Nutrition in Elderly Patients Undergoing Cardiac Surgery

DORIS RAPP-KESEK
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Entrance 70, Akademiska sjukhuset, 75185 Uppsala, Friday, April 20, 2007 at 09:15 for the
degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in
Swedish.

Abstract
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Many elderly undergo cardiac surgery. The prevalence of malnutrition in elderly is high and
increases with comorbidity. This thesis aims to clarify some aspects on performing surgery in
elderly concerning nutritional status, nutritional treatment and age-related physiology.

Study I: 886 patients were assessed preoperatively by body mass index (BMI) and
S-albumin and postoperatively for mortality and morbidity. Low BMI increased the relative
hazard for death and low S-albumin increased the risk for infection. BMI and S-albumin are
useful in preoperative evaluations

Study II: we followed energy intake in 31 patients for five postoperative days. Scheduled
and unscheduled surgery did not differ in preoperative resting energy expenditure (REE).
REE increased by 10-12% postoperatively, more in unscheduled CABG. Nutritional
supplementation increased total energy intake. All patients exhibited postoperative energy
deficits, less prominent in the supplemented group. There were no differences in protein
synthesis or muscle degradation.

Study III: in 16 patients, we measured stress hormones and insulin resistance before
surgery and for five postoperative days Patients were insulin resistant on the first two days.
We saw no clearly adverse or beneficial effects of oral carbohydrate on insulin resistance or
stress hormone response.

Study IV: 73 patients, with early enteral nutrition (EN), were observed until discharge or
resumed oral nutrition. EN started within three days in most patients. In a minority, problems
occurred (gastric residual volumes, tube dislocation, vomiting, diarrhoea, aspiration
pneumonia). In the cardiothoracic ICU individually adjusted early EN is feasible.

Study V: in 16 patients, splanchnic blood flow (SBF) enhancing treatments (dopexamine
(Dpx) or EN) were compared. Dpx increased systemic blood flow, but had only a transient
effect on SBF. EN had no effect on systemic blood flow or SBF. Neither Dpx, EN or the
combined treatment, exhibited any difference between groups on systemic or splanchnic VO2,
or oxygen extraction ratio.

Keywords: elderly, nutrition, CABG, cardiac surgery, outcome, insulin resistance, enteral
nutrition, splanchnic blood flow, BMI, albumin, 3-methylhistidine, alfa-l-antitrypsin

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The thesis is based on the following original papers, which will be referred to by their Roman numerals.


V Rapp-Kesek D, Joachimsson P, Karlsson T. Splanchnic blood flow and oxygen consumption: effects of enteral nutrition and dopexamine in the elderly cardiac surgery patient. (accepted for publication in Acta Anaesthesiologica Scandinavica).*

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# Abbreviations

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<tr>
<td>APACHE II</td>
<td>Acute Physiology And Chronic Health Evaluation II</td>
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<td>BMI</td>
<td>body mass index</td>
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<td>CABG</td>
<td>coronary artery bypass grafting</td>
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<td>CO, CI</td>
<td>cardiac output and index</td>
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<tr>
<td>CPB</td>
<td>cardiopulmonary bypass</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>ECC</td>
<td>extra-corporeal circulation</td>
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<td>EN</td>
<td>enteral nutrition</td>
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<td>FFM</td>
<td>fat-free mass</td>
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<td>FM</td>
<td>Fat mass</td>
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<td>GRV</td>
<td>gastric residual volume</td>
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<td>HbA1c</td>
<td>glycated haemoglobin concentration</td>
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<tr>
<td>HOMA</td>
<td>homeostasis assessment model for insulin resistance and β-cell-function</td>
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<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
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<tr>
<td>ICG</td>
<td>indocyanine green</td>
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<tr>
<td>ICU</td>
<td>intensive care unit</td>
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<tr>
<td>IGF-1</td>
<td>insulin-like growth factor 1</td>
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<td>IHD</td>
<td>ischaemic heart disease</td>
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<tr>
<td>LOS</td>
<td>length of stay</td>
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<tr>
<td>OER</td>
<td>oxygen extraction ratio</td>
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<td>PEM</td>
<td>protein-energy-malnutrition</td>
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<tr>
<td>P\text{max}</td>
<td>maximum expiratory flow</td>
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<tr>
<td>P\text{max}</td>
<td>maximum inspiratory flow</td>
</tr>
<tr>
<td>POD</td>
<td>postoperative day</td>
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<tr>
<td>REE</td>
<td>resting energy expenditure</td>
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<tr>
<td>SBF, SBFI</td>
<td>splanchnic blood flow and splanchnic blood flow index</td>
</tr>
<tr>
<td>TPN</td>
<td>total parenteral nutrition</td>
</tr>
<tr>
<td>VO\text{2}, VO\text{2I}</td>
<td>oxygen consumption and oxygen consumption index</td>
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</table>
Introduction

Background
Seventeen percent of the population in Sweden was over 65 years old in 2005. Life expectancy is increasing. In 2005, the expected mean survival of women aged 65 and 80 years was calculated to 20 and 9 years respectively. Corresponding figures for men aged 65 and 80 years were 17 and 7 years (3).

