course.

The studies described in this thesis focus on performance and capacity measures of physical determinants of functional status, operationalizing them as physical activity and physical fitness, respectively. Physical activity is defined as 'any bodily movement produced by skeletal muscles that results in caloric expenditure'.[33] Physical fitness is considered as a set of attributes that people have or achieve relating to their ability to perform physical activity.[34]

Frailty

Frail people often lack the adaptive capacity to cope with events that put various physiological systems under pressure. Bortz related adaptive capacity and allostasis to the redundant structure and function of organ systems. In this view, excess capacity provides organ systems with a high level of resilience to environmental perturbation of the physiological system.[35] Review of a wide range of body systems consistently reveals that 30% of maximal function represents a threshold for adequate function.[35] This implies that most organ systems can sustain a 70% of loss of function before manifest system failure occurs, which is termed frailty. A decline in organ function approaching or even crossing the threshold of 30% will have serious consequences for an adequate functional status, as visualized in Figure 1.2; for example, difficulties with walking and other daily activities

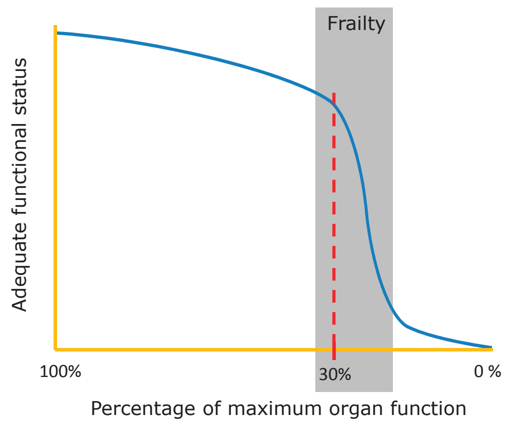

Figure 1.2 Relation between organ function and functional status showing that frailty occurs at 30% of the maximal function.

such as getting out of a chair and climbing stairs. Muscle strength, anaerobic and aerobic power, and coordination are considered biomarkers of frailty and the cause of decreased physical activity. The reverse is also true: frailty can lead to diminished physical activity.

Model of preoperative and postoperative course

We used a modification of the model of Topp[36] to visualize functional decline and recovery after hospitalization (including the preoperative period) and surgery (see Figure 1.3). Many patients show a satisfactory functional recovery during the postoperative period because they have an adequate stress response and regain their pre-hospitalization level of functioning (see Figure 1.3a). These patients are able to withstand the allostatic load, whereas some patients do not recover fully. Figure 1.3b shows the situation of a patient with a poorer preoperative physical condition (partly due to a decline during the waiting

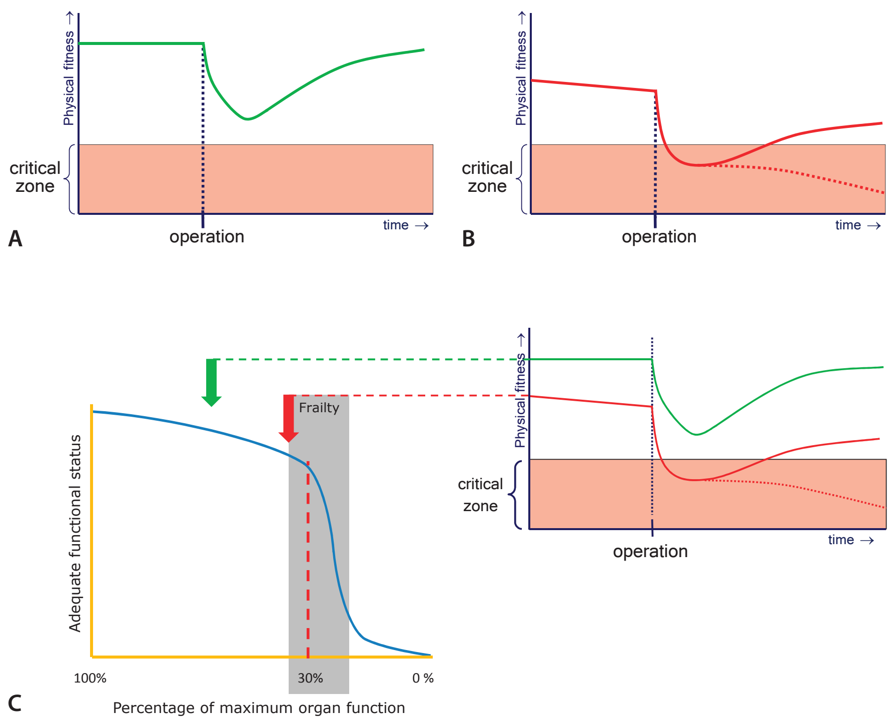

Figure 1.3 Preoperative physical condition and postoperative course (based on Topp et al.[36]). **(A)** Good preoperative physical condition and postoperative recovery keeping the patient away from the critical zone. **(B)** Poor preoperative physical condition puts the patient in the critical zone with limited recovery. **(C)** Preoperative physical condition related to frailty.

period) who is not able to respond to the physical stress of surgery, which leads to a poor postoperative course and brings that patient into the critical zone. Functional recovery is limited, making the patient susceptible to postoperative complications and even death. This type of patient is characteristic of a group that can be termed the "frail elderly" – older patients who are unable to successfully cope with surgery and hospitalization. Figure 1.3c combines the visualization of the frailty model with the concept of Topp et al. and shows frail patients at high risk of postoperative complications.

Risk stratification

The first step in preoperative care is to identify frail patients, patients who are at high risk of functional decline into the critical zone (red arrow on the curve in Figure 1.3C). Evidence shows that the preoperative physical condition of patients awaiting surgery is an independent risk factor for postoperative complications, functional recovery, and mortality after major abdominal and thoracic surgery[37-39] although the specific determinants responsible for this increased risk have not yet been identified.

Preoperative exercise training

Risk stratification enables physiotherapists to identify patients eligible for preoperative exercises to optimize their physical condition prior to elective surgery. Long-term training appears to be beneficial in older individuals.[40,41] It improves their preoperative condition, possibly making them better able to withstand the consequences of surgery and hospitalization, as represented in Figure 1.4. In this figure, these patients are less susceptible to complications and functional decline in the postoperative period. However, the time available for training before elective surgery is often limited, especially with

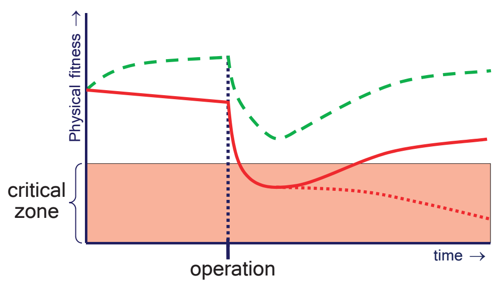

Figure 1.4 Assumed effect of preoperative exercise training (in the model based on Topp[36]).

oncological abdominal and thoracic surgery. Little research is available on the effect of short-term training for older patients in the preoperative period.[42] To date, inspiratory muscle training has been shown to decrease the incidence of postoperative pulmonary complications.[42,43] High-intensity training for other muscles and aerobic exercise training are possible in older patients; however, potential adverse effects of very strenuous training (such as musculoskeletal injuries, cardiac events and temporary reduced immunity) should be taken into account.[44-46]

Aim and outline of the thesis

The aim of the studies reported in this thesis was to investigate the role of physical fitness and physical activity in recovery after major surgery (specifically abdominal and non-cardiac thoracic surgery). In the following chapters, we investigate the following research questions:

- What is the relationship between determinants of physical fitness / physical activity and recovery from elective abdominal and thoracic surgery in older patients (chapters 2–4).
- What is the effect of a short course of physical training given preoperatively on preoperative physical fitness and on the postoperative course (i.e., recovery of respiratory function, postoperative pulmonary complications, and length of hospital stay) (chapters 5–6).

The study described in Chapter 2 reviews the predictive value of the determinants of physical fitness on postoperative cardiopulmonary complications. The prospective cohort study reported in Chapter 3 investigates the association between determinants of physical fitness and physical activity in older patients and postoperative recovery (mortality, length of stay, and discharge destination). The explorative study presented in Chapter 4 focuses on preoperative respiratory fitness and addresses the appropriateness of using concepts such as 'complexity' and 'variability' when determining the postoperative recovery of respiratory function, and thereby the appropriateness of stratifying the risk of postoperative complications. The study described in Chapter 5 investigates the feasibility and preliminary effect of preoperative training of respiratory fitness (i.e., the inspiratory muscles) on postoperative pulmonary complications in older patients scheduled for elective abdominal surgery, and that reported in Chapter 6 investigates the feasibility and preliminary effect of a broad preoperative therapeutic exercise programme for older patients scheduled for elective abdominal surgery. The results of the studies are summarized and discussed with reference to the current literature in Chapter 7. The chapter closes with a discussion of the clinical relevance of findings and suggestions for future research.

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2

Predictive indicators of preoperative physical fitness on the incidence of cardiopulmonary complications after abdominal and non-cardiac thoracic surgery: a meta-analysis

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Submitted for publication

ABSTRACT

Pre-surgery physical fitness has proved to be lower in patients in patients with postoperative cardiopulmonary complications (PCPC) after thoracic and abdominal surgery. This meta-analysis summarised the risk estimates of PCPC for the various components of preoperative physical fitness. After a systematic search of medical databases, fourteen prospective cohort studies were included. Maximal aerobic capacity (VO_{2max}) was the most frequently studied component (n=10) besides stair climb test (n=3) and a two-minutes-exercise test (n=1). Twelve studies reported on lung surgery, one on abdominal surgery and one on both types of surgery. Eight studies reported on PCPC, three on postoperative pulmonary complications (PPC) and three on both complications. The pooled odds ratios (random model) for the risk of PCPC 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 VO_{2max} <15 ml/kg/min were explained by methodological quality and degree of fitness of the study population. The pooled odds ratios (random model) for the risk of PPC 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 (fixed model) for inability of climbing three flight of stairs was 2.1 (95% CI 1.2–3.7). We conclude that physical fitness, expressed as VO_{2max}, is predictive for the development of PCPC in patients after lung surgery. More needs to be learned about the role of physical fitness in the outcomes of patients who undergo abdominal surgery.

INTRODUCTION

Cardiopulmonary complications are common after thoracic and abdominal surgery[1-3] and are a major cause of mortality, morbidity, prolonged hospital stay, and increased medical consumption.[4,5] Several surgery- and patient-specific factors are known to increase the risk of postoperative complications, such as location of the incision in relation to the diaphragm and the type of anaesthesia used,[6] older age (>60 years), and history of chronic obstructive pulmonary disease (COPD) and smoking.[5,7,8] More recently, pre-surgery physical fitness has also been identified as major predictor of postoperative cardiopulmonary complications. Poor physical fitness affects the ability of a person to cope with hospitalization and surgery[9] and may compromise postoperative functional recovery, potentially leading to postoperative complications.[10-12] Physical fitness is an integrated measure and includes several components, such as cardiorespiratory fitness and muscle function,[13] and can be measured in different ways. Knowledge of those aspects of physical fitness that are associated with the incidence of postoperative complications could help improve the quality and efficiency of the outpatient preoperative screening procedure.

A meta-analysis by Benzo et al. revealed cardiorespiratory fitness, expressed as maximal oxygen consumption (VO_{2max} in ml/kg/min), to be significantly lower in patients who developed clinically relevant cardiopulmonary complications after lung surgery compared with patients without complications.[14] This highlights the importance of VO_{2max} measurements to clinical decision-making and perioperative care in these patients. In practice, a maximal exercise test to exhaustion to assess cardiorespiratory fitness is expensive and a major burden for patients just before an operation, and especially for older patients. This raises the question whether maximal tests are always necessary and desirable – perhaps they could be replaced by more cost-effective submaximal tests. The meta-analysis by Benzo et al. reported differences in VO_{2max} between patients with or without complications, whereas in clinical practice a cut-off value is needed to identify patients at risk of cardiopulmonary complications. To address these issues, this meta-analysis includes submaximal exercise tests to estimate patients' physical fitness and focuses on risk estimates. The study is not restricted to lung surgery but also includes other types of non-cardiac thoracic surgery and abdominal surgery, with a view to establishing the predictive value of preoperative physical fitness for the risk of cardiopulmonary complications after abdominal and non-cardiac thoracic surgery.

METHODS

A systematic literature search was performed in the electronic databases MEDLINE, Embase, The Cochrane Database of Systematic Reviews, The Cochrane Central Register of Controlled Trials and CINAHL until December 2011.

Inclusion criteria were as follows:

- Study design: longitudinal prospective study design.
- Patients: adults (>18 years old) undergoing non-cardiac thoracic or abdominal surgery.
- Independent variables: studies investigating indicators of preoperative physical fitness and activity, e.g. muscle strength, aerobic/anaerobic exercise capacity, physical function testing, and activity level.
- Outcome variables: postoperative cardiopulmonary complications consisting of arrhythmia, myocardial infarction, heart failure, and pulmonary embolism; and postoperative pulmonary complications (classified according to the criteria of Kroenke[15,16]).
- Data analysis: studies providing risk estimates for postoperative cardiopulmonary or pulmonary complications.
- Studies published in English.

Exclusion criteria were as follows:

- Patients undergoing cardiac, urological, gynaecological, paediatric, video-assisted thoracoscopic (VATS) surgery, or organ transplantation surgery.

The reference lists of retrieved articles, including review articles, were also searched for relevant articles. Titles and abstracts were first screened by two independent assessors (L.A.T. and E.W.S.). If the two assessors could not reach agreement, a third assessor (J.J.D.) made the final decision whether to include or exclude the study.

The methodological quality of observational studies was determined by two independent assessors (L.A.T. and E.W.S.), using the STROBE statement.[23] The level of agreement was represented by Cohen's kappa. The maximum Strobe score is 34 points: articles with a Strobe score of 24 or higher (>70%) were considered to be of 'high methodological quality', articles with scores between 17 and 23 (50–70%) were considered to be of 'moderate methodological quality', and articles with scores below 17 (<50%) were considered to be of 'low methodological quality'. Then the type of study, number of participants, surgical procedures, complications (subgroups), complication rate, and preoperative risk factors, including physical fitness, were recorded.

Studies that were clinically homogeneous regarding postoperative complications and components of physical fitness were included in the meta-analysis, which was performed using the Comprehensive Meta-Analysis Program (CMA, version 2.2.064). Heterogeneity was assessed with the Cochrane Q statistic and calculation of an I^2 value with thresholds for low (25%–49%), moderate (50%–74%), and high (>75%) levels of heterogeneity. Random effect models were used when heterogeneity was present (I^2>25%); otherwise fixed effect models were used. Existing heterogeneity was examined by meta-regression of the following categorized variables: age, physical fitness of the study population, methodological quality, and publication year. Significant variables ($p<0.05$) were used for subgroup analysis.

RESULTS

The literature search identified 452 articles. After removal of duplicates and clearly irrelevant articles, 412 abstracts were reviewed, of which 361 were excluded. Four relevant articles were identified from the reference lists. Of the 55 potentially eligible articles, 41 were excluded after the full text was read, mainly because of methodological issues (e.g. retrospective studies) or non-applicable independent variable (i.e. physical fitness not used). Two studies were rejected because they were written in a language other than English (Chinese and Lithuanian). This resulted in 14 studies meeting the inclusion and exclusion criteria (see Figure 2.1).

Cardiorespiratory fitness expressed as maximal aerobic capacity (VO_{2max}, VO_{2peak}, percentage of predicted $VO2_{max}$ and peak work rate) was the most investigated indicator of physical fitness (n=10),[17-26] followed by ability to perform a stair climb test (n=3)[27-29] and a 2-minute exercise test (n=1).[30] Eight studies provided data on postoperative cardiopulmonary complications,[19,20,23,24,26,27,29,30] three studies data on postoperative pulmonary complications,[18,25,28] and three studies data on both complications.[17,21,22] Twelve studies involved lung surgery,[17-21,23-29] one abdominal surgery,[22] and one abdominal and thoracic surgery.[30] Eight studies were of good[18,19,23,25-28,30] and six were of low methodological quality.[17,20-22,24,29] Level of agreement in assessing the methodological quality (Cohen's kappa) was .86 ($p<0.05$). Table 2.1 summarizes the results of the included studies.

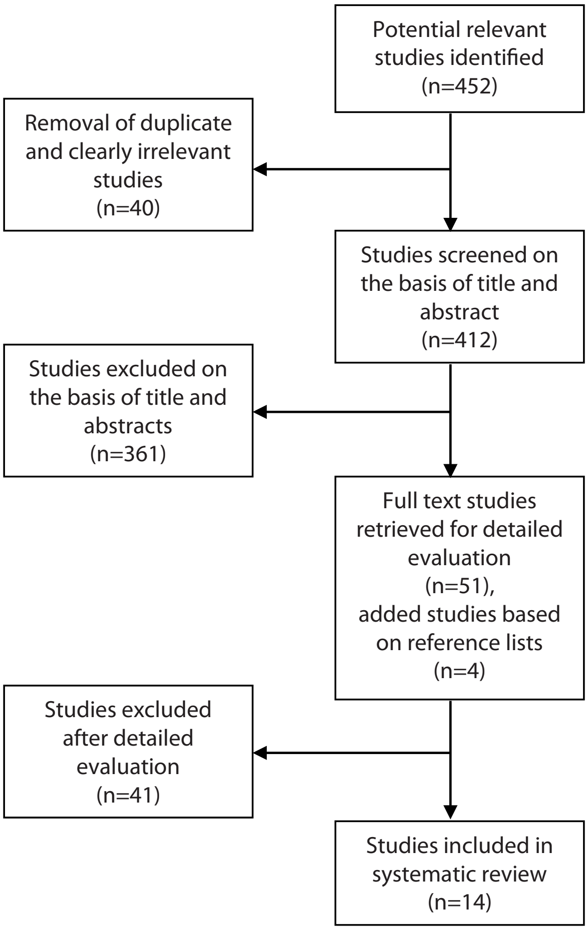

Figure 2.1 Flow chart of included articles.