Cardiovascular disease is one of the major causes of morbidity and mortality and an increasing number of elderly patients is being considered for cardiac surgery. Between 1999 and 2005, the proportion of patients aged over 65 years in cardiac surgery has increased from 56% to 60%. For patients older than 80 years, the increase was from 5% to 8% (3).

To provide effective surgical care to an elderly population, the impact of ageing on the physiologic performance of the individual patient must be understood. Ageing is associated with declining physiologic reserves and an increased susceptibility to disease. Many physiological activities occur near the critical threshold of failure. Reserves that may be needed during surgical stress are not present, which predisposes to organ system failures.

The conditions of elderly cardiac surgery patients differ from those in a younger patient group. Chronic degenerative diseases are more common and affect outcome after cardiac surgery. Diabetes occurs in 13-35% (51, 109, 133, 142), chronic obstructive pulmonary disease (COPD) in 7,8- 35% (7, 19, 109, 142), peripheral vascular disease in 14,9- 21% (7, 109, 142) and cerebrovascular disease in 5,9- 19% (109, 142) of the cardiac surgery patients. Furthermore, chronic disease is associated with increased prevalence of malnutrition.

Cardiac surgery in the elderly has been studied quite extensively (89, 109, 121, 144, 166). However, not much attention has been paid to the importance of nutritional factors for outcome and the latter are not included in commonly used cardiac surgery scoring systems like Higgins (76),
Parsonnet (118) and EuroScore (107). Preoperative risk factors mainly concern heart function, emergency or planned surgery, age, gender or co-morbidity. Even though all cardiac surgery patients have their weight and length determined (necessary for calculation of pump flow in CPB), this is often not mentioned in the demographic description of the studies.

When assessed and used, low weight or body mass index (BMI) always negatively correlates to mortality and morbidity. For the elderly, BMI ≤24 kg/m² is predictive of an increased risk for mortality (55, 133) and underweight patients have a significantly higher co-morbidity (127). In patients older than 80 years, there are twice as many with BMI ≤22 kg/m² compared to younger patients (6).

The combination of co-morbidity and malnutrition affects the postoperative course and outcome. Protein-energy malnutrition is associated with postoperative complications, delayed wound healing (46), altered immune response (35, 97), decreased muscle strength (71), prolonged hospital stay (161) and increased mortality (50).

This thesis aims to clarify some aspects on performing surgery in the elderly concerning nutritional status, nutritional treatment and age-related physiology.

Physiologic functions in ageing

Heart
Left ventricular compliance decreases and blood pressure increases, with a resulting tendency for left ventricular hypertrophy. The ageing heart increases preload and stroke volume in order to preserve cardiac output. The physiological changes are further aggravated by atherosclerosis. In these conditions, even a moderate hypovolaemia may result in a compromised function.

Lungs
Chest wall compliance decreases. Respiratory muscle strength decreases which reduces maximum inspiratory and expiratory strength up to 50%. Closing capacity increases and is greater than the functional residual capacity even when seated in subjects older than 65 years. PO₂ decreases with age and due to the fact that a majority of the coronary artery bypass
grafting (CABG) patients are former smokers. An impaired lung function can still be seen three months after cardiac surgery (151).

**Kidney**

At the age of 85, 40% of the nephrones are sclerotic and the remaining nephrons are hypertrophic. Compared to young adults, renal blood flow and glomerular filtration rate is reduced by approximately 50%. The capacity for regulation of the fluid and acid-base balance and concentration capacity of the kidney decreases as well as the sense of thirst, which leads to an increased susceptibility for dehydration. Drug elimination by the kidneys is impaired.

**Immunological function**

The immune system in the elderly is characterised by an increased susceptibility to infections, an increased appearance of autoantibodies and monoclonal immunoglobulins and an increase in tumorigenesis. This may not show in the unchallenged state. Subjects older than 60 years have a high incidence of anergy to delayed hypersensitivity skin tests. The febrile response may be blunted, because of a decrease in inflammatory reaction and a lower cytokine response (67, 120).

**Central nervous system**

Hypothalamic insufficiency, together with decreased basal metabolic rate and changes in the threshold for peripheral vasoconstriction and shivering, decreases the ability to generate and conserve heat (56). Sensory perception of all senses declines steadily with ageing (62). Pain perception is altered, which may lead to inadequate pain treatment. The prevalence of dementia rises steadily with age, approximately doubling every five years from 1.5% in those aged 65-70 years to nearly 25% in those over age 85 years. The stress of surgery or acute illness and hospitalisation can cause cognitive decline and delirium in persons over 70 years, even when baseline cognitive function appears normal (18, 28).

**Gastrointestinal system**

The gastrointestinal physiology in elderly is particular (188). Total hepatic blood flow decreases with age (188). Cardiopulmonary bypass is considered to decrease splanchnic blood flow further and create a mismatch between oxygen transport and consumption (115).
Gastric acid secretion per se is not impaired in elderly. Atrophic gastritis is however more common. Gastric emptying is slower, which increases the risk for aspiration and atony. Even though gastrointestinal absorption in general is not impaired in elderly, malabsorption secondary to bacterial overgrowth may occur in spite of adequate diet. There is an increasing tendency to form biliary stones and to contract cholecystitis in the elderly.

**Diabetes, insulin resistance**

For subjects older than 65 years the prevalence of diabetes in 1987 was 16% as compared to 4.3% in the total Swedish population (8). Insulin resistance increases with starvation, fasting, trauma (34) and surgery (27, 98). Patients are characterised by an acquired insulin resistance in the postoperative period after CABG (53) and acute myocardial infarction (110). Hyperglycaemia and insulin resistance are known factors associated with adverse prognosis (126, 177, 187). Insulin resistance and protein catabolism may be attenuated by glucose or carbohydrate administration before surgery (98, 113, 154).

**Physiologic response to drugs**

Pharmacokinetics and pharmacodynamics are altered in the elderly. There are differences in absorption, distribution and elimination, as well as impaired drug metabolism, due to decreased hepatic and renal function, reduced gastric acid secretion, gastric emptying and splanchnic blood flow. Slower metabolism could be due to reduced activity of metabolic enzymes or reduced availability of essential endogenous cofactors.

Regional blood flow in the kidney or intestine has been shown to increase by inotropes i.e. dopamine and dopexamine in healthy young subjects, but not in elderly with (186) or without arteriosclerosis (12, 58).

**Nutrition**

**Evaluation of nutritional status**

Preoperative nutritional status is of importance for outcome in both surgical and non-surgical disease. Providing adequate amounts of protein and energy as well as other nutrients, improves function and outcome in the elderly (23, 31, 128, 168). Practical problems may impair nutrient intake during the whole period of illness and surgery (64, 68). This can be due to the sensory
changes in taste and smell, ill-fitting dentures, muscular weakness and/or impaired gastrointestinal absorption.

The preoperative evaluation of older patients should be directed at identifying physiologic deficits and co-morbid conditions that are likely to place the individual at an increased risk for postoperative complications.

Energy requirements
A low intake, while in hospital, impairs recovery and increases complications even in patients who are well-nourished pre-admittance (161). Preoperative intake rather than the actual requirement (68) determines postoperative food intake. Even relatively healthy patients have difficulties in regaining involuntary weight loss (68, 140).

The metabolically active, fat-free mass (FFM) cannot be determined accurately neither in obese nor in malnourished patients and it is therefore difficult to calculate energy requirements. Obesity lowers the contribution of FFM. Resting energy expenditure (REE) may be reduced due to the decrease in muscle mass and physical activity (170). Protein-depleted post surgical patients or patients with a low BMI may become hypermetabolic with an increased REE (5, 32, 77). In planned surgery on elderly patients, actual energy requirements are difficult to approximate. When measured, preoperative REE varies from 20 to 30 kcal kg$^{-1}$ d$^{-1}$ (24, 95, 99, 165, 172). After surgery, REE may remain unchanged (95, 165) or increase (24, 99). Depending on the condition (25, 26, 145, 159, 171) variations in REE are even greater in critically ill patients, from 20 to more than 40 kcal kg$^{-1}$ d$^{-1}$. Weight after surgery or aggressive fluid resuscitation may increase by more than 15% (159) and can therefore distort the calculations of energy requirements.

Malnutrition and muscle turnover
With stress due to illness, trauma, infection or even planned surgery, elderly are at risk for developing protein-energy-malnutrition (PEM). This leads to an increase in metabolic demands and catabolism, which is not always met by an increase in energy intake. The resulting tissue breakdown leads to impaired function of different organs and risk for other complications generating a vicious circle. Malnutrition affects the immune system, as shown in vaccination studies (97). This leads to an increased susceptibility for infections and impaired wound healing. In the gastrointestinal system, malnutrition results in muscular and mucosal atrophy. This affects digestion, absorption, gut-associated immune function and drug metabolism.
Healthy, as well as frail elderly have a lower muscle mass than younger (36, 185). Lean body mass may be reduced by up to 40% at the age of 80 years, with loss of muscle cells and increase in body fat. All muscle function is depressed by malnutrition, resulting in a decreased cardiac, respiratory and ambulatory capacity.

Protein cannot be stored like carbohydrate or lipids and the amount of body protein is a balance between synthesis and degradation. Muscle protein synthesis is reduced with advancing age, and it takes more energy and protein to restore lost lean body mass (71). After stress i.e. surgery or infection, elderly do not easily regain their original weight (139, 180), and their muscle strength may fall to low levels which impairs postoperative recovery (178). It is unclear whether decreased muscle synthesis is primary or secondary to decreased physical activity or due to some other factor in the process of ageing. On the other hand, total protein catabolism is not reduced.