All studies using a cut-off point of 15 and 20 mL/kg/min for VO_{2max} were included in a meta-analysis for postoperative cardiopulmonary and postoperative pulmonary complications separately. The results of the meta-analysis for postoperative cardiopulmonary complications as outcome measure are shown in the forest plots in Figure 2.2. The overall effect sizes (odds ratio) for VO_{2max} <15 mL/kg/min and VO_{2max} <20 mL/kg/min were 4.9 and 2.5, respectively (see Figure 2.2). Both groups showed low to moderate heterogeneity. For studies using a cut-off point of 15 mL/kg/min, meta-regression analysis showed a significant relationship between the risk of postoperative cardiopulmonary complications

Table 2.1 Summary of studies presenting odds ratios for the risk of postoperative cardiopulmonary complications and postoperative pulmonary complications by physical fitness

Author Year	MQ	N	Age	Surgical procedures	Complication rate (major PPC)	Indicators physical fitness	Cut-off point	Odds ratio	95% CI	Sensitivity	Specificity
Postoperative cardiopulmonary complications											
Bayram[17] 2007	21	55	59 (20–74)	Lung surgery p-b-l	35%	VO_{2max}	<15 mL/kg/min	2.1	0.7–6.7	63%	56%
Brutsche[19] 2000	25	125	63 ± 11	Lung surgery p-b-l-w-s	25%	VO_{2max}	<15 mL/kg/min <60% pred mL/kg/min <90% pred mL/kg/min	8.1 11.3 4.2	2.7–24.4 2.1–59.3 1.6–10.8	35% 19% 74%	94% 98% 59%
Dales[20] 1993	19	46	n.a.	Lung surgery p-l-w-t	32%	VO_{2max}	<1250 mL/min <80% pred mL/min	4.2 0.7	1.1–15.6 0.2–2.5	67% 53%	68% 39%
Markos[21] 1989	23	55	63 (14–80)	Lung surgery p-b-l-t	17%	VO_{2peak}	<15 mL/kg/min <20 mL/kg/min	1.2 1.7	0.4–4.3 0.4–7.2	40% 80%	65% 29%
Nugent[22] 1998	21	36	72.2 (57–85)	Abdominal surgery Aortic repair	23%	VO_{2max}	<20 mL/kg/min	1.4	0.3–7.3	63%	45%
Smith[24] 1982	22	22	55.7 ± 9.2	Lung surgery p-l-w-t	32%	VO_{2max}	<15 mL/kg/min <20 mL/kg/min	35 12.6	2.6–475.3 1.4–97.9	71% 100%	93% 67%
Wang[26] 2000	24	40	64 ± 10	Lung surgery b-l-w-s-	33%	VO_{2max}	<15 mL/kg/min	11.1	2.9–46.6	58%	89%

Table 2.1 continues on next page

Table 2.1 *Continued*

Author Year	MQ	N	Age	Surgical procedures	Complication rate (major PPC)	Indicators physical fitness	Cut-off point	Odds ratio	95% CI	Sensitivity	Specificity
Postoperative cardiopulmonary complications											
Brunelli[27] 2008	24	640	66.7 ± 9.3	Lung surgery	23%	Stair climbing	<12 metre climbing	2.1	1.1–3.7	13%	93%
				p-b-l-w-s			<22 metre climbing	2.3	1.5–3.4	69%	50%
Pate[29] 1996	22	11	63.6 ± 4.9	Lung surgery	64%	Stair climbing	<3 flights stair	2.1	0.1–63.4	14%	100%
				p-l-w-s-t			(<11 metre climbing)				
Gerson[30] 1990	25	177	73	abdominal/ non-cardiac	22%	Cycle exercise test	Unable to cycle>2 min	7.8	2.8–22.2	42%	91%
				thoracic surgery			and HR>99 bpm				
Richter Larsen[23] 1997	27	97	64.3±8.9 (38–80)	Lung surgery p-l-w-t	32%	Work rate	<70 Watt	4.0	1.5–11.0	39%	86%
Postoperative pulmonary complications											
Bayram[17] 2007	21	55	59 (20–74)	Lung surgery p-b-l	20% (7%)	VO_{2max}	<15 mL/kg/min	36.1	2.0–653.0	100%	61%
Bobbio[18] 2009	25	73	66.7 ± 8.7	Lung surgery b-l-s	26% (19%)	VO_{2max}	<15 mL/kg/min	2.6	0.8–9.0	32%	85%
							<18.7 mL/kg/min	5.6	1.8–17.6	52%	84%
							<20 mL/kg/min	5.0	1.0–23.9	89%	37%

Author Year	MQ	N	Age	Surgical procedures	Complication rate (major PPC)	Indicators physical fitness	Cut-off point	Odds ratio	95% CI	Sensitivity	Specificity
Postoperative pulmonary complications											
Markos[21] 1989	23	55	63 (14–80)	Lung surgery p-b-l-t	17%	VO_{2peak}	<15 mL/kg/min <20 mL/kg/min	0.5 0.7	0.1–2.9 0.1–3.4	25% 63%	61% 30%
Nugent[22] 1998	21	36	72.2 (57–85)	abdominal lsurgery Aortic repair	13% (10%)	VO_{2max}	<20 mL/kg/min	0.7	0.1–6.0	50%	42%
Torchio[25] 1998	24	54	62 ± 10.2	Lung surgery p-b-l-o	29% (5%)	VO_{2max}	<20 mL/kg/min	4.1	0.8–20.6	88%	37%
Girish[28] 2001	24	83	67 39–84	abdominal/ non-cardiac thoracic surgery	25%	Stair climbing	<6 metre <10 metre <12 metre <15 metre	15 5.9 6.3 4.2	2.8–80.1 1.8–18.7 2.1–18.4 0.9–19.9	38% 48% 71% 95%	97% 90% 77% 32%
Gerson[30] 1990	25	177	73	abdominal/ non-cardiac thoracic surgery	14%	Cycle exercise test	Unable to cycle>2 min and HR>99 bpm	7.1	23.2–15.9	28%	95%

P, pneumectomy; l, lobectomy; bl, bilobectomy; s, segment resection; w, wedge resection; t, thoracotomy; o, other.

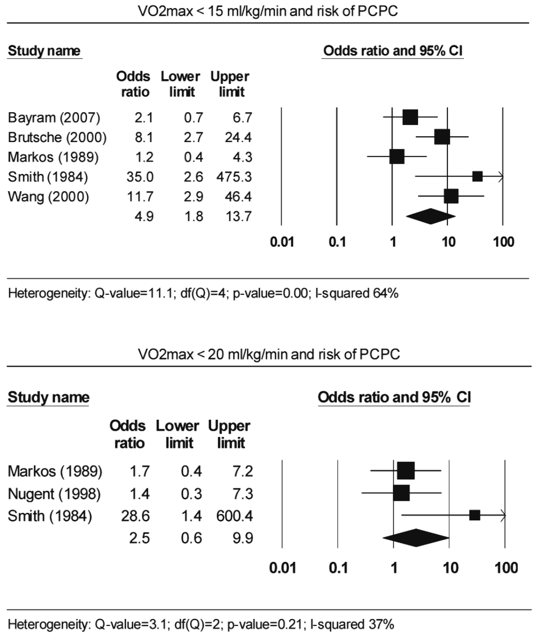

Figure 2.2 Forest plot of the odds ratios and 95% confidence intervals reported in studies of the association between VO_{2max} <15 mL/kg/min and <20 mL/kg/min and postoperative cardiopulmonary complications (PCPC) (random model).

(expressed as odds ratios) and the methodological quality of the studies and the degree of physical fitness (measured as the mean VO_{2max} of the total study population) (Figure 2.3), but not significant associations between the risk of these cardiopulmonary complications and age or publication year. Studies of high methodological quality revealed homogeneity and an overall odds ratio for postoperative cardiopulmonary complications of 9.3. The likelihood of cardiopulmonary complications was higher in studies including patients with a higher cardiopulmonary fitness (mean VO_{2max} of the total population >17.5 mL/kg/min) than in studies including patients with a lower cardiopulmonary fitness (odds ratio 10.6 versus 1.7, respectively; see Figure 2.3). The results for both groups showed homogeneity (I^2 0%).

The results of the meta-analysis of four studies reporting on postoperative pulmonary complications are shown in the forest plots in Figure 2.4. The likelihood of pulmonary complications was similar in the groups with a low and high cardiopulmonary fitness

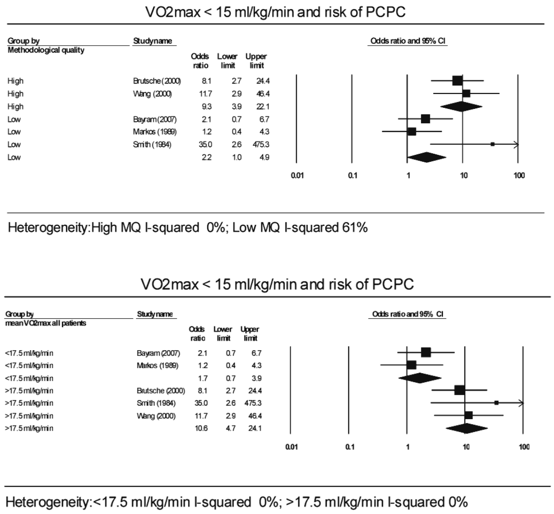

Figure 2.3 Forest plot of subgroup analysis of the effect of methodological quality and mean VO_{2max} of the total study population on the association between VO_{2max} <15 mL/kg/min and postoperative cardiopulmonary complications (PCPC).

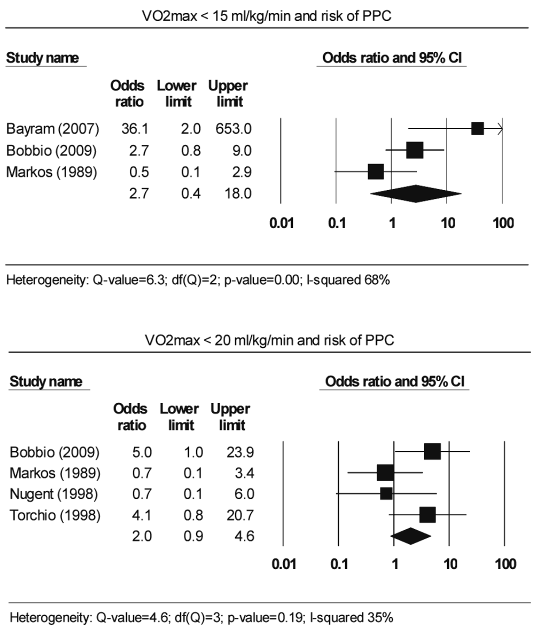

Figure 2.4 Forest plot of the odds ratios and 95% confidence intervals reported in studies of the association between VO_{2max} <15 mL/kg/min and <20 mL/kg/min and postoperative pulmonary complications (PPC) (random model).

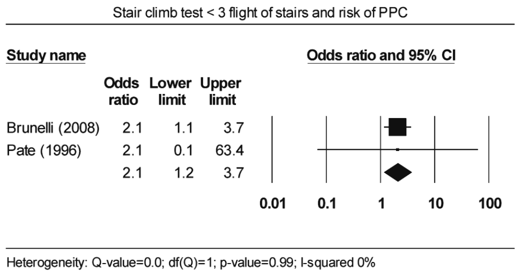

Figure 2.5 Forest plot of the odds ratios and 95% confidence intervals reported in studies of the association between the stair climb test (<3 flight of stairs) and postoperative cardiopulmonary complications (PCPC) (fixed model).

(VO_{2max} <15 and 20 mL/kg/min, respectively), with pooled odds ratios of 2.7 and 2.0, respectively. Meta-regression analysis did not identify variables for subgroup analysis.

Two studies investigated physical fitness and the risk of postoperative cardiopulmonary complications using a stair climb test (<12 m or three flights). Both studies revealed a higher likelihood of complications (odds ratio 2.1) in patients who could not climb three flights of stairs (see Figure 2.5).

DISCUSSION

This meta-analysis provided evidence that poor physical fitness, defined as VO_{2max} of 15 mL/kg/min or lower or inability to climb three flights of stairs, is a predictor of cardiopulmonary complications after lung surgery (overall OR 4.9 and 2.1, respectively). Physical fitness measured as VO_{2max} seemed to be a more robust predictor of cardiopulmonary complications than of pulmonary complications. The 15 mL/kg/min threshold provided a high specificity and low sensitivity (see Table 2.1), meaning that while the detection rate for patients 'not at high risk' is high, a substantial proportion of patients 'at high risk' are not detected. The opposite is true for the cut-off value of 20 mL/kg/min (see Table 2.1), which had a high detection rate for patients 'at high risk'. This finding suggests that both cut-off values should be used. The high specificity of the 15 mL/kg/min cut-off value seems appropriate for deciding whether to operate (no wrong decision to withhold surgery) and the high sensitivity of the 20 mL/kg/min cut-off value is appropriate for screening and decisions about perioperative management (no wrong decision to withhold 'high- risk' treatment).

Although the current review was limited to cardiopulmonary complications, the results are in line with those reported by Colice et al.[31] and Beckels et al.,[16] who also included mortality as postoperative complication. Our recommendations about the use of the two cut-off points of VO_{2max} (15 and 20 mL/kg/min) are in agreement with theirs. Most studies have used the cut-off points of 15 and 20 mL/kg/min, as recommended in the literature. Two studies used ROC curve analysis to establish cut-off points, which were 15 mL/kg/min[26] and 18.7 mL/kg/min.[18] A ROC curve analysis of all studies could further validate the recommended cut-off points, but only one study provided the original data21 required for this analysis.

Cardiopulmonary fitness expressed as VO_{2max} (mL/kg/min) may be biased by body weight; however, none of the included studies provided sufficient data to correct the results of the meta-analysis for weight (only one study expressed cardiopulmonary fitness as mL/kg).[20] The same applies to bias by age, which could be corrected by presenting the results as percentage of the predicted VO_{2max}, which takes age and gender into account (two studies presenting this unit of measurement made use of different cut-off points[19,20]).

Besides VO_{2max}, the height climbed by patients on a stair climb test was the most commonly used measure of physical fitness. This test is considered a surrogate for the VO_{2max} and represents a low technology and more cost-effective exercise regimen.[32] The current study provides evidence that patients who cannot climb three flights of stairs are at risk of postoperative cardiopulmonary complications; however, this result is based on just two studies and is dominated by one author. The value of the stair climb test may be improved by including the time it takes to climb the stairs, as indicated by a number of authors,[32-34] especially as workload (as VO_{2max}) incorporates a measure of time (its unit is joules per second). This rationale argues for a test measuring the height climbed in 1 minute. In the study of Koegelenberg et al., cut-off points for a climbing speed of 12 m/min and 15 m/min were found to correspond with VO_{2max} cut-off points of 15 mL/kg/min and 20 mL/kg/min, respectively.[33] As weight will also influence performance on a stair climb test,[32] both factors (time and body weight) should be taken into consideration in future studies.

Most of the meta-analyses yielded heterogeneous results. Subgroup analysis for different levels of physical fitness resulted in homogeneous effect sizes in studies in which the 15 mL/kg/min cut-off point was used for risk stratification. The studies that included fitter individuals (mean VO_{2max} of patients >17.5 mL/kg/min) reported higher odds ratios for postoperative complications than did studies with less fit participants (mean VO_{2max} <17.5 mL/kg/min; pooled odds ratio 10.6 and 1.7, respectively). This can be explained by smaller difference between patients at risk and not at risk for postoperative complications in the latter group. The mean VO_{2max} for the patients not at risk for complications was 21.1 and 16.8 mL/kg/min for the fitter and less fit group, respectively. In other words, studies that include physically fit patients generate higher odds ratios. Clinicians should take this into account when interpreting the results of studies.

Although odds ratios are widely used, they are difficult to interpret. They are often considered to be equivalent to the relative risk. But this inaccuracy always entails overestimation of risk, which increases with the incidence of the dependent variable, in this study the postoperative complication rate. The high odds ratios in the studies of Smith et al.[24] and Bayram et al.[17] (35 and 36, respectively) were because empty cells precluded the calculation of odds ratios with the inverse variance method. Adding 0.5 to each cell provides the usual solution for this problem,[35] but may give rise to high values. The Peto method is recommended for calculating odds ratios when empty cells occur[35] and reduced the risk to more reliable values. We did not use this method because it assumes effect ratios are close to unity and that there are similar numbers of individuals in the at-risk and not-at-risk groups.[36]

Our search string identified 452 potentially relevant studies, to which 4 studies were added by checking the reference lists of full-text articles. This suggests that our search string was sensitive. Only 2 articles had to be excluded because they were published in a language other than English. As more than 90% of the studies reported on lung cancer surgery, our findings might not be directly transferable to abdominal surgery. Moreover, most of the studies were published before 2005, which raises questions about the validity of the results because surgery and anaesthesia techniques have changed over time; however, we did not find great differences in postoperative complication rates over the years. Recent studies investigated differences in physical fitness between patients who did, or did not experience complications,[37-40] but these studies were excluded because they did not provide risk measures. They did report significantly lower levels of physical fitness in patients with cardiopulmonary complications, corroborating the importance of physical fitness.

Future research should investigate the effects of physical fitness on the postoperative course of patients scheduled for abdominal surgery, using a comprehensive measure of physical fitness and physical activity as proposed by Feeney.[37,41] Physical fitness is a potentially modifiable factor even in older patients. Several researchers recommend a preoperative exercise programme ('prehabilitation') to improve patient outcomes after major thoracic or abdominal surgery.[42-46] This experimental research should be expanded to further clarify the role of physical fitness.