Prior weight loss is a useful parameter for assessment of outcome (14). Subjects, with a loss of more than 5% of initial body weight over a 1-year-period, have a significantly higher mortality rate than non-weight-losing subjects (54). This association is strongest at BMI <24 kg/m², which is suggested as a suitable cut-off point for malnutrition at age over 70 years. However, already patients older than 50 years with a BMI < 27 kg/m², experience an increased in-hospital mortality (45).

Normal weight has other implications in healthy younger than in elderly or seriously ill people. With a comparable BMI, elderly have a lower fraction FFM (71). Similarly, chronically ill patients have a lower fraction FFM than healthy controls with a similar BMI (94). This means that a patient with a normal or even high BMI may suffer from PEM. Furthermore, BMI may not correctly estimate nutritional status in the presence of oedema or ascites (33).

**Enteral nutrition**

Enteral nutrition (EN) is the most physiologic method of administering artificial/supplementary nutrition. Early EN has been shown to have beneficial effects on the patient’s immunocompetence, as well as on intestinal integrity and motility. Furthermore, there is a more efficient utilisation of nutrients and a better glucose homeostasis (9, 10, 52, 69, 92, 105, 147). Biliary secretion and emptying of the gall bladder is maintained (41). Splanchnic blood flow may increase (102). Even in critically ill patients it therefore seems reasonable to start EN early, if possible (16, 87).
Aims

The aims of this thesis are:

I. To investigate serum albumin concentration (S-Albumin) and body mass index (BMI) as markers of outcome regarding mortality and frequency of infections in cardiac surgery patients.

II. To study the postoperative energy intake in patients undergoing unscheduled, as opposed to elective coronary artery bypass grafting (CABG). To assess if it is possible to influence energy intake and whether increased energy intake has an effect on protein synthesis and skeletal muscle degradation.

III. To investigate whether a preoperative oral carbohydrate load in elderly CABG patients affects muscle strength, insulin resistance and stress hormone response.

IV. To assess the extent of the problems associated with early enteral nutrition (EN) in a cardiothoracic intensive care unit.

V. To compare the effects of EN and dopexamine on systemic oxygen consumption, splanchnic oxygen consumption, cardiac output and splanchnic blood flow on the first postoperative day after cardiac surgery, when the acute haemodynamic effects of cardiopulmonary bypass have declined. To investigate if there is a possible synergistic effect of these two treatments.
Patients and methods

Patients

The populations underlying the papers I-V were recruited from patients undergoing surgery at the Department of thoracic and cardiovascular surgery, Uppsala University Hospital, a tertiary care centre for patients in the region. All studies were approved by the Ethic’s Committee of the Uppsala University, Uppsala, Sweden. Demographic data are given in table 1.

Table 1. The numerals of the populations relate to the corresponding papers.

<table>
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<tr>
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<th>III</th>
<th>IV</th>
<th>V</th>
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<tr>
<td>n</td>
<td>886</td>
<td>31</td>
<td>18</td>
<td>73</td>
<td>16</td>
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<tr>
<td>Age (years)</td>
<td>67±9.5</td>
<td>67±8</td>
<td>72±3</td>
<td>64±12</td>
<td>72±4</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>27±4</td>
<td>25±2</td>
<td>27±2</td>
<td>26±4</td>
<td>27±3</td>
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<tr>
<td>Gender</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>female n</td>
<td>230</td>
<td>9</td>
<td>3</td>
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<tr>
<td>male n</td>
<td>656</td>
<td>22</td>
<td>15</td>
<td>50</td>
<td>5</td>
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<td>S-albumin (g/L)</td>
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<td>34±3</td>
<td>43±3</td>
<td>41±2</td>
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<td>ECC (min)</td>
<td>106±46</td>
<td>86±19</td>
<td>105±39</td>
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<td>Valve surgery n</td>
<td>224</td>
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Population I
All patients who underwent cardiac surgery between July 1, 1999 and June 30, 2000 were prospectively assessed for inclusion in paper I. Inclusion criteria were cardiac surgery with extra corporeal circulation (ECC) for valve procedures, CABG or a combination of those. Data for a total of 886 patients was collected from the cardiac surgery database of the department and then completed with case histories from referring hospitals.

Population II
In paper II, 31 patients undergoing CABG were studied. Ten elective CABG-patients made up the elective control group. Twenty-one patients were admitted for unstable angina pectoris. They were divided into two groups; an unstable control group and an unstable, supplemented group. Patients with diabetes mellitus or other metabolic diseases, renal insufficiency and severely impaired left ventricular function were excluded. Patients were evaluated preoperatively and for five days after surgery.