In conclusion, our results suggest that physical fitness, expressed as VO_{2max}, is a strong predictor of the development of cardiopulmonary complications in patients after lung surgery. More needs to be learned about the role of physical fitness in the outcomes of patients who undergo abdominal surgery.

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3

The association of preoperative physical fitness and physical activity with outcome after scheduled major abdominal surgery

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Anaesthesia 2013; 68:67-73

ABSTRACT

We studied whether reported physical activity and measurements of fitness (hand, leg and inspiration) were associated with postoperative in-hospital mortality, length of stay and discharge destination in 169 patients after major oncological abdominal surgery. In multivariate analysis, adequate activity level (OR 5.5, 95% CI 1.4–21.9) and inspiratory muscle endurance (OR 5.2, 95% CI 1.4–19.1) were independently associated with short-term mortality, whilst conventional factors, such as age and heart disease, were not. Adequate activity level (OR 6.7, 95% CI 1.4–3.0) was also independently associated with discharge destination. The factors that independently associated with length of hospital stay were: COPD (HR 0.6, 95% CI 0.3–1.1); 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). For all postoperative outcomes physical activity and fitness significantly improved the predictive value compared to the use of known risk factors as age and comorbidities. We conclude that preoperative questionnaires of physical activity and measurements of fitness contribute to the prediction of postoperative outcomes.

INTRODUCTION

The preoperative identification of high-risk patients may reduce postoperative complications.[1] Risk factors associated with complications after major abdominal and thoracic surgery include age and smoking, as well as comorbidities, such as diabetes, COPD, and heart disease.[2-7] Risk evaluation may also include functional status,[8-10] which predicts postoperative outcome in older patients.[11-13]

A poor physical condition and functional status reduces the ability of a person to cope, mentally and physically, with hospitalization and surgery[14] and may compromise postoperative functional recovery, potentially leading to postoperative complications, death, and protracted and sometimes permanent loss of mobility.[2,9,11,15,16] Some authors recommend preoperative evaluation of functional status,[8,17,18] but inexact definitions may preclude its use in research.[19] Functional status has physical, psychological, and social elements, but it is often evaluated crudely, for example with ASA grade[20] and activities of daily living.[21] Functional status is usually based upon the WHO International Classification of Functioning, Disability and Health.[22] This classification distinguishes between activity, reported by questionnaire, and observed physical ability, the combination of which may refine prognostic information.[23]

We believe that this is the first prospective cohort study to investigate the association of this combination of questions and physical tests with the following short-term outcomes after scheduled major abdominal surgery in patients older than 59 years: mortality, length of hospital stay, and discharge destination.

METHODS

We prospectively recorded data for patients older than 59 years scheduled for oncological colorectal surgery between June 2006 and June 2009, at Gelderse Vallei Hospital in Ede, the Netherlands. We excluded from analyses patients we assessed as unable to do the fitness tests, based upon the results of a physical activity readiness questionnaire.[24] The study protocol was approved by the local Medical Ethics Committee of the Gelderse Vallei Hospital.

All patients were referred to the physical therapy outpatient department, as part of the multidisciplinary work-up, between one and three weeks before surgery. The physical therapist offered some patients physical training if their surgery was scheduled more than two weeks in advance. We recorded: age; diagnoses of diabetes, COPD, coronary heart disease, heart failure, metastatic cancer, and histories of smoking or productive cough.

We asked patients the frequency, duration and intensity of various activities over the previous 14 days, such as cycling, gardening and walking, using the LASA physical activity questionnaire (LAPAQ).[25]

An experienced physical therapist tested physical fitness by mobility and muscle function (ICF domains d4 and b7, respectively).[22] Mobility was measured as the time taken to rise from an armchair, walk 3 meters, turn, walk back, and sit down again (known as 'timed up-and-go', TUG).

Function was measured in the hand, leg and inspiratory muscles. Handgrip strength was recorded as the highest measurement in the dominant hand, using a digital device three times, separated by intervals of 30 seconds (Mechatronics Instruments BV, the Netherlands).[28] Leg power and endurance were measured as the time taken to rise from a treatment couch, adjustable in height, 10 times with the arms folded across the chest.[26-28] Maximal inspiratory muscle strength and respiratory cumulative energy were measured with the MicroRPM and MicroRMA respectively (Micro Medical Ltd., Rochester, England).[29]

All patients in this study received usual care. The questionnaires and physical tests were not masked from the healthcare providers.

All assessments were made at the same appointment, always in the following sequence: mobility; leg strength; inspiratory strength; hand strength; questionnaire. We recorded: in-hospital mortality, discharge destination (to the home environment or to a nursing home), and length of hospital stay (in days). We used discharge destination as an outcome for three reasons: patients usually want to return home; it reflects functional recovery; it is an important item for health insurers because of the high costs of admission to a nursing home.

Data were analysed with the software package IBM SPSS Statistics 19.0 (SPSS Inc., Chicago, IL). We dichotomised the results of the questionnaire and each fitness test for two outcomes – mortality and discharge destination – with the best discriminatory point on a receiver operating characteristic curve, as long as the area under curve was more than 0.6. We performed univariate logistic regression for the association of each factor with mortality and discharge destination, and univariate Cox regression for associations with length of stay. We entered significant factors ($p<0.1$) in a multivariate regression analysis for all three outcomes. To obtain a valid assessment of the added value of the physical activity and fitness factors, the significant conventional risk factors were forced into the model. Statistical significance of models was determined by -2 log likelihood values for the regression models and a p-value <0.05 for the chi-square tests. The predictive value for mortality and discharge destination was estimated by the C-index and positive and negative predictive values, the goodness of fit was assessed by the Hosmer & Lemeshow test.

RESULTS

We analysed data from 175 patients referred to the department of physical therapy between June 2006 and June 2009. The operation was cancelled in six patients because of deterioration of their medical condition or at the patient's request. Nine patients were not referred for screening because bowel pathology was not initially recognized as the cause for their symptoms. Table 3.1 lists patient and surgical characteristics.

Table 3.1 Preoperative characteristics including conventional risk factors in 169 subjects

Gender; male/female	99/70
BMI; kg.m^{-2}	26 ± 5
Surgery	
Colon resection (open)	61 (36%)
Colon resection (endoscopic)	14 (8%)
Rectosigmoid resection (open)	72 (42%)
Rectosigmoid resection (endoscopic)	22 (13%)
Open surgery duration; mins	110 (44)
Endoscopic surgery duration; mins	170(53)
Reoperation	31 (18%)
Preoperative radiotherapy	41 (24%)
Conventional risk factors	
Age	
60–69 years	61 (36%)
70–79 years	82 (49%)
>80 years	26 (15%)
Metastatic cancer	15 (9%)
Diabetes	30 (18%)
COPD	15 (9%)
Heart diseases	19 (11%)
Smokers	24 (14%)
Productive cough	23 (14%)

BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Thirteen patients (8%) died in hospital, a median (IQR [range]) of 19 days (10–28 [8–39]) after surgery. No patient died after discharge within this period. We compared mortality rates between two groups of patients, above and below a value for each factor, identified through ROC curve analyses: mobility, 11 seconds; stand-sit repeats, 27 seconds; inspiratory pressure, 90cm H_2O; respiratory cumulative energy 41J; hand strength, 233N; questionnaire 416 kcal. Table 3.2 lists the univariate relative risks and subsequent multivariate odds ratios for each factor. Both the questionnaire score and cumulative respiratory energy were associated with in-hospital mortality. A model containing only

Table 3.2 Preoperative characteristics including conventional risk factors in 169 subjects

			Univariate analyses		Multivariate analyses	
	N	% total	Relative risk (95% CI)	p-value	Forced* Odds ratio (95% CI)	Not forced Odds ratio (95% CI)
Conventional factors						
Age						
60–70 year	61	36%	1			
70–80 year	82	49%	2.6 (0.6–12.1)	0.20		
>80 year	26	15%	4.7 (0.9–24.0)	0.04		
Metastatic cancer	15	9%	3.1 (0.9–10.0)	0.06	3.0 (0.6–14.7)	
Diabetes	30	18%	1.4 (0.4–4.7)	0.60		
Heart disease	19	11%	1.4 (0.3–6.0)	0.62		
COPD	15	9%	0.9 (0.1–6.1)	0.88		
Smoking	24	14%	0.5 (0.1–3.7)	0.48		
Productive cough	23	12%	2.8 (0.9–8.2)	0.07	3.2 (0.7–14.2)	2.9 (0.7–12.5)
Physical activity and fitness						
LAPAQ; kcal						
<416 kcal	60	37%	5.8 (1.7–20.2)	0.0002	5.6 (1.4–22.6)	5.5 (1.4–21.9)
TUG; sec						
>11 sec	24	15%	4.8 (1.8–13.0)	0.001		
CRT; sec						
>27 sec	62	40%	2.2 (0.7–7.6)	0.18		
MIP; cm H_2O						
<90 cm H_2O	104	65%	3.0 (0.7–13.1)	0.12		
RCE; J						
≤41 J	48	32%	4.7 (1.5–14.5)	0.003	5.0 (1.4–18.6)	5.2 (1.4–19.1)
HGS; N						
<233 N	37	24%	2.7 (1.0–7.6)	0.05		

*Inclusion of physical activity and fitness increased the chi-square from 5.85 to 20.12 and the p-value from 0.12 to 0.0004: their inclusion also increased the c-index (95% CI) from 0.67 (0.51–0.84) to 0.82 (0.69–0.95). LAPAQ, LASA physical activity questionnaire; TUG, timed up-and-go; CRT, chair rise time; MIP, maximal inspiratory pressure; RCE, respiratory cumulative energy; HGS, hand grip strength.

conventional factors was not associated with mortality (p=0.12) but the model including physical fitness and activity factors was associated with in-hospital mortality (p=0.0005), confirmed by a significant difference in the log likelihood values of the two models (85.33 versus 66.62, p=0.001). 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. The frequencies of patients correctly and incorrectly predicted to die were 18 and 72 per 1000 for the conventional model and 30 and 28 for the model also including physical activity and fitness, respectively. The frequencies of patients correctly and incorrectly predicted to survive were 851 and 59 per 1000 patients for the conventional model and 895 and 47 for the model also including physical activity and fitness, respectively. The goodness of fit hypothesis of all models was not rejected by the Hosmer and Lemeshow test. Sixteen survivors were discharged to a nursing home and 140 to home.

ROC curve analyses generated different preoperative discriminatory values for discharge destination: mobility, 8 seconds; stand-sit repeats, 26 seconds; inspiratory pressure, 90cm H_2O; respiratory cumulative energy 60J; hand strength, 270N; questionnaire 530kcal. Both the questionnaire score and maximal inspiratory pressure were associated with discharge destination as determined by multivariate analysis. A model containing only conventional factors was not associated with discharge destination (p=0.51) but the model including physical fitness and activity factors was associated with discharge destination (p=0.004), confirmed by a significant difference in the log likelihood values of the two models (97.23 versus 68.61; p=0.003). The c-index for the model including the physical fitness and activity factors was 0.80 versus 0.66 for the model with conventional factors. The frequencies of patients correctly and incorrectly predicted to discharge to a nursing home were 26 and 116 per 1000 for the conventional model and 59 and 137 for the model also including physical activity and fitness, respectively. The frequencies of patients correctly and incorrectly predicted to discharge to home were 782 and 77 per 1000 patients for the conventional model and 760 and 44 for the model also including physical activity and fitness, respectively. The goodness of fit hypothesis of all models was not rejected by the Hosmer and Lemeshow test. The median (IQR [range]) length of stay was 12 (9–21[4–130]) days. Discriminatory values for the association with physical activity and fitness were: mobilisation, 8 seconds; stand-sit repeats, 25 seconds; inspiratory pressure, 90cm H_2O; respiratory cumulative energy 375 J; handgrip strength, 240 N; questionnaire 530 kcal. Table 3.3 shows the association of various factors with length of stay as determined by univariate Cox regression analysis. Diabetes, COPD, activity level and maximal inspiratory pressure were associated with increased length of stay on multivariate regression. Addition of physical activity and fitness factors to the model with only conventional factors confirmed a significant difference in the log likelihood values (p=0.002). The chi-square value improved from 9.85 (p=0.007) to 16.47 (p=0.00002).

Table 3.3 Univariate and multivariate Cox regression analyses for associations between factors and postoperative length of stay. The inclusion of questionnaire results (LAPAQ) and the maximal inspiratory pressure (MIP) increased the statistical association with postoperative length of stay.

			Univariate analyses		Multivariate analyses	
	N	% total	Hazard ratio (95% CI)	p-value	Forced* Hazard ratio (95% CI)	Not forced Hazard ratio (95% CI)
Conventional factors						
Age						
60–70 year	61	36%	1			
70–80 year	82	49%	0.9 (0.6–1.3)	0.59		
>80 year	26	15%	0.9 (0.6–1.5)	0.75		
Metastatic cancer	15	9%	0.8 (0.5–1.5)	0.52		
Diabetes	30	18%	0.6 (0.4–0.9)	0.02	0.7 (0.5–1.2)	
Heart disease	19	11%	0.9 (0.5–1.4)	0.58		
COPD	15	9%	0.5 (0.3–0.9)	0.03	0.6 (0.3–1.2)	0.6 (0.3–1.1)
Smoking	24	14%	0.9 (0.6–1.3)	0.52		
Productive cough	23	12%	0.8 (0.5–1.3)	0.37		
Physical activity and fitness						
LAPAQ; kcal						
<530 kcal	79	48%	0.6 (0.4–0.8)	0.0004	0.6 (0.4–0.8)	0.6 (0.4–0.8)
TUG; sec						
>8 sec	66	42%	0.8 (0.6–1.1)	0.15		
CRT; sec						
>25 sec	81	52%	0.8 (0.5–1.1)	0.10		
MIP; cm H_2O						
<90 cm H_2O	104	65%	0.6 (0.4–0.9)	0.003	0.6 (0.5–0.9)	0.6 (0.5–0.9)
RCE; J						
≤375 J	122	82%	0.7 (0.4–1.1)	0.10		
HGS; N						
<233 N	40	26%	0.9 (0.6–1.3)	0.44		

*Inclusion of physical activity and fitness increased the chi-square from 9.85 to 16.47 and the p-value from 0.007 to <0.0001: their inclusion decreased the -2 log likelihood from 1303.49 to 1176.78 (p=0.002).
LAPAQ, LASA physical activity questionnaire; TUG, timed up-and-go; CRT, chair rise time; MIP, maximal inspiratory pressure; RCE, respiratory cumulative energy; HGS, hand grip strength.

DISCUSSION

This study revealed that preoperative physical activity and physical fitness are statistically significant and independent predictors of postoperative recovery in addition to conventional predictors. Individual determinants of physical activity and physical fitness were significantly correlated with one or more of the postoperative outcome measures. The same was true for three conventional risk factors; age, diabetes, and COPD. The performance of the prediction models for mortality, discharge destination and length of stay were all significantly improved by addition of the physical activity and fitness factors. In the multivariate regression analyses, physical activity, measured with a questionnaire, was the only factor that was significantly correlated with all outcome measures after correction for mutual correlation in logistic regression analyses. Thus LAPAQ was the most robust predictor of postoperative recovery identified in this study.

Compared with the conventional factors, the physical activity and physical fitness factors predominated in explaining the variance in the postoperative measurements. Age was the most important conventional predictor, but was statistically overruled by the physical activity and physical fitness factors in regression analyses. This suggests that physiological age, i.e. the way that age affects physical functioning, is a better predictor than chronological age. Our results hold even when age was forced into the model. This seems to justify the addition of the physical activity and fitness factors to preoperative evaluation. The major role of physical activity as a preoperative predictor of postoperative outcome is consistent with recent research showing that the activity level, measured with an accelerometer, is correlated with postoperative complications.[30] It is also consistent with the general recommendation that older people should adopt and/or maintain a physically active lifestyle.[31] Robinson et al. also included comorbidities and functional measures in the prediction of postoperative mortality and found functional measures to be of added value.[12] These authors made a plea toward a preoperative assessment using geriatric-specific markers. Independent functioning in terms of self-reported ADL is a frequently mentioned predictor of the postoperative course[32-35]: our findings with the 'timed up-and-go' test, a capacity-based measure of ADL, confirmed its importance. In the univariate analysis, handgrip strength was significantly correlated with mortality and discharge destination, which corroborates the results of three studies evaluating handgrip strength as single predictor.[36-38] The handgrip strength cut-off for mortality was very similar to that reported by Chen et al. for patients with oesophageal cancer.38 The predictive role of respiratory function is not widely recognised, but is probably due to the additional deterioration in inspiratory muscle function after major abdominal and thoracic surgery.[39]

Although we included patients scheduled for elective colon surgery, the results could probably be extrapolated to other abdominal or thoracic surgery, because physical activity and fitness reflect the general capacity of the body to withstand the physiological and functional effects of major surgery.[40] A potential limitation of this study was our assessment of physical fitness. We did not use cardiorespiratory function as a marker of frailty. A bicycle ergometry test or stair-climb test could complement the assessments used here to predict the postoperative course.[5,41] The study was also limited by the number of participants, which limited the statistical power of the study, especially because the mortality rate was low. This study focused on the short-term functional recovery: we suspect that the factors we identified would also associate with long-term survival, which is recommended as follow-up research.

The results of this study emphasise the role of physical activity and physical fitness in the preoperative evaluation of elderly patients and the need to include these factors in prediction models of postoperative recovery after major surgery. An accurate preoperative evaluation enables a timely start to be made to appropriate interventions to prevent postoperative complications and provides the patient with information to enable him/her to give truly informed consent.

Acknowledgements

The authors were grateful to Dr John Carlisle for his helpful comments on earlier drafts of this paper.

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4

Linear and nonlinear analyses of respiratory patterns in preoperative evaluation

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Submitted for publication

ABSTRACT

Introduction: The adaptive capacity of the respiratory system is of vital importance to cope with its functional decline after major abdominal and thoracic surgery and to prevent postoperative pulmonary complications. In this 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 for use in the preoperative stratification and by use of a short-term sample time (3–5 minutes).

Methods: Six young healthy volunteers (controls: 2 female/4 male; age 24±4 years) and 10 persons indicated as high-risk for postoperative pulmonary complications (patients: 4 female/6 male; 71±13 years) were included. All subjects performed a respiratory test covering 70 eupneic breathing cycles. Variability of the pressure curve was quantified by the coefficient of variation (CV) of the inter-breath intervals and the amplitudes. Complexity was determined as sample entropy (SE). Differences between the groups were analyzed by the Mann Whitney U test.

Results: The median CV of the inter-breath intervals was 0.11 (IR 0.09–0.15) for controls and 0.10 (IR 0.07–0.13) for patients ($p=0.45$). The median CV of the amplitudes of the inspiratory curves was 0.19 (IQR 0.13–0.22) and 0.13 (IR 0.09–0.20) for controls and patients, respectively ($p=0.19$). For the expiratory curves the median was 0.22 (IR 0.13–0.31) for controls and 0.12 (IR 0.07–0.22) for patients ($p=0.16$). The median SE was 0.29 (IQR 0.22–0.43) for controls and 0.19 (IR 0.14–0.24) for patients ($p=0.03$).

Conclusion: We demonstrated the feasibility of linear and nonlinear measures in the preoperative assessment of the adaptive capacity of the respiratory system. Sample entropy significantly distinguished young/healthy persons from persons at high risk for postoperative pulmonary complications after major abdominal and thoracic surgery.

INTRODUCTION

General surgery stresses the human physiological system. Major abdominal and thoracic surgery induce a sharp postoperative decrease in respiratory function putting patients at risk to develop postoperative pulmonary complications (PPCs),[1] especially in frail patients. PPCs are the leading causes of postoperative morbidity and mortality and increase hospital length of stay, medical consumption and, hence, costs in patients after major abdominal and thoracic surgery.[2-4] Screening and training of the respiratory muscle function is increasingly part of the preoperative care in abdominal and thoracic surgery.[5-8] It aims for evaluating and optimizing the adaptive capacity of the respiratory system.

At present, the respiratory function and its adaptive capacity are assessed by the mere strength and endurance of the inspiratory muscles. Here we advocate a supplementary approach to relate adaptive capacity with the variability and other dynamical characteristics of respiratory signals. The breathing pattern is not a strictly periodic movement but arises from stochastic, nonlinear biological mechanisms interacting with a fluctuating environment[9] and display seemingly erratic variations in frequency and shape. These variations may be quantified by conventional statistics, e.g., the variance breath-to-breath intervals and amplitudes of the respiratory pattern. This approach primarily addresses the randomness or stochasticity of the observed variations and implies that the generating (physiological) process is linear, at least by good approximation. Alternative measures may explicitly speak to the nonlinear dynamics underlying the observed variation, which may indeed stem from interactions between many participating components of the process under study.[10] The variations are thus not merely erratic but may show so-called complex characteristics, to think of long-term correlations, 1/f spectral distributions, and so on. These characteristics are often considered to depend on age[11-13] (rigid and little fluctuations in the variable under study) and, e.g., the presence of disease[14-16] (large fluctuations and loss of control). In both cases one can observe effects on the adaptive capacity of the physiological system.

Most studies studying the variability of respiratory signals built on reasonably long recording times.[17,18] providing the opportunity to investigate a huge arsenal of complexity-related measures. Our focus on preoperative assessments of the adaptive capacity of the respiratory system, however, demands to consider short recording times, which hampers many quantitative approaches such as fractal dimensions and scaling properties. We here used entropy as an appropriate measure,[19] it appears particularly robust when considering data sets containing brief signals.

To assess the adaptive capacity of the respiratory system by use of linear and nonlinear analyses in preoperative clinical practice, we posed the following research question: what is the feasibility of a brief sample protocol (3–5 minutes) in determining the difference of variability and entropy of the respiratory pattern between young healthy adults and older patients who are known to be at risk for a postoperative pulmonary complication after major abdominal and thoracic surgery?

METHODS

Subjects

Six male and four female patients representing the so-called the high-risk group were included in this exploratory observational study (mean age: 71 ± 13 years). They were all at high risk for postoperative pulmonary complications after abdominal or thoracic surgery, i.e. met at least one of two risk factors: age >65 years and COPD.20-22 Seven of them were aged 65 years or older and six of them were diagnosed with COPD. Three patients met both conditions. In additional we included six young and healthy volunteers as a control group (four males and two females; mean age: 24 ± 4 years).

Patients were under treatment at the department of physiotherapy (Gelderse Vallei hospital). The controls were recruited among university students and employees of the hospital. All subjects were asked for informed consent for participation in the study. The local Medical Ethics Committee of the Gelderse Vallei Hospital approved the study protocol.

Procedure & measurement

Respiratory signals were obtained by use of the Respiratory Muscle Analyzer (MicroRMA /Micro Medical Limited, Rochester, UK). This device continuously registers mouth pressure at a sampling rate of 10 Hz. The resistance of the device was preset to zero by the investigator and patients were instructed to breath normally because eupneic breathing is considered the optimal presentation of adaptive capacity.[23] The test covered 70 breathing cycles (i.e. approx. 300 sec.; corrected for breaks during the test).

Data analysis

Visual inspection of the respiratory signals readily revealed a qualitative difference in signal variations between the patients and controls. We illustrate this in Figure 4.1 showing the respiration curves of a representative control (Figure 4.1A) vis-à-vis a patient at high risk for a postoperative pulmonary complication (Figure 4.1B). Both curves cover a period of 22 seconds in the second minute of the test.

We quantified outcome measures data using Matlab® (version 2011b; Mathworks Inc. Natwick, MA). Variability of the respiratory signals was determined as the coefficient of variation of the inter-breath intervals, i.e. distances between maximums of the inspiratory pressure curve and the coefficient of variation of the inspiratory and expiratory amplitude of the pressure curves. The entropy was estimated via the sample entropy (SE).[19] In brief, sample entropy represents the negative natural logarithm of the conditional probability that two sequences similar for *M* points remain similar at the next point with tolerance *r*. The *r*-value was set on 0.15 based on analysis by Lake.[24]

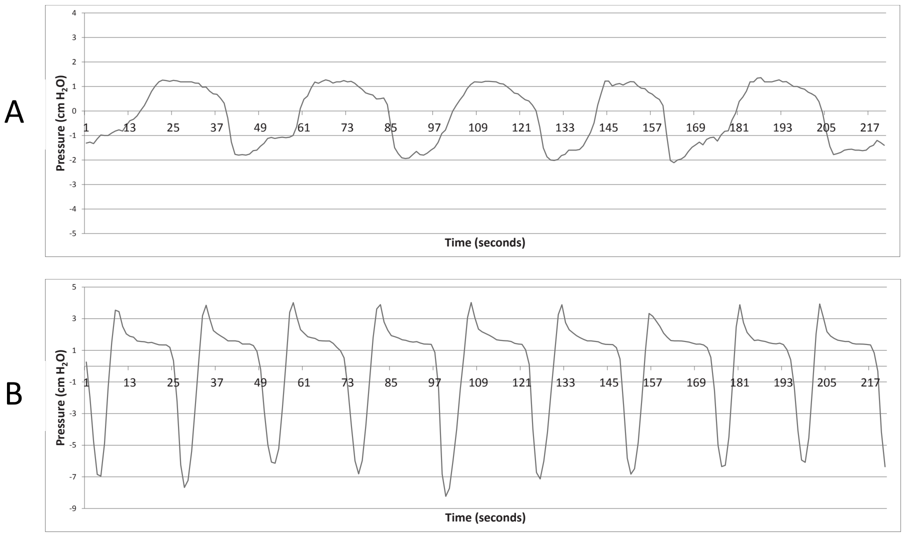

Figure 4.1 Breathing pattern of a young healthy volunteer **(A)** and a patient at risk for a postoperative pulmonary complication **(B)** during the second minute of the recording.

Statistics

SPSS Statistics (version 19.0, SPSS Inc., Chicago, IL) served for the statistical analysis. Characteristics of study participants were summarized using means and standard deviations in case of continuous variables or frequency and percentage distributions in case of categorical variables. Coefficients of variations (CV) of inter-breath intervals, amplitudes of the pressure curves and sample entropy (SE) were expressed as median and interquartile range (IR). Differences in coefficients of variation between the two groups were estimated with a non-parametric independent sample t-test (Mann-Whitney U-test). Correlations between the linear and nonlinear measures were computed using Spearman's rank correlation.

RESULTS

All subjects completed the test successfully. The breathing frequency was 15.4 (± 1.8) and 18.6 (± 4.5) breaths per minute for the control and patient group, respectively.

The median CV of the inter-breath intervals was 0.11 (IR 0.09–0.15) for controls and 0.10 (IR 0.07–0.13) for the patients (Mann Whitney U test; p=0.45). The median CV of the amplitudes of the inspiratory curves were 0.19 (IR 0.13–0.22) and 0.13 (IR 0.09–0.20) for controls and patients, respectively (Mann Whitney U test; p=0.19). For the expiratory curves the median CV was 0.22 (IR 0.13–0.31) for controls and 0.12 (IR 0.07–0.22) for patients (Mann Whitney U test; p=0.16). Finally, the median SE was 0.29 (IR 0.22–0.43) for the controls and 0.19 (IR 0.14–0.24) for the patients (Mann Whitney U test; p=0.03). See Figure 4.2 for boxplots of the above-mentioned analyses.

The CVs showed a significant mutual correlation. By contrast no significant correlation was found between the CVs and the corresponding SEs (see Table 4.1).

Table 4.1 Spearman's rank correlations between linear and nonlinear measurements

		Coefficient of variation	
	Sample entropy	CV IBI	CV amplitude (exp)
CV IBI	0.42 (p=0.10)		
CV amplitude (exp)	0.33 (p=0.21)	0.60 (p=0.02)*	
CV amplitude (insp)	0.31 (p=0.24)	0.72 (p<0.01)*	0.52 (p=0.04)*

CV, coefficient of variation; IBI, inter-breath interval.
* p<0.05.

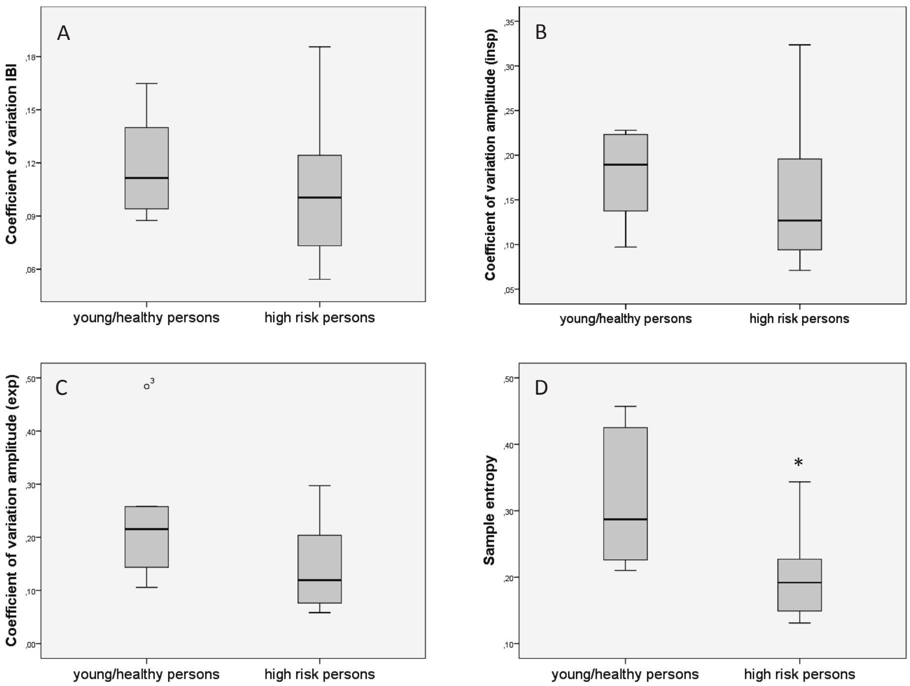

Figure 4.2 Boxplots showing the differences between persons at high risk for postoperative pulmonary complications and young/healthy controls for the coefficient of variation of the inter-beat interval (p=0.45) **(A)**, of the inspiratory amplitude (p=0.19) **(B)**, and of the expiratory amplitude (p=0.16) **(C)** as well as the sample entropy (p=0.03) **(D)**.

DISCUSSION

Our study demonstrates that variability and complexity-related measures of breathing patterns can be determined reliably even when using a brief recording protocol. A complexity-related measure, here the sample entropy, helped to distinguish between the control group, consisting of young and healthy volunteers, and the patient group with patients at high risk for postoperative pulmonary complications.

The brief recording protocol dictating eupneic breathing yielded stationary respiratory signals, which is prerequisite for all subsequent analysis, be it linear or nonlinear. By the same token, the sample was large enough to allow for reliable estimate of the complexity-related measure sample entropy.[1] In fact the entropies revealed more pronounced

[1] Other measures addressing the complexity of nonlinear dynamics like fractal dimensions or scaling characteristics of the autocorrelation (e.g. the Hurst exponent) typically require much longer (non-periodic) signals.

differences between controls and patients than coefficients of variations did. These findings agree with the idea that the respiration system is a biological system that is characterized by non-linear dynamics resulting in irregularity and complexity. The linear measures did show greater variability in the control group albeit less marked and in fact not significant (the latter maybe due to low power). The weak correlation between the linear and nonlinear measures may be considered indicative for their generic difference.[25] Investigating both sides of the coin, the linear and the nonlinear one, can thus provide additional insight in clinically relevant aspects of breathing patterns.

Variability and complexity of physiological signals in relation to pathology and aging has been investigated in detail for heart function by assessment of the heart rate variability (HRV)[26] but to a much lesser extent for respiratory function. While there are no studies investigating linear and nonlinear properties of respiratory signals for the purpose of risk stratification in abdominal and thoracic surgery, it is important to realize that our results agree with those found in other patient groups. Recently Veiga and co-workers demonstrated less nonlinear complexity in respiratory patterns in asthmatic patients with airway obstruction compared to healthy persons.[27] This study also computed the entropy by use of brief recordings. Furthermore, scaling exponents determined via detrended fluctuation analysis (DFA) of a two hours recording differed between healthy elderly male compared to young male in research of Peng.[12] Besides differences between patients and healthy controls, other studies focused on the assessment of the adaptive capacity of the respiratory system in order to distinguish patients who can be successfully separated from mechanical ventilation and who cannot. Recently, White and co-workers demonstrated lower sample entropy of the respiratory signal in patients who failed to separate from mechanical ventilation.[17] Interestingly, such weaning failure patients seem to exhibit significantly reduced sample entropy, Lyapunov exponents, and increased DFA exponents[18] suggesting non-trivial temporal correlations in the breathing patterns.

Such complex temporal characteristics in the mouth pressure signal may be attributed to both the output of the respiratory center in the brainstem and to lung mechanics (dynamic properties of the lung tissue and bronchial muscles). The latter's influence, however, appears limited since patients who are mechanically ventilated through a machine-controlled assistance mode without any variability, do not display any signs of complex dynamics. This advocates a neural origin of the here-discussed, complexity-related variability above mere mechanical features of the respiratory system.[28]

Our feasibility study compared variability and entropy of the respiratory signal of young and healthy persons with that of patients at risk for pulmonary complications based on consisting preoperative criteria. This is a first step in the development of a comprehensive assessment in the preoperative care that addresses the random and complex nature of breathing alike. For the sake of demonstration we chose to maximize contrast between the groups under study, i.e. young and healthy volunteers versus patients at high risk for postoperative pulmonary complications, most elderly and sometimes frail people. The promising results of our study call for investigating a less favorable contrast in the study population as present in elderly patients scheduled for major abdominal and thoracic surgery. Future research should also include the postoperative course as outcome measure for the validation of the use of linear and nonlinear measurements in the preoperative risk stratification. Finally, it is interesting to question if effects of inspiratory muscle training on postoperative pulmonary complications[5,29] can be associated with the non-linear dynamics of the respiratory signal. In fact, exercise has already been shown to improve the autonomous regulation of the heart as reflected by nonlinear indexes (DFA exponents and entropy measures) of the heart rate variability[30] but future study should address this in more detail.

Conclusion

We demonstrated the feasibility of linear and nonlinear measures in the preoperative assessment of the adaptive capacity of the respiratory system. Sample entropy of a brief sample of the respiratory pattern distinguished young and healthy persons from patients at high risk for postoperative pulmonary complications after major abdominal and thoracic surgery. Complexity-related measures of the respiratory system seem valid parameters for use in the risk stratification in the preoperative care of patients scheduled for major surgery affecting the postoperative respiratory function.

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5

Prevention of pulmonary complications after upper abdominal surgery by preoperative intensive inspiratory muscle training: a randomized controlled pilot study

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Clinical Rehabilitation 2008; 22:134-42

ABSTRACT

Objective: To investigate 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.

Design: Single-blind randomized controlled pilot study.

Setting: Gelderse Vallei Hospital Ede, the Netherlands.

Subjects: Twenty high-risk patients undergoing elective abdominal aortic aneurysm surgery were randomly assigned to receive preoperative inspiratory muscle training or usual care.

Main measures: Effectiveness outcome variables were atelectasis, inspiratory muscle strength and vital capacity, and feasibility outcome variables were adverse effects and patient satisfaction with inspiratory muscle training.