Population III
Eighteen patients who subsequently underwent surgery for CABG were included in the investigation. The patients were selected from the waiting list, whenever the opportunity arose to perform the necessary measurements. Inclusion criteria were age more than 65 years. Patients with known diabetes or other metabolic diseases were excluded as well as patients with severely impaired respiratory, circulatory or renal function. Patients were evaluated preoperatively and for six days after surgery.

Population IV
The study was conducted in the cardiothoracic intensive care unit (ICU). Seventy-one consecutive patients, in whom a prolonged ventilator treatment and artificial nutrition was anticipated, were included on the first postoperative day. Two cardiology patients with severe heart failure requiring intubation and ventilator treatment were also included. The surgical patients had from one to five complications (e.g. postoperative bleeding requiring re-operation, inotropic drugs or mechanical support, heart failure, respiratory failure, renal failure or cerebrovascular complications). Patients were followed until they had resumed oral intake or discharge.

Population V
In paper V, the patients were selected among those scheduled for surgery the following day and meeting the inclusion criteria (age >65 years, CABG or aortic valve surgery, normal left ventricular and renal function). Patients with metabolic diseases other than diabetes mellitus were excluded from the study. Nineteen patients were assessed for the investigation. Of these, three
patients were still on ventilator, inotropes or showed signs of confusion in the morning following surgery and were thus excluded from the study.

**Anaesthesia and surgery**

The patients were anaesthetised according to the routines at our clinic. On the evening before surgery they were given flunitrazepam orally. In the morning before surgery premedication was administered as 1.0-1.3 ml Morphine-scopolamine® Meda (morphine 10 mg/ml + scopolamine 0.4 mg/ml).

Anaesthesia was induced with alfentanil, pancuronium and thiopentotalsodium. The patients were intubated and ventilated with oxygen/air mixture. Anaesthesia was maintained with isoflurane and fentanyl as needed. Arterial blood pressure, central venous pressure and urinary output were monitored.

In paper II only Ringer’s lactate was administered during surgery and until the first postoperative morning. Glucose 100 mg/mL with 40 mmol sodium and 20 mmol potassium (1 ml kg⁻¹ h⁻¹) was administered after induction until the first postoperative morning in papers I, III and V.

CABG (and valve procedures in papers I and V) were performed according to standard. Cardiopulmonary bypass (CPB) was performed in mild to moderate hypothermia (30-34°C) with a membrane oxygenator, cristalloid cardioplegia and cristalloid priming solution. At rewarming a propofol (Diprivan®)-infusion was started and continued postoperatively until weaning from the ventilator.

**Methods**

**Paper I: Preoperative evaluation of serum albumin and BMI**

Data for a total of 886 patients was collected from the cardiac surgery database of the department and then completed with case histories from referring hospitals. For 70 patients (8%) case histories could not be retrieved. An individual unique 10-digit national registration number, allocated to all Swedish residents at the time of birth or permanent residency, allowed complete follow-up with respect to survival by linkage to the Swedish Cause of Death Register and a continuously updated population register. By use of these combined registers, all patients could be assigned a date of death or identified as being alive on 31 December 2001.

Preoperative assessment included age, gender, BMI, left ventricular function, diabetes (insulin-dependent as well as non-insulin-dependent), smoking habits, S-Albumin and C-reactive protein (CRP).
Patients were followed postoperatively with regard to in-hospital stay, infections and mortality. Mortality was defined as death from any cause. Infection was defined as any condition treated with antibiotics (in addition to routine prophylactics) by attending physicians. The infections were categorised as follows: infections related to the surgical trauma (in sternal, graft leg or cannulation incisions), infections of the lower urinary tract, pneumonia, fever and miscellaneous (dental and decubital infections, increasing CRP, septic episodes, positive cultures from catheter tips).

The relationship between all continuous variables (BMI, S-albumin, age) and risk of death and infection was explored. All continuous variables were tested in their original continuous form, a logarithmic form and with a set of multiple dichotomous variables representing ranges, defined by commonly used or standard cut-off points. In the multivariate analyses the variables were used in the optimal form i.e. with the best discriminatory power. For analysing categorised variables a set of multiple dichotomous variables was used. Variables significantly related to mortality or infection in the univariate analysis were considered in the multivariate analysis (p< 0.05).

**Statistics (paper I)**
All statistical calculations were performed with SAS 6.12 statistical procedures computer software (SAS Institute Inc., Cary, NC, USA). Descriptive statistics are given as mean±standard deviation. Student’s t-test was used in order to test for differences in in-hospital stay. Uni- and multivariate analyses performed to identify factors related to death (by any cause) were based on the standard Cox proportional hazard model (39). The relative hazard (R.H. = exp(β)) was used as a measure of the risk of death in different categories, where β is the basic parameter in the Cox model. The relative hazards are given with their 95% confidence intervals (C.I.).

Uni- and multivariate analyses based on the logistic regression model were performed to assess risk factors related to the risk of sustaining at least one infection. The results are presented in the form of odds ratios (O.R.) with 95% C.I.