Results: 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; $p=0.001$). Eight patients in the control group and three in the intervention group developed atelectasis ($p=0.07$). The median duration of atelectasis was 0 days in the intervention group and 1.5 days in the control group ($p=0.07$). No adverse effects of preoperative inspiratory muscle training were observed and patients considered that inspiratory muscle training was a good preparation for surgery. Mean postoperative inspiratory pressure was 10% higher in the intervention group.

Conclusion: 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.

INTRODUCTION

The incidence of clinically relevant postoperative pulmonary complications after upper abdominal surgery varies from 5% to 30%, depending on their definition and the type of surgery.[1-5]

Postoperative pulmonary complications are the leading cause of postoperative morbidity and mortality and increase hospital length of stay, medical consumption, and hence costs.[1,6-8] Consequently, it is imperative, both for patients and society, to prevent postoperative pulmonary complications. Physical therapy appears to be effective as postoperative treatment[9-13] and may lower the incidence of postoperative pulmonary complications when given preoperatively, as suggested and demonstrated by Weiner et al.[14] and Nomori et al.[15] in fragile, high-risk patients. Recently, Hulzebos et al.[16,17] showed preoperative physical therapy to be effective in high-risk patients who underwent a coronary artery bypass procedure. The question is whether preoperative physical therapy prevents the postoperative pulmonary complications that occur in high-risk patients after other types of surgery, such as elective upper abdominal surgery. As in thoracic surgery, but based on a distinct physiological mechanism,[18] upper abdominal surgery also induces a sharp postoperative decrease in respiratory function, a decrease which can lead to the development of postoperative pulmonary complications.[19]

The aim of this pilot study was twofold: (a) to investigate the 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, and (b) to assess the feasibility of preoperative inspiratory muscle training.

PATIENTS AND METHODS

Patients

Twenty high-risk patients were recruited from the surgery outpatient department of the Gelderse Vallei Hospital in Ede, the Netherlands. The primary inclusion criteria were elective surgery for aneurysm of the abdominal aorta with a scheduled delay until surgery of at least two weeks, and at least one of the following risk factors: age >65 years, smoking less than two months before surgery, chronic obstructive pulmonary disease (COPD), and overweight (body mass index (BMI) >27 kg/m^2).[20-22] Eligible patients also had to be proficient in Dutch and able to perform a valid spirometry test. Exclusion criteria were cerebrovascular disorders, immunosuppressive treatment <30 days before the operation, neuromuscular diseases, lung surgery in the medical history, cardiovascular instability, and treatment by a physical therapist within eight weeks before elective abdominal aortic aneurysm surgery. Signed informed consent forms were collected from all patients, and the protocol was approved by the medical ethics committee of the University Medical Center Utrecht and of the Gelderse Vallei Hospital, the Netherlands.

Procedure

In this single-blind randomized controlled trial, the patients were referred from the surgery outpatient department of the Gelderse Vallei hospital. After inclusion, the informed consent procedure, and evaluation of baseline characteristics, an independent research assistant randomly assigned the patients to the intervention group (n=10) or the control group (n=10) by opening a sealed and numbered envelope (Figure 5.1). The patients in the intervention and the control groups entered the study at least 2–4 weeks before surgery. After the baseline assessment, the patients in the intervention group started the intervention under the guidance of an experienced physical therapist; the patients in the control group received care as usual. All patients were seen the day before surgery, and all patients received usual postoperative care. The main postoperative outcome was atelectasis as diagnosed at the base of X-rays by a blinded radiologist.

Intervention

The intervention group took part in a training programme (six sessions, six days a week for at least two weeks before surgery) designed to increase the strength and endurance of the inspiratory muscles.[14,15] Each session consisted of 15 minutes of inspiratory muscle training; one session/week was supervised by the same physical therapist and the other five sessions were unsupervised. The subjects were instructed to keep a daily diary during the study and were trained to use an inspiratory threshold-loading device (Threshold Inspiratory Muscle Training; Respironics, Pittsburgh, PA, USA). With this device, patients inspire against a threshold load whereas expiration is unimpeded. The inspiratory load is calibrated in cmH_2O and can be increased as required. The subjects started breathing at a resistance equal to 20% of their maximal inspiratory pressure (MIP), measured at baseline, for 15 minutes a day.[23] The resistance was increased incrementally, based on the rate of perceived exertion (RPE) scored by the patient on the Borg Scale. If the RPE was <5, the resistance of the inspiratory threshold trainer was increased incrementally by $2cmH_2O$.

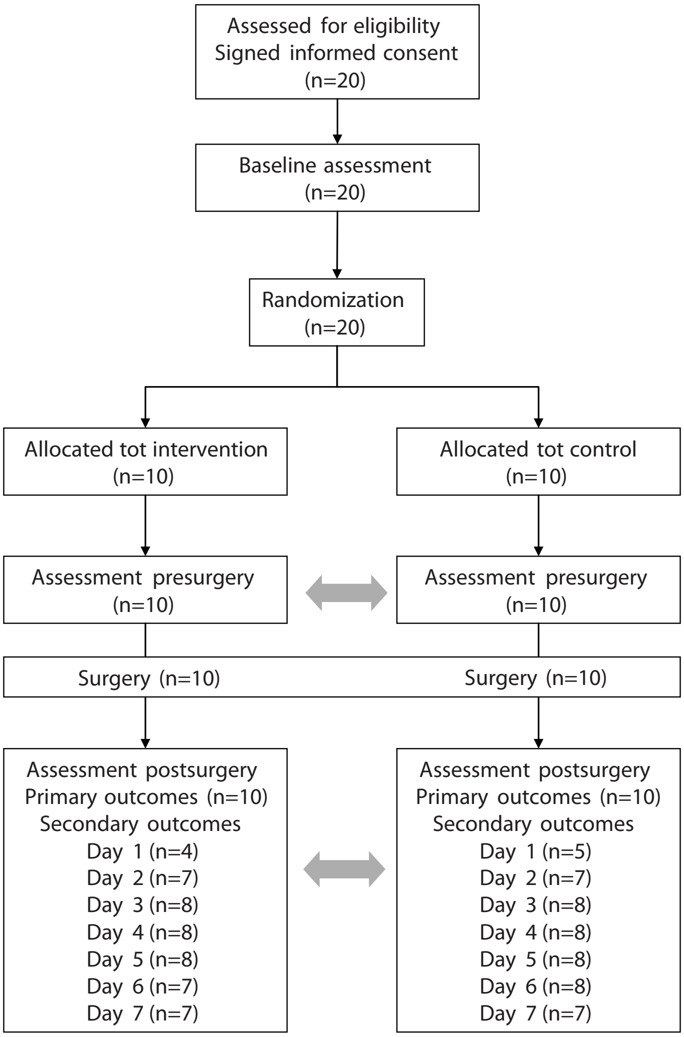

Figure 5.1 Flowchart of the study.

Usual care

In the preoperative period the control and the experimental groups received care as usual, consisting of instruction in (a) diaphragmatic breathing,[24-26] (b) deep inspirations with the aid of incentive spirometer,[1,10-13,27-29] and (c) coughing and 'forced expiration techniques' (FET).[11,13,27] The control group received this usual care one day before surgery, and the intervention group 2–3 weeks before surgery during the intervention.

Postoperative physical therapy interventions (for both groups) consisted of stimulating deep inspirations (partly with the aid of the incentive spirometer), diaphragmatic inspiration, FET and coughing. Furthermore, patients were encouraged to sit rather than lie and early mobilization was stimulated, which has a positive effect on functional residual capacity (FRC).[30]

Measurements

The main outcome measure was postoperative pulmonary complications, operationalized as atelectasis, which is considered a 'precursor' of more clinically relevant postoperative pulmonary complications.[19] A blinded radiologist evaluated radiographs of the lung base for the presence of atelectasis.

Feasibility was evaluated as the occurrence of adverse effects during testing or training and patient satisfaction. During the intervention, the participants registered adverse events in their daily diaries. Participant satisfaction was determined two weeks after discharge from hospital by means of a questionnaire (see Table 5.2).

Secondary outcome measures were postoperative respiratory function determined by MIP, inspiratory muscle endurance, and the inspiratory vital capacity (VC). Inspiratory muscle strength, expressed as MIP at residual volume, was assessed with a hand-held respiratory pressure meter (MicroMPM; MicroMedical, Rochester, UK). The MIP is thought to mainly reflect the inspiratory muscle force.[31] The respiratory muscle force tests were standardized as described in ATS/ERS Statement on Respiratory Muscle Testing.[31] The highest 1-second averages recorded in five consecutive attempts are reported. Inspiratory muscle endurance was assessed with incremental threshold loading.[32] Starting at 30% of the MIP, resistance was increased incrementally every 2 minutes by 10% of the MIP. Endurance is expressed as the highest resistance (in cmH_2O) that could be sustained for 2 minutes without interruption of inspiration. The inspiratory vital capacity (IVC) was measured with a portable spirometer (SpiroPro; Sensor Medics, Bilthoven, The Netherlands) with the patient in a sitting position, as described by the American Thoracic Society.[33] The highest values measured in three consecutive attempts are reported.

Data analysis

Data were analysed with SPSS version 10.1 statistical software (SPSS Inc., Chicago, IL, USA). All collected data were checked for completeness and normality. Intention-to-treat analyses were used to compare the preoperative outcomes and the incidence of atelectasis between the two groups. The incidence and prevalence of atelectasis was analysed with the Fisher exact test and the Mann–Whitney U-test, respectively. Patient satisfaction with inspiratory muscle training training was recorded in a frequency table. Differences in the preoperative MIP and inspiratory muscle endurance within and between the intervention and the control groups were tested with the paired and independent t-tests, respectively. Postoperative MIP and IVC were analysed by repeated measures analysis of variance with treatment as the between-subject factor.

RESULTS

The baseline characteristics of the 20 patients are listed in Table 5.1. The patients in the intervention group were significantly older than the patients in the control group (70

Table 5.1 Baseline characteristics of the patients

	Control N=10	Intervention N=10
Women / men	7/3	8/2
Age in years (SD)	59 (6)	70 (6)*
MIP in cmH_2O (SD)	83 (15)	68 (19)
IM endurance in cmH_2O (SD)	39 (10)	32 (8)
Smokers (number of patients)	6	6
COPD (number of patients)	1	1
BMI (kg/m^2)	25	26
Coughing (number of patients)	4	3
Rand 36 (physical dimension)	74 (19)	77 (20)
IVC (litres)	3.1 (1.0)	3.1 (0.7)
Surgery duration (hours)	2.9 (1)	3.3 (1.7)

* significant difference (p=0.001) between control and intervention group. MIP, maximal inspiratory pressure; IM, inspiratory muscle, COPD, chronic obstructive pulmonary disease; BMI, body mass index; IVC, inspiratory vital capacity.

± 6 years versus 59 ± 6 years, respectively; p=0.001). Two patients in the control group dropped out because they were not registered at the department of physical therapy when they were admitted to hospital and thus follow-up was not possible. Two patients in the intervention group could not be followed up during the first seven days after surgery because of acute reoperation for blood vessel occlusion in the leg. One of these two patients developed sepsis and renal insufficiency and died 35 days after surgery.

Atelectasis

Eight patients in the control group and three patients in the intervention group developed atelectasis (Fisher exact test p=0.07). Atelectasis was evident on radiographs for a median of 0 days in the intervention group and 1.5 days in the control group (Mann–Whitney U-test p=0.07).

Patient satisfaction

Eight participants in the intervention group returned the questionnaire two weeks after discharge from hospital and indicated they were motivated to complete the preoperative intervention and that it prepared them for surgery (Table 5.2). All participants reported their daily inspiratory muscle training workout in their diaries. No participants dropped out and no adverse events were reported.

Table 5.2 Patient appreciation of treatment (n=8)

	Disagree				Agree
	1	2	3	4	5
The aim of the treatment was clear to me				*	*******
I was motivated to complete treatment				**	******
The home work exercises took a lot of time	***	*	**	**	
During the exercises, the perceived exertion was high	*	*	***	**	
I exercised with pleasure				**	******
I benefited from the once-weekly supervision				**	******
I think the treatment prepared me well for the operation			*	*	******

Respiratory function

Before surgery, the mean MIP increased from 68 ± 19 cmH_2O to 72 ± 22 cmH_2O (paired t-test p=0.32) at the end of the preoperative training period in the intervention group; over the same period the mean MIP decreased from 83 ± 15 cmH_2O to 80 ± 24 cmH_2O in the control group (paired t-test p=0.60). There was no significant difference between the groups (independent t-test p=0.29). Before surgery, mean inspiratory muscle endurance increased from 32 ± 8 to 43 ± 14 cmH_2O (paired t-test p=0.05) after training in the intervention group and from 39 ± 10 to 43 ± 9 cmH_2O (paired t-test p=0.36) in the control group over the same period. There was no significant difference between the intervention and control groups (independent t-test p=0.12). ANCOVA analysis showed that the length of the training did not significantly affect the change in MIP (p=0.97) and inspiratory muscle endurance (p=0.76).

MIP and IVC values on postoperative days 1 to 7 were higher in the control group than in the intervention group (Table 5.3), but these differences were not statistically significant

Table 5.3 Mean maximal inspiratory pressure (MIP) and inspiratory vital capacity (IVC) (SD) in intervention and control groups in the first seven postoperative days

	Postoperative day						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
MIP							
Intervention group							
Number of patients that could be measured	2	7	8	8	8	7	7
MIP	42 (1)	42 (5)	47 (6)	50 (7)	54 (10)	53 (13)	55 (14)
Control group							
Number of patients that could be measured	4	7	8	8	8	8	7
MIP	39 (8)	49 (14)	56 (17)	57 (18)	64 (21)	66 (20)	67 (16)
IVC							
Intervention group							
Number of patients that could be measured	4	8	8	8	7	6	7
IVC	1.5 (0.6)	1.5 (0.6)	1.7 (0.6)	2.1 (0.7)	2.1 (0.7)	2.1 (0.3)	2.3 (0.4)
Control group							
Number of patients that could be measured	5	6	6	6	6	6	5
IVC	1.5 (0.3)	1.8 (0.5)	2.2 (0.8)	2.3 (0.7)	2.4 (0.8)	2.6 (0.9)	2.9 (0.8)

(repeated measures analysis of variance p=0.42 and p=0.73, respectively). Because the baseline MIP was different between the two groups, the postoperative MIP was also expressed as the percentage of the MIP at baseline (Figure 5.2). When calculated in this way, the mean postoperative MIP was 10% higher in the intervention group but this difference was not statistically significant (repeated measures analysis for the first five days, p=0.36). In the intervention group, the MIP decreased on day 6 after surgery, which was when patients were discharged.

DISCUSSION

This study fits the present-day development of preventive health care methods.[34-36] In conclusion, the clinical message of this study is that (a) inspiratory muscle training is both well tolerated and appreciated by patients who have to undergo elective abdominal aortic aneurysm surgery and (b) inspiratory muscle training seems to reduce the incidence of postoperative atelectasis in this patient group. The results indicated that, after surgery, inspiratory muscle function recovered faster in the patients in the intervention group; however, this improvement appeared not to affect the postoperative inspiratory vital capacity.

Patient-centred care is a focus of many health care systems.[37] Patients evaluated the care provided by the physical therapist by completing a satisfaction questionnaire. Results

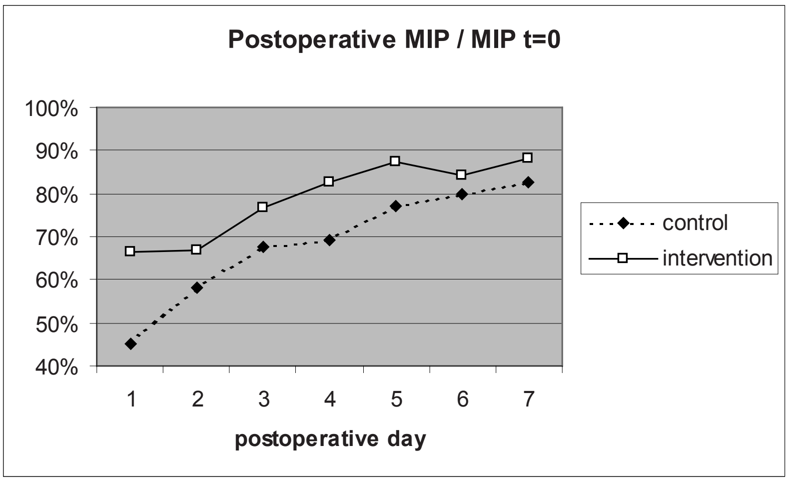

Figure 5.2 Age-corrected postoperative maximal inspiratory pressure (MIP) expressed as the percentage of the MIP measured before surgery (at the beginning of the intervention).

showed that acceptance of and compliance with inspiratory muscle training were high and there were no side-effects. The statement 'I think the treatment prepared me well for the operation' in particular received high (positive) scores.

The baseline characteristics of the two groups were not comparable, as the patients in the intervention group were significantly older than those in the control group. Because age is associated with both maximal inspiratory pressure[32,38] and the risk of a postoperative pulmonary complication,[19,39,40] we calculated individual postoperative maximal inspiratory pressure values as a percentage of the preoperative maximal inspiratory pressure; however, it is not possible to adjust the incidence of postoperative pulmonary complications for age in this way, and so the effect of preoperative inspiratory muscle training in terms of a diminished occurrence of atelectasis is probably underestimated. The inequality between the groups can be explained by the small number of patients included in the study. This also means the results should be evaluated with caution.