**Paper II: Dietary supplementation and evaluation**
Upon arrival at the ICU an infusion of 10% glucose was started in the unstable, supplemented group and continued until the next morning. After blood sampling, a normal breakfast was served. Regular hospital food was served for lunch and dinner and increased on demand. Oral nutritional supplements were given three times daily. The nurses made active efforts to
stimulate these patients to eat and were more active in treating nausea. If the patients were unable to eat, nutrition was supplemented intravenously.

The elective control and the unstable control groups were managed according to a conservative nutritional routine: No glucose infusion was given on the day of surgery. On the first postoperative day, only liquids were administered perorally. Subsequently, the patients were offered regular hospital food. The amount was increased at the patients’ wish, but no active attempts were made to stimulate the patients to eat.

Patients were followed postoperatively for five days and the daily energy intake was recorded.

**Resting energy expenditure**

Resting energy expenditure (REE) was measured prior to premedication on the morning of surgery and on the second postoperative day with a Deltatrac®, Datex, Finland. The result was compared to REE computed by Harris-Benedict equation.

**α₁-antitrypsin**

A population model was developed using the non-linear mixed effect modeling approach. In this approach, typical values for individuals, inter-individual variability and intra-individual variability are estimated. The tested models were fitted to the measured plasma concentrations by a non-linear mixed effect modeling program, NONMEM version VI (1).

The equations defining the concentration changes in α₁-antitrypsin (65, 66, 79) describe the compartmental model for the concentrations (µmol/L) in the central compartment $c_1$ and peripheral compartment $c_2$.

\[
\begin{align*}
\frac{dc_1}{dt} &= -k_{10} \cdot c_1 - k_{12} \cdot c_1 + k_{21} \cdot c_2 + \frac{\Phi(t)}{V_1} \\
\frac{dc_2}{dt} &= k_{12} \cdot c_1 - k_{21} \cdot c_2
\end{align*}
\]

$k_{10}, k_{12}, k_{21}$ represent the inter-compartmental fractional rate constants (hour⁻¹). These were fixed to 0.01, 0.08 and 0.04 respectively, as in Karlsson et al (85). The volume in the central compartment $V_1$ was fixed to the plasma volume, i.e. 3 L.

$\Phi(t)$ represents the plasma appearance rate of α₁-antitrypsin, that may be considered an indicator of the visceral protein synthesis (85).

Several different functions were used to model the appearance rate. Graphical evaluation of the goodness of fit and the objective function value
(OFV) was used to select between models. By empiric approach, the best fit to the data was found with a transit compartment model (2), with $\Phi(t)$ determined by equation

$$\Phi(t) = \frac{Pool_{tr} \cdot k_{tr} \cdot (k_{tr} \cdot t)^n \cdot e^{-k_{tr} \cdot t}}{n!}$$

$n! = \sqrt{2\pi \cdot n^{n+0.5} \cdot e^n}$ is the continuous Stirling approximation of the factorial of $n$
$n$ is the number of transit compartments
Pool$_{tr}$ is the initial pool of acute phase protein in the transit compartment
$k_{tr}$ is the fractional rate (hour$^{-1}$) constant between each transit compartment calculated as $n \cdot \frac{1}{MTT}$, where MTT is the mean transit time in hours.

3-Methylhistidine

Urine was collected for 24 hours from the morning of the 2nd postoperative day (POD 2) until the morning of POD 3. The urine was pooled and muscle protein breakdown was assessed by 3-Methylhistidine excretion. The food given was ovo-lacto-vegetarian on postoperative day 1 and 2 because of the urine-sampling for 1- and 3-Methylhistidine in the morning of day 3 (136, 153, 157). A possible intestinal contribution to the 3-Methylhistidine excretion was estimated by simultaneously measuring 1-Methylhistidine (136, 153) Plasma 1- and 3-Methylhistidine was analysed by a modified HPLC method (152).

Paper III: Insulin resistance after cardiopulmonary bypass

Plasma glucose was measured on an automated clinical chemistry instrument (Hitachi 912, Roche Diagnostics, Bromma, Sweden). HbA1c was measured with an automated HPLC system (Variant II, Bio-Rad Laboratories AB, Sweden). Serum concentrations of cortisol, growth hormone (GH), insulin, and C-peptide were measured on an automated fluorescence detection system (Autodelfia, Wallac Oy, Turku, Finland). Glucagon, Pancreatic polypeptide and insulinlike growth factor I (IGF-1) were measured with a commercial RIA kit (Linco, St. Charles, MI, USA, EuroDiagnostica, Malmö, Sweden and Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Plasma epinephrine and norepinephrine were measured on a semi-automated HPLC-system with electrochemical detection (Tillqvist Analys AB, Sweden). Chromogranin A was measured with competitive radioimmunoassay (160).
Carbohydrate loading
The study group was given 400 ml of a 12.5% carbohydrate drink (Nutricia Preop®, Nutricia, Zoetermeer, Netherlands) in the evening on the day before surgery and in the morning on the day of surgery.