Despite the relatively small groups, we found a nearly significant ($p=0.07$) reduction in atelectasis in the intervention group compared with the control group. Atelectasis is considered to be a subclinical sign and may predispose a patient to more clinically relevant postoperative pulmonary complications such as pneumonia.[19] In particular, atelectasis occurring from the second postoperative day onward is considered to affect the oxygenation of blood and mucus transport.[1] Thus the lower incidence of atelectasis is relevant and is consistent with earlier results.[14,19] Although previous studies have shown inspiratory muscle training to increase inspiratory muscle strength and endurance,[23,41] the training period lasted several months whereas the preoperative training period was only 2–4 weeks. We found that preoperative inspiratory muscle training increased inspiratory muscle strength and endurance, although this effect was not statistically significant because of the small group size. Nomori et al.,[15] Weiner et al.[14] and Hulzebos et al.[17] reported significant differences in their larger studies. Indeed, all studies with large numbers of patients have found short-term preoperative inspiratory muscle training to increase inspiratory muscle strength and endurance (Table 5.4).

Studies involving more patients are needed to determine whether preoperative inspiratory muscle training has a positive effect on other postoperative complications such as pneumonia. Assuming an effect size of 0.20 (conservative estimate) and a power of 0.80, in total 196 subjects would be needed to reveal an effect on the incidence of more relevant postoperative pulmonary complications.

Table 5.4 Studies that investigated the effect of preoperative short-term inspiratory muscle training (IMT) on maximal inspiratory pressure (MIP) and inspiratory muscle (IM) endurance

Study	N	Mean age (years)	Training period (weeks)		MIP	Endurance IM
Nomori et al.[15]	50	55	Range	2-4	↑ *	↑ *
Weiner et al.[14]	84	59	Range	1-3	↑ *	-
Hulzebos et al.[16]	26	70	Range	2-4	↑	-
Hulzebos et al.[17]	251	66	Mean	4 (2–13)	↑ *	↑ *
This study	20	70	Mean	7 (2–16)	↑	↑

* Significant $p<0.05$.

Clinical messages

- Postoperative pulmonary complications are common and a major cause of morbidity and mortality after aortic aneurysm surgery.
- Preoperative insipiratory muscle training is both well tolerated and appreciated by patients and seems to reduce the incidence of postoperative atelectasis in this patient group.

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6

Preoperative exercise program for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study

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Clinical Rehabilitation 2010; 24(7):614-22

ABSTRACT

Objective: Investigation of the feasibility and preliminary effect of a preoperative short-term intensive exercise program for elderly patients scheduled for elective abdominal oncological surgery.

Design: Single-blind randomized controlled pilot study.

Setting: Ordinary hospital in the Netherlands.

Subjects: Forty-two elderly patients (>60 year).

Interventions: Patients were randomly assigned to receive a short-term intensive therapeutic exercise program to improve muscle strength, aerobic capacity, and functional activities, given in the outpatient department (intervention group; N=22), or home-based exercise advice (control group; N=20).

Main measures: Parameters of feasibility, preoperative functional capacity, and postoperative course.

Results: The intensive training program was feasible, with a high compliance and no adverse events. Respiratory muscle endurance increased in the preoperative period from 259±273 to 404±349 Joule in the intervention group and differed significantly from that in the control group (350±299 to 305±323 Joule; $p<0.01$). 'Timed up and go', Chair Rise Time, LASA Physical Activity Questionnaire, Physical Work Capacity, and Quality of Life (EORTC-C30) did not reveal significant differences between the two groups. There was no significant difference in postoperative complications and length of hospital stay between the two groups.

Conclusion: The intensive therapeutic exercise program was feasible and improved the respiratory function of patients due to undergo elective abdominal surgery compared to a home-based exercise advice.

INTRODUCTION

About 35% of patients experience postoperative complications after major abdominal surgery, including 9% postoperative pulmonary complications (defined as pneumonia and respiratory failure). The overall 30-day mortality rate is 10%.[1,2] Preoperative physical capacity is an important predictor of the postoperative course.[3-8] Because the physical capacity of elderly patients is often diminished due to a lack of regular physical activity, and especially prior to surgery,[9-12] improvement of their functional capacity may make them better prepared for hospital admission and facilitate recovery after surgery.[13]

Long-term training appears to be beneficial to elderly individuals[14,15]; however, the time available for training before elective surgery is often limited, and especially so with oncological surgery. Little research is available about the effect of short-term training in the preoperative period. Hulzebos et al. recently showed short-term preoperative inspiratory muscle training to be effective in increasing inspiratory muscle strength and reducing the incidence of postoperative pulmonary complications in high-risk patients who underwent a coronary artery bypass procedure.[16] A pilot study revealed potentially similar effects in elective abdominal aortic aneurysm surgery.[17] The primary aim of this pilot study is to investigate the feasibility of a short-term intensive therapeutic exercise program for elderly patients (>60 years) scheduled for elective abdominal oncological surgery and its effects on muscle strength, aerobic capacity, and functional activities. A secondary objective is to investigate whether such a program affects the incidence of postoperative complications and postoperative functional recovery.

METHODS

The study design was a single-blind pilot randomized controlled trial.

Patients were recruited from the Departments of Gastroenterology and Surgery of the Gelderse Vallei Hospital in Ede, an ordinary hospital in the Netherlands. Inclusion criteria were elective colon surgery (waiting period minimally two weeks and first surgical intervention for this pathology), age ≥60 years, and adequate cognitive functioning (a good understanding and accurate execution of instructions). Exclusion criteria were heart disease that prohibits or impedes exercise, severe systemic illness, recent embolism, thrombophlebitis, uncontrolled diabetes (fasting blood glucose of >400mg/dl), severe orthopedic conditions that prohibit or impede exercise, and wheelchair dependence.

The protocol was approved by the Medical Ethics Committees of both the University Medical Center Utrecht and the Gelderse Vallei Hospital Ede, both in the Netherlands.

All patients referred for preoperative physical therapy by the gastroenterologist or the surgeon went to the outpatient department of physical therapy, as part of the multidisciplinary preoperative work-up. Patient inclusion and exclusion criteria were checked, and patients were informed about the aims of the study and asked for their informed consent. After their functional status was evaluated (T=0), participants were randomly assigned (block randomization) using prepared envelopes, after stratification by age (60–70 years and age >70 years), to two treatment groups by two people not associated with the study. The patients allocated to the intervention group received a short-term intensive therapeutic exercise program in the outpatient department and the control group received a home-based exercise advice. The physical therapists and patients were not blinded to treatment assignment. Preoperative outcome measures (T=1) and the postoperative course (T=2) were assessed by an investigator who was unaware of the treatment allocation until after data analysis was completed.

Intervention

The subjects in the intervention group trained twice a week in the outpatient department of physical therapy of the Gelderse Vallei Hospital while waiting for surgery (2–4 weeks). The patients in the intervention group were informed about the importance of their physical condition to the postoperative course and were encouraged to adhere to the training program.

Each supervised training session lasted 60 minutes and included the following elements.

- Warm-up.[18]
- Resistance training of the lower limb extensors (with a maximum of 1 set of 8–15 RM, consistent with 60–80% of the 1-Repetition Maximum[18-21]).
- Inspiratory muscle training. Patients breathed against a variable resistance (10–60% of the maximal inspiratory pressure) for about 15 minutes (240 breathing cycles).
- Aerobic training. The subject trained at a moderate intensity of exercise (to 55–75% of maximal heart rate) or perceived exertion (between 11 and 13 on the Borg scale[18,20,22]; Aerobic training lasted 20–30 minutes to obtain optimal benefit.[18]

- Training functional activities according to the patients' capabilities and interest. This is essentially according to the regimen of de Vreede et al.[14]
- Cooling down.[18]

When not training in the outpatient department, subjects followed a home-based training program. This program prescribed walking (patients received a pedometer to monitor this activity) or cycling for a minimum of 30 minutes per day.[18] The intensity was determined on the basis of the perceived exertion (Borg scale score between 11 and 13). Subjects were supplied with a device for inspiratory muscle training, a threshold loading device. The threshold loading device was adjusted to a resistance equal to 20% of the maximal inspiratory pressure, measured at baseline, and subjects trained with the threshold loading device for 15 minutes per day. The resistance was increased incrementally based on the perceived exertion: if perceived exertion was <13, the resistance of the inspiratory threshold trainer was increased incrementally by 10% of the maximal inspiratory pressure.

The control subjects received home-based exercise advice. They were told of the importance of their physical condition to the postoperative course and were encouraged to be active for minimally 30 minutes a day in the period prior to hospital admission. They received a pedometer to monitor their activities. Once a week the pedometers were read out in the outpatient department by the therapist.

Both groups received instruction in (a) diaphragmatic breathing, (b) deep inspirations with the aid of incentive spirometry, and (c) coughing and "forced expiration techniques".[23,24]

Measurements

Demographics, preoperative risk factors, and measures of functional capacity and self-reported activities were prospectively recorded. Hand grip strength, a reliable measurement[25] and known to be an indicator of skeletal muscle mass and a predictor of the risk of postoperative complications,[26,27] was measured with a DigiMax hand force device (Mechatronics).

Feasibility was determined on the basis of (a) adherence to treatment/advice, (b) patient appreciation of the treatment/advice, recorded at the end of the preoperative period, and (c) adverse events.

Maximal aerobic capacity was determined with Physical Work Capacity 170.[28] Strength and power of the lower limb muscles was estimated by the chair rise time test.[25,29,30] MIP reflects inspiratory muscle force and was assessed with the MicroRPM (MicroMedical).[31,32] Inspiratory muscle endurance was measured with the MicroRMA (Mircomedical), which calculated the total energy expended against a load. Functional mobility was measured with the Timed "Up & Go" test, a reliable and valid test of functional mobility.[33]

Self-reported activities were measured with the LASA Physical Activity Questionnaire, in which patients report their activities of the past 14 days.[34] Walking time was measured with a pedometer with a 7-day memory (New Life Styles NL1000).[35] Quality of life was assessed with the EORTC Quality of Life Questionnaire (EORTC QLQ-C30/version 3) designed for patients with cancer.[36] Fatigue was measured with the abbreviated fatigue questionnaire (AFQ).[37]

Postoperative complications were registered according to the hospital registration system. Data about oxygen suppletion, saturation, fever, pain medication, sputum retention, coughing, and patient mobilization were collected on a postoperative registration form. Postoperative pulmonary complications were classified as hypoxia (defined as need for additional oxygen), atelectasis (diagnosed by a radiologist), pneumonia (defined according to classification of Arozullah[3]), and respiratory failure (defined as need for artificial respiration).

Data analysis

Data were analyzed with SPSS (version 15.1) statistical software (SPSS Inc. SPSS reference guide. Chicago: SPSS Inc, 1998). All collected data were checked for completeness and normality of distribution by means of the Kolmogorov-Smirnoff-test. Summary descriptive statistics were computed for the preoperative variables including frequencies, means, standard deviations, and percentages. Intention-to-treat analyses were used to compare outcomes between the two groups. Adherence to treatment in the intervention group was calculated as the percentage of scheduled visits to the outpatient department. A preoperative effect of the intervention on capacity and performance measures within and between the two groups was estimated with the paired and independent sample t-test for normal distributed data and the Wilcoxon-test and Mann-Whitney U-test for non normally distributed data, respectively. The effect of the intervention on the length of stay was estimated with an independent sample t-test for normal distributed data and Mann-Whitney U-test for non normally distributed data. Postoperative complications of the two groups were compared by means of chi-square test. The significance level for all tests was set at 0.05.

RESULTS

The baseline characteristics of the 42 patients are listed in Table 6.1. No significant differences were found between the groups, except that more patients in the intervention group had diabetes than in the control group (57% versus 5%; p=0.01). One patient of the intervention group decided not to have the operation, 2 weeks after inclusion.

The flow chart in Figure 6.1 shows the progress of the study population. Three patients in the intervention group dropped out in the preoperative period (two patients due to the death of their spouse and one patient was unable to combine the training with daily work). One patient in the control group did not come for the second preoperative measurement for personal reasons.

Table 6.1 Baseline characteristics of the patients

	Control N=20	Intervention N=22	p*
Age in years	68.8 (6.4)	71.1 (6.3)	0.23
Gender (m/w)	16/4	15/7	0.38
Smokers (y/n)	6/14	3/19	0.20
COPD (y/n)	3/17	3/21	0.90
Coughing (y/n)	2/18	2/20	0.92
Diabetes (y/n)	1/19	8/14	0.01
Hb women (mmol/ml)	8.6 (0.7)	6.4 (2.0)	0.04
Hb men (mmol/ml)	8.5 (0.8)	8.0 (1.6)	0.34
BMI (kg/m^2)	25.7 (3.1)	26.6 (3.6)	0.40
TUG (sec)	6.4 (1.3)	8.0 (3.6)	0.07
CRT (sec)	21.6 (4.7)	26.3 (6.7)	0.12
MIP (cm H_2O)	93.0 (25.4)	78.2 (32.6)	0.11
RMA Energy (Joules)	350 (299)	259 (273)	0.31
HGS (N)	430 (108))	375 (125)	0.14
LAPAQ Energy (kcal/day)	1006 (715)	782 (707)	0.31
LAPAQ Activities (min/day)	212 (110)	197 (152)	0.73
PWC (O_2 ml/kg/min)	31.6 (6.5)	30.3 (9.6)	0.62
AFQ	9.5 (6.2)	13.2 (7.3)	0.08
EORTC QLQ-C30 / GH	71 (20)	70 (23)	0.97
EORTC QLQ-C30 / FS	427 (52)	408 (67)	0.31
EORTC QLQ-C30 / SC	130 (89)	154 (122)	0.47
Surgery duration (minutes)	119 (57)	104 (47)	0.38

BMI, Body Mass Index; TUG, Timed Up and Go; CRT, Chair Rise Time; MIP, Maximal Inspiratory Pressure; RMA, Respiratory Muscle Analyzer; HGS, Hand Grip Strength; LAPAQ, LASA Physical Activity Questionnaire; PWC, Physical Work Capacity; AFQ, Abbreviated Fatigue Questionnaire; EORTC QLQ-C30 / GH /FS / SC, Quality of Life Questionnaires Global Health status / Functional Scale / Symptom Scale.
* Mann-Whitney U-test (continuous variables) or Chi square test (dichotomous variables).

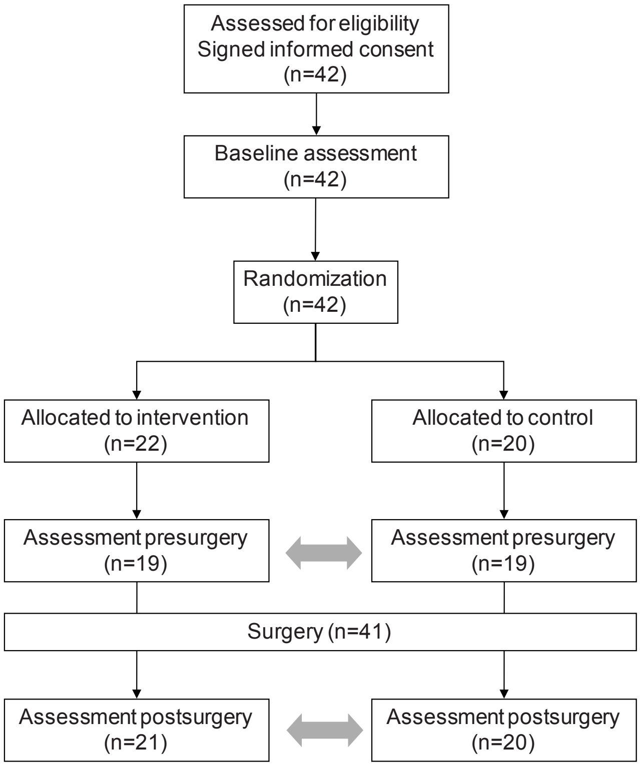

Figure 6.1 Flow chart of the study population.

The mean number of training sessions in the inpatient department was 5.1 ± 1.9. The attendance at training sessions was 97% in the intervention group. The mean number of steps/day recorded by the pedometer was 4980 and 5003 for the intervention group and control group, respectively. No adverse events were reported during outpatient or home training. In total, 37 patients completed the evaluation form (see Table 6.2). Both the intervention and the control groups appreciated the assigned "treatment", without there being a significant difference between the two groups (p=0.08). The perceived exertion was low for the home-based training program and moderate for the intensive outpatient training program (see Table 6.2).

The intensive outpatient training program led to a significantly greater improvement in inspiratory muscle endurance than the home-based program at T=1. There were no differences in other outcome measures between the two groups (see Table 6.3).

Table 6.2 Patient appreciation of treatment

		Disagree 1	2	3	4	Agree 5	
The aim of the preoperative treatment was clear to me	I	II			I	IIIIIIIIIIIIIII	p=0.54
	C				IIIII	IIIIIIIIIIIII	
During the fitness test, the perceived exertion was high	I	III		IIIIIIIII	IIIIII		p=0.54
	C	IIIIIII	II	III	IIIII	II	
In my opinion, the fitness test was useful	I	I		I	II	IIIIIIIIIIIIII	p=0.36
	C	II	I		IIII	IIIIIIIIIIII	
During the home-based exercises, the perceived exertion was high	I	IIIIIIII	I	IIII	III	I	p=0.91
	C	IIIIIIIII	II	III	III		
In my opinion, the home-based exercise program was useful	I	I		IIII	II	IIIIIIIIII	p=0.48
	C	I			IIIII	IIIIIIIIIIII	
During the training in the outpatient department, the perceived exertion was high	I	III	II	III	IIIIIII	I	
	C	Not applicable					
In my opinion, the training in the outpatient department was useful	I	I		I	II	IIIIIIIIIIIII	
	C	Not applicable					
I think the treatment prepared me well for the operation	I	I			III	IIIIIIIIIIIIII	p=0.08
	C	I		III	IIIIII	IIIIIIII	

I, Intervention group; C, Control group.

There was no significant difference in postoperative complications and length of hospital stay between the two groups at T=2 (see Table 6.4).

Based on the similar amount of moderate activity (no difference between mean number of steps) in the intervention and control group, a *post hoc* analysis over the combined dataset revealed a significant point-biserial correlation of 0.5 (p=0.02) between the extent of activity (number of steps) and postoperative pulmonary complications. A Receiver

Table 6.3 Differences in capacity measures between the intervention and control groups

		Baseline (T=0)	Outcome (T=1)	p-value[1]	Difference I-C	p-value[2]
TUG (sec)	I	8.0 (3.6)	7.8 (3.3)	0.29	-0.2 (0.8)	0.34
	C	6.4 (1.3)	6.6 (1.2)	0.28	0.2 (0.7)	
CRT (sec)	I	26.3 (6.7)	26.6 (6.2)	0.74	0.3 (4.1)	0.87
	C	21.6 (4.7)	21.2 (6.1)	0.81	-0.3 (4.2)	
MIP (cm H_2O)	I	78 (33)	92(26)	<0.001	14 (13)	0.09
	C	93 (25)	98 (26)	0.33	5 (21)	
RMA energy (Joule)	I	259 (273)	404 (349)	<0.001	146 (160)	<0.01
	C	350 (299)	305 (323)	0.07	-44 (279)	
LAPAQ Energy (kcal/day)	I	782 (707)	980 (771)	0.05	198(541)	0.15
	C	1005 (714)	1657 (3400)	0.78	652 (3368)	
LAPAQ Activities (min/day)	I	197 (152)	236 (157)	0.11	39 (130)	0.18
	C	211 (110)	280 (399)	0.68	69 (399)	
PWC (O_2 ml/kg/min)	I	29.4 (9.5)	27.6 (6.5)	0.47	-1.7 (8.4)	0.16
	C	31.6 (6.5)	32.9 (6.9)	0.26	1.3 (6.4)	
AFQ	I	13.2 (7.5)	12.7 (6.6)	0.80	-0.5 (6.8)	0.91
	C	9.5 (6.2)	8.8 (4.3)	0.59	-0.7 (3.4)	
EORTC QLQ-C30 / AG	I	70 (23)	72 (19)	0.96	2 (19)	0.88
	C	71 (20)	68 (18)	0.24	-3 (13)	
EORTC QLQ-C30 / FS	I	408 (67)	413 (64)	0.43	5 (56)	0.72
	C	427(53)	425 (67)	0.98	-2 (39)	
EORTC QLQ-C30 / SC	I	154 (122)	119 (98)	0.62	-35 (125)	0.20
	C	130 (90)	155 (117)	0.18	25 (75)	

I, Intervention group; C, Control group; TUG, Timed Up and Go; CRT, Chair Rise Time; MIP, Maximal Inspiratory Pressure; RMA, Respiratory Muscle Analyzer; LAPAQ, LASA Physical Activity Questionnaire; PWC, Physical Work Capacity; AFQ, Abbreviated Fatigue Questionnaire; EORTC QLQ-C30 / GH /FS / SC, Quality of Life Questionnaires Global Health status / Functional Scale / Symptom Scale.

[1] Wilcoxon test.

[2] Mann-Whitney U-test.

operating characteristic curve (Area Under the Curve=0.79) revealed 4000 steps per day to be a clinically pragmatic and relevant cut-off point for adequate physical activity. The choice of this cut-off point was confirmed by the difference in the count of the postoperative pulmonary complications in patients with a physical activity of more than 4000 steps and those with less than 4000 steps per day(chi-square test p<0.01; see Table 6.5).

Table 6.4 Postoperative course

Postoperative complications	I	9 (45%)	p=0.65
	C	8 (38%)	
PPC*	I	5 (24%)	p=0.93
	C	5 (25%)	
Pneumonia	I	1 (5%)	p=0.27
	C	3 (15%)	
Length of stay	I	16.2 (11.5)	p=0.31
	C	21.6 (23.7)	

I, Intervention group; C, Control group; PPC, Postoperative complication.
* PPC: atelectasis, hypoxia or pneumonia.

Table 6.5 PPC related to physical activity (measured by pedometer) in both the intervention and control group

		PPC*	
		no	yes
Activity	<4000 steps per day	8	9
	>4000 steps per day	23	1

p<0.001.

DISCUSSION

The intensive therapeutic exercise program was feasible and improved the respiratory function, but did not significantly change preoperative aerobic capacity and functional capacity of patients due to undergo elective abdominal surgery compared to a home-based exercise advice. Also the postoperative course of both groups did not differ significantly.

We investigated the feasibility and effectiveness of a preoperative intensive therapeutic exercise program for elderly patients, as an aspect of preoperative care, as proposed by Craig, et al.[38] The patients adhered to the intensive training program and did not report discomfort or adverse effects. The patients in both groups appreciated their "treatment" (training program or advice) and felt that it prepared them well for surgery. While there was a significant improvement in inspiratory muscles function in the intensive outpatient training group, the incidence of postoperative pulmonary complications did not significantly differ from that of the control group. This is in contrast with the positive results of inspiratory muscle training achieved in patients scheduled for elective coronary artery bypass graft (CABG) or aneurysma aorta abdominalis (AAA) surgery.[16,17] An explanation for this difference could be that the study was underpowered and that colon surgery has a more subtle effect on diaphragm function than CABG and AAA, both procedures which are performed closer to the diaphragm.[39] Also the difference in mechanical ventilation time, which is of substantial influence on diaphragm function,[40] may explain the discrepancy. A *post hoc* sub-analysis of the data of the patients with low respiratory function (MicroRMA energy <150 Joule) indicated that these patients may benefit the most from the intervention, so that the intervention should be offered to patients with a higher risk profile.

The intervention may be more effective if it lasts longer, is of higher frequency (more training sessions per week under supervision), or is more intensive (high intensity). While the intervention improved inspiratory muscle function in the preoperative period, it did not have a significant effect on the aerobic capacity or on functional measures. The intensity of exercise was in accordance with general recommendations for elderly patients18 but was probably insufficient to achieve a rapid improvement, as is required in a preoperative period of 3–4 weeks on average. Recently, a high-intensity interval training regimen led to metabolic adaptation in 2 weeks[41] and proved to be safe in elderly patients (aged 75 ± 11 years).[42]

A weakness of the study could be that we did not investigate the effect of an intensive therapeutic exercise program but instead compared it with a low cost home-based exercise advice. There is a rationale for keeping patients active during the preoperative period. The diagnosis "cancer" has a tremendous impact on a person's existence and behavior.12 One item in the LASA Physical Activity Questionnaire (activities in the 2 weeks preceding admission) revealed that 60% of the patients were less active than normal. It is possible that the home-based exercise advice meets the requirement to preserve or optimize patients' physical condition during the preoperative period. The preoperative LASA Physical Activity Questionnaire scores and the daily number of steps recorded revealed that patients in both the intervention and control groups showed a higher activity level than at baseline, at study inclusion. A *post hoc* analysis revealed an association between the moderate activity of both groups and the incidence of postoperative complications .

Another limitation of this study is the number of patients wich is not powered to detect significant effects on all outcome measures.

In conclusion, we recommend that high-risk patients be included in future studies and that the exercise protocol be made more intensive.

Clinical messages

- Elderly patients appreciate and can safely participate in a preoperative intensive therapeutic exercise program.
- General aerobic training parameters for elderly indivduals recommended in the literature appear to be inadequate to obtain a short-term increase in physical capacity.
- A low-cost home-based exercise advice seems to have a positive effect on physical activity sufficient to preserve or optimize the physical condition of non-frail elderly individuals during the preoperative period before abdominal surgery.

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7

General discussion

Surgery is increasingly common in older patients,[1] and advances in anaesthetic and surgical techniques have enabled surgery to be performed even in the oldest old.[2] The incidence of major abdominal surgery in the Netherlands is about 80, 150, and 120 per 10,000 inhabitants in the age groups 40–65, 65–80, and 80 years and older, respectively. In total, 35,000 major abdominal surgical procedures are performed annually in people aged 65 years and older (source, Kiwa Prismant, 2012). As the population is ageing, it is anticipated that the number of operations will continue to increase in the future. However, the incidence of adverse postoperative outcomes is still higher in older patients than in younger patients.[3] This may complicate successful surgery, if success is defined as an improvement in the medical condition, recovery without postoperative complications, and a good postoperative functional status. Successful postoperative recovery depends on the ability of patients to cope with the physiological changes induced by surgery and its immediate aftermath. The research described in this thesis focused on the preoperative functional status of patients as a modifiable predictor of postoperative outcomes such as mortality and functional recovery. On the basis of our findings and in agreement with fellow researchers in this field, we conclude that patients' preoperative functional status is a potential modifiable factor that is substantially associated with postoperative recovery. Short-term, high-intensity exercise programmes might be one way to improve preoperative functional status.

Current developments

The studies reported in this thesis reflect the increased interest in the functional status of the patient beyond the pathology or illness that makes hospitalization and surgery necessary. This new focus is illustrated by the switch to more functional parameters as performance indicators for the quality of hospital care.[4] Recovery of nutritional status is already considered an indicator of the quality of hospital care, and it is expected that the recovery of functional status will also become an indicator. A lack of recovery is considered an adverse outcome, an iatrogenic complication that deserves serious attention. Dutch hospitals have devoted themselves to reducing 'avoidable damage' in a 'safety management system' (VMS Safety programme) for hospitalized patients. 'Frail elderly' is one theme and aims to prevent functional decline due to hospitalization in patients aged 70 years and older. While these performance indicators focus on the functional status as clinical outcome measure, this thesis focuses on the preoperative functional status as a potential complicating/risk factor for the postoperative period, a factor that is modifiable in the preoperative period.

This concern about hospital-associated functional decline is international. Malani et al. and Covinsky et al. called for recognition of the importance of the functional status in relation to hospitalization and surgery in articles published in the Journal of the American Medical Association (JAMA), a highly influential journal in health care.[5,6] A number of articles have been published on the role of preoperative functional status, including the development of training programmes (also called prehabilitation).[7-14] All these developments reflect a shift from a solely medical to a more functional health-based paradigm both before and during hospitalization and surgical care. More knowledge is needed in this area. The studies described in this thesis contribute to this knowledge base, focusing on the preoperative setting.

Thesis research

The research described in this thesis is consistent with the concept of health recently proposed by the WHO,[15] in which health is defined as 'the ability to adapt and to self-manage'. The studies focused on physical aspects of health, defined as the ability of a person to mount a protective response, to reduce the potential for harm, and to restore an equilibrium when confronted with physiological stress.[15] In other words, the ability of patients to adapt to the physiological stress of an operation. An important aspect of preoperative care is the assessment and optimization of patients' adaptive capacity as a component of functional status.

Methodologically, the thesis can be divided in two distinct parts, each of them answering a specific research question, as stated in Chapter 1. The first part consists of *observational* research that provided convincing evidence that preoperative physical fitness and physical activity are associated with postoperative recovery after elective abdominal and thoracic surgery in older patients (Chapters 2–4). A review of the literature (meta-analysis) demonstrated a significant association between preoperative physical fitness and postoperative outcomes. Most of the studies included in this meta-analysis involved patients due to undergo lung surgery and were based on the rationale that a loss of lung tissue in lung surgery could give rise to a postoperative decline in VO_{2max}. Consequently, the convincing results were limited to preoperative maximal cardiorespiratory fitness in lung surgery patients and did not apply to other components of physical fitness or other types of surgery.

To complement these results for abdominal surgery and for a broader range of determinants of physical fitness and physical activity, a prospective cohort study was performed involving older patients scheduled to undergo abdominal, or more specifically oncological colorectal, surgery. The frailty concept explained in the introduction of this thesis (Chapter 1) formed the theoretical basis for this study. Findings revealed that physical activity (as measured with an activity questionnaire) and physical fitness (as measured with muscle strength/endurance and functional mobility) were significantly and strongly associated with the postoperative outcomes mortality, length of stay, and recovery of functional mobility. This was particularly true for physical activity and strength and endurance of the inspiratory muscles. The addition of these variables to prediction models involving conventional factors significantly improved the prediction of mortality, discharge destination, and length of stay. These observational studies ended with an exploratory study evaluating an alternative and new way to assess the preoperative adaptive capacity of the respiratory system, which is based on the assumption that the respiratory system has an adequate internal network of multiple control systems with the capacity to maintain an existing equilibrium (homeostasis) or to achieve a new equilibrium (allostasis) after perturbation of the system.[16] The shape of the breathing pattern, established by recording air flow and pressure, reflects the complex output of this network. Evaluation of these recordings with the help of non-linear measures proved to be an innovative and promising tool in the preoperative respiratory work-up.

Observational research does not provide answers to cause–effect relationships. This requires experimental research, which in this case addressed the second research question of this thesis. Two pilot RCTs showed that older patients (>60 years of age) can be trained in a relatively short time (2–3 weeks) to improve their physical condition and revealed a trend effect of preoperative inspiratory muscle training on the incidence of postoperative (pulmonary) complications. The feasibility of preoperative training was further underlined by the appreciation of patients, their high compliance with the training programme, and the lack of adverse events among the patients studied (Chapters 5 and 6). The first experimental pilot study investigated the effect of preoperative training on inspiratory muscle endurance and strength. These muscles were investigated because there is a neurogenic decline in the function of the diaphragm muscles during and after abdominal (and also thoracic) surgery, a decline which is regarded as a major cause of postoperative pulmonary complications.[17] In addition, the above-mentioned observational studies showed respiratory function to be significantly associated with postoperative outcomes (mortality and length of stay). Although the RCT was conducted as a pilot and feasibility study only, it nevertheless revealed a borderline effect on the incidence of postoperative complications. This study was included in a recent meta-analysis by Valkenet et al., which revealed a significant overall effect of inspiratory muscle training on postoperative pulmonary complications.[18] Other components of physical fitness identified in the observational study justified a second pilot RCT investigating the feasibility and effect of a more general physical fitness training programme on postoperative complications, length of stay, mortality, and functional recovery. Unfortunately, this short-term training programme did not significantly affect preoperative and postoperative outcomes. The study was included in a systematic review by Jack et al.,[8] which concluded that a short-term, preoperative exercise programme can influence physical fitness, also in older patients, even if it is uncertain that this approach has a positive effect on the surgical outcome. These results highlighted the need for a well-powered, high-quality RCT to clarify the postoperative effects of preoperative training.

The research studies described in this thesis were conceived and carried out by health professionals in the real-life healthcare setting of a community hospital. The studies directly addressed clinical questions and made use of usual care measurements. An advantage of this approach is that results can readily be applied to day-to-day clinical practice. For example, the predictors of postoperative recovery identified in the observational study are feasible and can be relatively easily incorporated into clinical practice. Also the use of limited exclusion criteria increased the external validity of findings, improving their generalization. According to the idea of comparative effectiveness research that refers to 'real world' settings, our experience is that accurately recorded routine clinical treatment data are an important source of information for applied scientific research. However, clinical practice research has its limitations: comprehensive and expensive equipment is usually not available, so that usual care measures have to be used, and study populations are limited in terms of the number of patients available. That is why two RCTs were performed to address the feasibility and preliminary effects of a preoperative training programme. Adequately powered studies require multicentre trials.

Figure 7.1 shows the position of the study findings in the model presented in the first chapter. The studies provided information about the association between the beginning (functional status) and end (postoperative outcome measures) of the process. The 'black box' in the middle refers to knowledge of the interaction between functional status, surgical stress, activity level, and postoperative outcome, knowledge that is relevant to

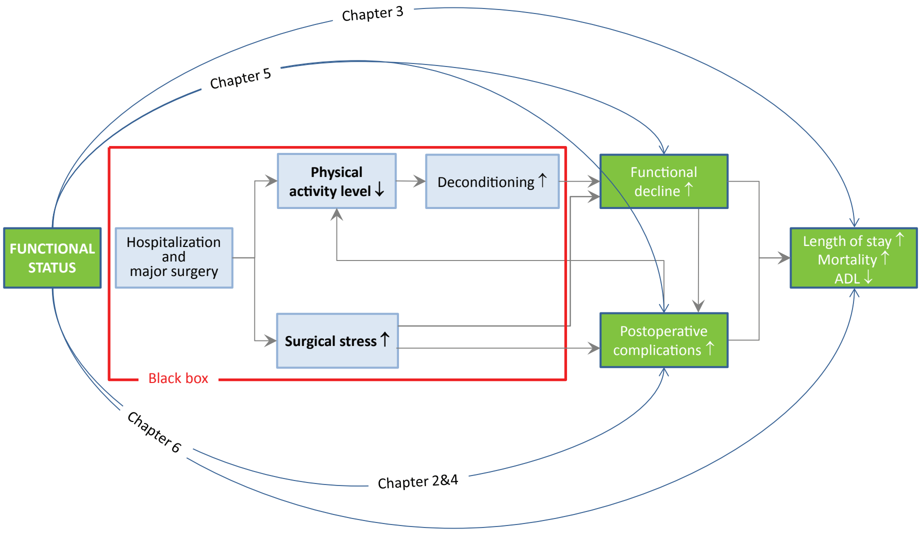

Figure 7.1 Position of study findings in a scheme visualizing possible effects of surgery and hospitalization in older patients and the role of preoperative functional status.

designing appropriate exercise training programmes. For example, an adequate functional status could be considered a requirement for early postoperative ambulation, which in turn prevents functional decline and postoperative complications. Preoperative training should be aimed at the level of fitness required to perform activities of daily living (ADL). Because lower leg muscle function is closely related to functional mobility and ADL,[19] preoperative training should focus on the strength of these muscles. Another more physiologically based rationale refers to the immune system. The immune response is also a part of the adaptive capacity, with a person's level of immunity appearing to be associated with their level of physical activity.[20] This is consistent with the importance of the level of physical activity as predictor of postoperative recovery, as found in the observational study described in Chapter 3.