Assessment of insulin resistance: HOMA
Homeostasis model assessment (HOMA) was used to evaluate insulin resistance (HOMA-IR) and β-cell activity (HOMA-B) (104). HOMA, based on insulin and glucose determination in the fasting state, is easily obtained and simplifies longitudinal assessment of insulin sensitivity throughout the perioperative period.

Assuming that a subject with a normal weight, aged less than 35 years has a 100% β-cell function and an insulin resistance of 1, the values for the patients can be assessed from the insulin and glucose concentrations by the equations (104):

$$\beta - cell\ function(\%) = 20 * \frac{Insulin\ concentration}{Glucose\ concentration - 3.5}$$

and (near approximation) (175):

$$Insulin\ resistance = \frac{Insulin\ concentration * Glucose\ concentration}{22.5}$$

Plasma glucose concentrations are given as mmol/L and serum insulin concentration as mU/L. HOMA-IR >1.0 indicates insulin resistance and HOMA-B <100% decreased β-cell function.

Gastric Emptying Measurements
Gastric emptying was assessed as described by Nygren (114), with some modifications. In the morning on the day of surgery the patients in the study group were given 400 ml of Preop® mixed with 20 MBq 99mTc-labeled human albumin colloid (Solco Nanocoll, Solco Basle Ltd, Birsfelden, Switzerland).

Repeated recordings by gamma camera were performed in the supine position. Static anterior and posterior registrations were obtained with a double head gamma camera (Maxxus, General Electric, Milwaukee, WI, USA) equipped with a low-energy general-purpose collimator. The acquisition was performed in a 128*128 matrix with an acquisition time of 2 minutes. In between recordings the patients were allowed to position themselves at will.
Evaluation of the gastric content was made on a Hermes workstation (Nuclear Diagnostics AB, Stockholm, Sweden). Regions of interest (ROI) were selected over the activity in ventricle and the gastric content was calculated as geometric mean activity from anterior and posterior images ($\sqrt{\text{anterior} \times \text{posterior}}$). After correction for physical decay, the activity at the different recordings was expressed as a percentage of the initial value (time 0).

**Respiratory function**

We evaluated respiratory muscular function as peak expiratory flow (PEF), $P_{\text{max}}$ (maximum inspiratory flow) and $P_{\text{e max}}$ (maximum expiratory flow) measurements before surgery and on POD 6. The ratio between the values on POD 6 and preoperative measurements was calculated. PEF was measured with a miniWright Peak flow meter (AIRMED, Clement Clarke Int. Ltd, Essex, England). $P_{\text{max}}$ and $P_{\text{e max}}$ were assessed with PiMAX, (MPM Micro Medical Ltd, Medanz, Starnberg, Germany).

**Paper IV: Effects of enteral nutrition and dopexamine on splanchnic blood flow**

**Evaluation of complications with an enteral feeding protocol**

EN was started either on the first postoperative day, or when it became obvious that the patient would remain on artificial ventilation for several days. The patients were sedated and the enteral feed was delivered by a pump device in a nasogastric tube. Administration time was 20 hours/d. Gastric residual volume was assessed daily. Enteral feeding was started at 10-20 ml/h and increased by 10 ml/h each day. Supplementation with parenteral nutrition was given according to the patient’s needs, i.e. REE as calculated by the Harris-Benedict-equation.

The patients were assessed daily by the attending nurses for vomiting, tube dislocation, diarrhoea and gastric residual volume according to the study protocol. Aspiration pneumonia was defined as a rise in temperature and/or CRP and typical findings in the routine radiographs as evaluated by the radiologists.
Paper V: Nutritional supplementation after coronary-bypass surgery

**Evaluation of splanchnic blood flow, cardiac output and oxygen consumption**

The investigation was started in the morning after surgery with the patients in fasting conditions. Interventions were performed in two consecutive phases, 180 minutes each (Figure 1).

![Figure 1. Study design.](image)

The placement of the hepatic venous catheter was confirmed on the first postoperative day by x-ray. Patients were then randomised to receive either dopexamine (Dopacard®, Cephalon Pharma, Copenhagen, Denmark) at a rate of 1.0 µg kg⁻¹ h⁻¹ or enteral nutrition with a bolus of 100 ml followed by 50 ml h⁻¹. The enteral formula used was Isosource® (Novartis, Basel, Switzerland). Blood samples were collected for blanks. An indocyanine green (ICG) infusion (ICG-Pulsion; Pulsion Medical Systems, Munich, Germany), was started. Baseline samples were collected, and the study infusions for the first phase were started.

Cardiac output (CO) was measured by the thermodilution technique and SBF by ICG extraction. Samples were drawn from the radial artery and hepatic vein catheters in triplicate and mean values were used for analysis. At the same time points, samples for analysis of blood gases, blood glucose and lactate were collected from the hepatic vein, the pulmonary and radial arteries.
After the initial 180 minutes, the second phase of intervention was started. Either dopexamine or enteral nutrition was added and thus the patients in both groups were receiving both enteral nutrition and dopexamine.