Recommendations for future research

As the studies of this thesis and the literature have found preoperative functional status to be associated with the postoperative course, future research should focus on functional status as a modifiable factor. If a cause–effect relationship exists, patients will benefit from preoperative interventions to improve their functional status. In the absence of a rationale, as indicated in the above section, current preoperative interventions use general training programmes for elderly patients that focus on strength, aerobic, and functional training, which is neither cost effective nor a targeted approach. Instead, research should identify which aspects of training programmes (strength, (an)aerobic capacity, or functional mobility[21]) are appropriate for individual or specific groups of patients, as recommended by Hoogeboom et al.[22] Future research on the effects of preoperative exercise training should also address the optimization of training parameters, among which intensity. High-intensity training is necessary to achieve improvements given the often short time available before surgery. Frail older patients can tolerate high intensities[23] but overtraining is always possible and should be avoided because this puts the patient in an even worse preoperative condition than without training.[24] The challenge is to optimize the training parameters, aiming a maximal improvement without overtraining, which is a real hazard in older people.[25]

Neither our or other studies provided RCT-strength evidence that preoperative training of general physical fitness parameters affects patients' postoperative outcomes. From a methodological point of view, a well-powered RCT should provide this missing evidence. However, it can be questioned whether this is an ethically sound approach. The strong evidence for the relationship between preoperative physical activity and physical fitness and the postoperative course, together with the biological plausibility of this approach (showing a relationship between the physical condition and the adaptive capacity of the body system), raises the question whether new RCT research with the use of a control group without any form of intervention can be justified. This issue addresses the therapeutic obligations of clinicians to their patients and makes the distinction between a research and treatment approach apparent.[26] Literature proposes 'clinical equipoise' as a requirement for the random assignment of patients. It is defined as a state of professional uncertainty about the relative therapeutic merits of treatments and is a much-debated issue.[27,28] According to de Graaf et al.,[29] we should find out whether there is a lack of agreement among expert clinicians about the relative merits of alternatives to preoperative training. In addition, research designs other than RCTs are possible, such as a stepped wedge design and comparative effectiveness research.

Besides intervention studies, the exploratory study that evaluated complex breathing patterns using non-linear measures should be extended, for instance, by investigating whether non-linear measures distinguish between older people at risk or not at risk of postoperative complications and whether these measures can help guide physiotherapists implementing, monitoring, and evaluating the progress of preoperative inspiratory muscle training.

Recommendations for clinical practice

The results reported in this thesis and in the literature support the recommendation that physical activity and physical fitness factors be incorporated into the preoperative work-up. A cut-off point of 15 ml/kg/min for VO_{2max} for physical fitness, as found in de meta-analysis, implies that patients have to be able to walk briskly or cycle at moderate speed.[30] The activity level determined with the activity questionnaire corresponds to light household activities and/ or walking for 1–2 hours a day. This suggests that a moderate level of physical activity should enable patients to undergo surgery successfully. This is in accordance with Dutch Standard for Healthy Physical Activity Behaviour and other research prescribing moderate physical activity for health.[31] For cost-effective care, patients should be asked a few questions about their level of physical activity, to identify those at risk of postoperative problems, because it is time-consuming and expensive to test the physical activity and fitness of all patients, when only a few might have a poor physical condition.

The function of waiting time in relation to the patients' preoperative condition should be reconsidered. Waiting time is currently considered idle time that has to be kept as short as possible. Indeed, the waiting period is used as a performance indicator for the quality of hospital care. Given the lack of RCT evidence and budgetary restrictions, doctors are not motivated to delay surgery in order to optimize the physical condition of their patients. This, in turn, prevents research to provide evidence, creating a vicious circle. We think that the time between the decision to operate and actual surgery should be used to optimize the physical condition of frail and elderly patients and be included as a standard part of the preoperative protocol. Depending on a patients' medical status and preoperative physical condition, the duration of the preoperative period should be adjusted to ensure that the patient has the physical condition necessary to undergo surgery.

Physical activity status was found to be a robust predictor of the postoperative course, consistent with the literature showing a strong association between physical activity and health outcomes such as disability[32] and life expectancy.[33] This association also highlights the decrease in habitual physical activity in Western society.[34] To achieve a more adequate level of physical activity, there needs to be a change in the mind-set of patients, their family, and healthcare and social workers.[35,36] Being in an adequate physical condition gives patients an advantage should they need surgery, as it promotes a successful recovery from surgery and successful ageing.[37]

In conclusion, the studies described in this thesis highlight the role of physical activity and physical fitness in patients scheduled for abdominal and thoracic surgery. We hope that our findings will be implemented in the preoperative care setting and contribute to a more functional health-based approach to hospital and surgical care, with as goal to ensure that patients leave hospital in the same, if not better, functional condition as when they were admitted: it's a question of 'the better in, the better out'.

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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.

Nederlandse samenvatting

Het **eerste hoofdstuk** beschrijft het belang van een goede fysieke fitheid van patiënten die een zware operatie moeten ondergaan. Fysieke fitheid geeft een indruk van het vermogen van een patiënt om adequaat te reageren op *surgical stress*, dit is de fysiologische stressreactie tijdens en na een operatie. Na een operatie herstelt een groot deel van de patiënten goed, maar een ander deel ondervindt nadelige gevolgen zoals complicaties, functionele achteruitgang en zelfs overlijden. Dit klinisch beloop na de operatie is in de preoperatieve polikliniek al gedeeltelijk te voorspellen aan de hand van klassieke medische en demografische factoren zoals leeftijd, roken en bijkomende ziektes. In dit proefschrift onderzoeken we of, en zo ja, in welke mate de preoperatieve fysieke fitheid het klinisch beloop na de operatie voorspelt bij oudere patiënten (>60 jaar) die een buik- of thoraxoperatie ondergaan. Daarnaast onderzoeken we in dit proefschrift of het mogelijk is de fysieke fitheid van risicopatiënten in de preoperatieve fase te trainen om daarmee het postoperatieve herstel te bevorderen.

Hoofdstuk 2 geeft een overzicht van de wetenschappelijke literatuur over preoperatieve fysieke fitheid als risicofactor voor hart- of longcomplicaties na buik- en thoraxoperaties. Veertien prospectieve cohortstudies gaven vooral informatie over het maximale aerobe uithoudingsvermogen (VO_{2max}) bij patiënten die een longoperatie ondergingen. De resultaten zijn verwerkt in een meta-analyse die de risico's op een hart- of longcomplicatie van alle studies heeft samengevat als gepoolde odds ratios (OR). Voor patiënten met een laag uithoudingsvermogen (VO_{2max} <20 ml/kg/min) heeft de meta-analyse geen significant verhoogd risico op een complicatie aangetoond. Maar patiënten met een zeer laag uithoudingsvermogen (VO_{2max} <15 ml/kg/min) hadden bijna vijf keer zo veel kans op een hart- of longcomplicatie (OR 4.9; 95% CI 1.8–13.7). Twee artikelen rapporteerden over een traplooptest als maat voor de preoperatieve fitheid. Patiënten die geen drie verdiepingen konden traplopen hadden ruim twee keer zo veel kans op een hart- of longcomplicatie (OR 2.1; 95% CI 1.2–3.7). De conclusie van de meta-analyse is dat een erg laag aeroob uithoudingsvermogen een significante en onafhankelijke voorspeller is van postoperatieve hart- en longcomplicaties bij patiënten na longchirurgie. Er is echter een gebrek aan studies die andere componenten van de fysieke fitheid onderzoeken en aan onderzoeken bij patiënten die buikchirurgie moeten ondergaan.

In vervolg op het voorgaande hoofdstuk, onderzochten we in **hoofdstuk 3** andere componenten van fysieke fitheid. Dit deden we bij patiënten die een zware buikoperatie wegens darmkanker moesten ondergaan. In een prospectieve cohortstudie onderzochten we bij 175 patiënten (>60 jaar) in welke mate dagelijkse fysieke activiteit en fysieke fitheid het klinisch beloop na een operatie voorspelden. Dit is vergeleken met nu gebruikelijke klassieke risicofactoren (leeftijd, gemetastaseerd carcinoom, diabetes, COPD, hartaandoeningen, roken en hoesten). In multipele regressieanalyses bleek dat de fysieke activiteit en de fysieke fitheid het postoperatieve klinisch verloop beter voorspelden dan de klassieke factoren. Patiënten met een laag activiteitenniveau (activiteitenvragenlijst LAPAQ <416 kcal) hadden 5–6 keer zo veel kans om te overlijden (OR 5.5; 95% CI 1.4–21.9). Patiënten met een laag uithoudingsvermogen van de ademspieren (<41 Joule) liepen eenzelfde risico (OR 5.2, 95% CI 1.4–19.1). De kracht van het voorspellingsmodel is bepaald met een C-index (op een schaal van 0–1 waarbij 1 staat voor een perfecte voorspelling). De C-index van het model met fysieke activiteit en fitheid was 0.82 tegen 0.67 (p<0.001) voor het model met alleen de klassieke factoren. De C-index van het voorspellend model voor de ontslagbestemming (thuis of verpleeghuis) verbeterde ook significant door toevoeging van de fysieke factoren van 0.66 naar 0.80 (p<0.001). Multipele regressieanalyse gaf als uitkomst dat fysieke activiteit (HR 0.6, 95% CI 0.4–0.8) en inspiratiekracht (HR 0.6, 95% CI 0.5–0.9) onafhankelijke voorspellende factoren zijn voor de opnameduur. De conclusie is dat fysieke activiteit en fysieke fitheid significant bijdragen aan een betere voorspelling van het postoperatief verloop vergeleken met een voorspelling op basis van alleen klassieke factoren.

Advies voor clinici op grond van dit onderzoek is om preoperatief naast de klassieke risicofactoren ook parameters van fysieke fitheid te meten. Met deze gegevens is het mogelijk proactief patiënten te selecteren die baat kunnen hebben bij een behandeling die de fysieke fitheid van de patiënt voor en na de operatie optimaliseert.

Hoofdstuk 4 zoomt in op de ademhalingsspieren en introduceert een innovatieve manier om de ademspierfunctie te meten. Buik- en thoraxoperaties zijn de oorzaak van een extra functieverlies van het diafragma, de belangrijkste inademingsspier. Hierdoor hebben vooral oudere patiënten een verhoogd risico op postoperatieve longcomplicaties. In een exploratieve studie hebben we adempatronen beoordeeld op hun regelmatigheid. De verwachting is dat patiënten met een onregelmatiger, complexer adempatroon beter herstellen van een operatie. Een eerste stap in dit onderzoek was te kijken naar geschikte parameters die personen met een verhoogd risico op een longcomplicatie onderscheiden van een referentiegroep zonder verhoogd risico. Hiervoor werden het onderscheidend vermogen van gebruikelijke lineaire (variabiliteit) en minder gebruikelijke non-lineaire (entropy) analyses van het adempatroon getoetst. In de dagelijkse klinische praktijk van de preoperatieve screening is hiervoor alleen een korte sample (3–5 minuten) van het adempatroon beschikbaar. Een groep van zes jonge gezonde personen (referentiegroep) en een groep van tien personen met een verhoogd risico voor het krijgen van een postoperatieve longcomplicatie namen aan de studie deel. Zij voerden een ademtest uit met 70 ademcycli zonder externe weerstand. De variatiecoëfficiënten van de afstanden tussen de ademteugen en de amplitudes van de in- en uitademing verschilde niet significant tussen de controle- en de risicogroep. Een non-lineaire analyse via de sample entropy liet wel een significant verschil zien tussen de complexiteit van het adempatroon van de referentiegroep (mediaan 0.29; IQR 0.22–0.43) en de risicogroep (mediaan 0.19; IQR 0.14–0.24) (p=0.03). De conclusie is dat een non-lineaire analyse van een korte sample van het adempatroon een uitvoerbare en potentieel onderscheidende maat lijkt voor toepassing bij de preoperatieve risicostratificatie van patiënten die een zware operatie ondergaan die de ademfunctie aantast. Vervolgonderzoek moet de toegevoegde waarde van de non-lineaire analyses verder aantonen.

Na de observationele studies in de voorgaande hoofdstukken volgen in hoofdstuk 5 en 6 twee experimentele pilotstudies. Deze hebben de haalbaarheid onderzocht van preoperatieve training van de fysieke fitheid van oudere risicopatiënten.

In **hoofdstuk 5** hebben we in een pilotstudie de haalbaarheid en het potentiële effect van een training van de inademingsspieren op longcomplicaties (atelectase) onderzocht. Het onderzoek is uitgevoerd bij hoog-risicopatiënten die een operatie van een aneurysma van de buikslagader moesten ondergaan. Tweeëntwintig patiënten werden in een geblindeerde studie *at random* toegewezen aan de interventiegroep die een training van de inademingsspieren kregen of aan de controlegroep die de gebruikelijke preoperatieve zorg kregen. De patiënten konden de training goed uitvoeren en er waren geen nadelige bijwerkingen. De patiënten gaven in meerderheid aan dat de training een goede voorbereiding was op de operatie. Ondanks de randomisatie waren de patiënten in de interventiegroep onbedoeld significant ouder dan de patiënten in de controlegroep, respectievelijk 70 ± 6 jaren versus 59 ± 6 jaren (p=0.001). Toch waren er in de interventiegroep maar drie patiënten met een atelectase tegen acht patiënten in de controlegroep (p=0.07). Uit dit onderzoek trokken we de conclusie dat training van de inspiratiespieren goed door patiënten wordt getolereerd. Ondanks het feit dat het een pilotonderzoek betreft, was er een statistische trend dat de preoperatieve training de incidentie van atelectase bij patiënten na een zware buikoperatie vermindert.

In **hoofdstuk 6** onderzochten we de haalbaarheid en potentiële effecten van een kortdurend preoperatief trainingsprogramma voor oudere patiënten op het klinisch herstel na de operatie. In totaal 42 oudere patiënten (>60 jaar) die een oncologische buikoperatie moesten ondergaan, deden mee in deze *single* (voor de effectmeting) geblindeerde pilotstudie. Zij werden *at random* toegewezen aan een interventiegroep en controlegroep. De patiënten in de interventiegroep kregen een kortdurend intensief trainingsprogramma met als doel het verbeteren van spierkracht, aeroob uithoudingsvermogen en functionele activiteiten. De controlegroep kreeg een bewegingsadvies voor thuis. De haalbaarheid van het trainingsprogramma was goed. Patiënten waren tevreden over het trainingsprogramma en voor 97% aanwezig op de trainingen. Zij ondervonden geen nadelige bijwerkingen van de training. Preoperatief verbeterde het uithoudingsvermogen van de inspiratiespieren significant (146 ± 160 Joule) vergeleken met de controlegroep (-44 ± 279 Joule) ($p<0.01$). De andere testen van de fysieke fitheid lieten geen significante verschillen zien tussen de twee groepen. De in deze pilotstudie gevonden postoperatieve verschillen in longcomplicaties en opnameduur dienen in vervolgonderzoek met voldoende power op significantie te worden getoetst. Aparte aandacht verdient het contrast in het onderzoek waarin de controlegroep een beweegadvies ontving. Een *post hoc*-analyse liet een sterke en significante associatie zien tussen het activiteitenniveau (gemeten met de LAPAQ, een activiteitenvragenlijst) en postoperatieve longcomplicaties over beide groepen. De conclusie van dit onderzoek is dat een intensief trainingsprogramma vergeleken met een bewegingsadvies voor thuis de ademfunctie significant verbeterde. Dit pilotonderzoek is de basis voor een *single blind* studie met voldoende statistische power om effecten te toetsen van een patiëntspecifieke preoperatieve fysieke training op het klinisch beloop na een operatie.

Het afsluitende **hoofdstuk 7** geeft een beschouwende samenvatting en interpretatie van de resultaten van de vijf onderzoeken in dit proefschrift en aanbevelingen voor de toekomst, zowel voor de praktijk als voor wetenschappelijk onderzoek.

- Observationeel onderzoek geeft overtuigend bewijs dat preoperatieve fysieke fitheid en in het bijzonder fysieke activiteit zijn geassocieerd met het postoperatieve herstel van patiënten na buik- en thoraxchirurgie. Toevoeging van deze preoperatieve fysieke factoren aan de set van klassieke medische en demografische factoren maakt een betere voorspelling van het postoperatieve klinisch beloop mogelijk.
- Het experimentele onderzoek in dit proefschrift toont de haalbaarheid aan van een intensieve preoperatieve training voor ouderen en geeft een trend voor het effect van inspiratoire ademspiertraining op de incidentie

van postoperatieve longcomplicaties. De onderzoeken zijn ontstaan en uitgevoerd in de praktijksetting van een ziekenhuis waardoor resultaten direct toepasbaar lijken in de dagelijkse praktijk. Samenwerking met andere ziekenhuizen en universitaire centra biedt voor de toekomst mogelijkheden om te werken met grotere patiëntengroepen en meer fundamenteel onderzoek te doen.

Op basis van de resultaten van dit proefschrift en de literatuur bevelen we aan fysieke fitheid en fysieke activiteit een plaats te geven in de preoperatieve polikliniek. Het observationeel onderzoek dient zich in de toekomst mede te richten op de fysiologische werkingsmechanismen of rationale(s) achter het postoperatieve functieverlies. Dit is belangrijk voor het bepalen van de juiste gerichtheid en intensiteit van de preoperatieve training. De effecten van deze training moeten duidelijk worden in gerandomiseerde studies met voldoende statistische power.

De resultaten van deze en toekomstige onderzoeken zullen bijdragen aan de transitie van een medisch georiënteerde ziekenhuiszorg naar een zorg die zich ook richt op de functionele gezondheid van de patiënt.