SBF was calculated by the following equation:

\[
SBF = \frac{\text{infused ICG amount} \times \text{min}^{-1}}{\text{arterial ICG concentration} - \text{hepatic venous ICG concentration}} \times \frac{1}{1 - Hcr}
\]

Hcr=haematocrit fraction

Oxygen consumption (VO₂) was calculated according to Fick’s principle. CO was measured by termodilution in using GE Solar 8000 surveillance system (GE Medical Systems, Milwaukee, Wisconsin, USA). We state the haemodynamic measures in index form, i.e. corrected for body surface area: cardiac index (CI), splanchnic blood flow index (SBFI) and oxygen consumption index (VO₂I). Blood gases were analysed with an ABL 725 analyser (Radiometer, Copenhagen, Denmark).
Results

Paper I

The patients were followed for 22±6 months. During follow-up mortality was 7 %, with an early mortality (within 30 days from surgery) of 4 %. Thirty percent of the patients were found to have an infection. Infected patients had a longer hospital stay than patients without any infection, 19±11 days vs. 11±4 days respectively. Patients 55 years of age or younger had a shorter length-of-stay (LOS) in hospital than patients older than 75 years, 11±9 days vs. 16±9 days respectively. S-Albumin and BMI did not affect LOS.

Twenty-three percent of the patients were lean i.e. had a BMI of 24 or less. Lower BMI, lower S-Albumin, higher age, type of surgery, impaired left ventricular function and longer bypass time increased the risk for death in univariate analyses. In a multivariate analysis with all other variables in the model and BMI and S-Albumin considered one by one, low BMI increased the relative hazard for death, whereas S-Albumin did not. Lower S-Albumin, higher age, diabetes and longer bypass time increased the risk for infection in a univariate analysis. In a multivariate analysis with all other variables, low S-Albumin increased the risk for infection.

In summary, a low BMI increased the relative hazard for death and low S-Albumin increased the risk for infection.
Paper II

For demographic data see table 1. Preoperative REE was 20 kcal kg$^{-1}$ d$^{-1}$ and 21 kcal kg$^{-1}$ d$^{-1}$ respectively and did not differ between groups. On the second postoperative day, REE increased by 10-12%. The difference between REE measured by indirect calorimetry and the Harris-Benedict equation was on average 3%.

The urinary nitrogen excretion did not differ between the three groups. No difference in the plasma appearance rate of $\alpha_1$-antitrypsin could be demonstrated.

In the unstable supplemented group, the energy intake on POD 1 was 86% of the preoperative REE and increased to 90% on POD 3. In the control groups, energy intake on POD 1 was 34 and 46% respectively of the preoperative REE. The elective control group increased energy intake to 70-80% of REE, while the increase was smaller in the unstable control group, figure 2.

Figure 2. Normalised daily energy intake. Ratio actual intake/ measured.
* difference between the control groups and the unstable, supplemented group.
# difference the unstable, control group and the unstable, supplemented group.
There was no accumulated energy deficit day 1 to 5 in the unstable, supplemented group as compared to the elective and unstable control groups. See figure 3.

Figure 3. Cumulated energy balance postoperative day 1 to postoperative day 5. # (p<0,05) Energy deficit day 1 to 5 differed in the control groups from the unstable, supplemented group.

Surgery in elderly patients thus results in a higher REE postoperatively and makes the patients more susceptible to a decreased energy intake postoperatively. Motivated and active staff increases the patients’ voluntary food intake.
Paper III

For background parameters see table 1.

**Glucose and insulin**

HbA1c was 4.7±0.13 mmol/L in both groups. Plasma glucose was normal at baseline and elevated on POD 1 and 2. On POD 6, plasma glucose concentrations had returned to baseline in the controls and were slightly above baseline in the carbohydrate group.

Insulin concentration at baseline was higher in the carbohydrate group. Insulin concentration in both groups increased on POD 1 and 2 and subsequently returned to baseline on POD 6. Insulin resistance, as measured by HOMA-IR, increased in both groups on POD 1 and 2 and returned to baseline on POD 6. There was no difference between the groups in the ratios of HOMA-IR on POD 1, 2 and 6 vs baseline, figure 4. β-cell activity in the carbohydrate group, as measured by HOMA-B, showed a peak at induction. In the control group it was lower, with no changes throughout the study period.

![Figure 4](image-url)

**Stress hormones**

No difference was seen between the groups at baseline. Epinephrine and norepinephrine concentrations were higher on POD 1 in both groups. The carbohydrate group had higher concentrations of norepinephrine on POD 1 than the controls. The concentrations of cortisol and glucagon were higher.
postoperatively than at baseline in both groups, with no obvious difference between groups. Growth hormone (GH), chromogranin A and pancreatic polypeptide concentrations did not differ significantly between the two groups or over time. IGF-1 showed a decreasing trend postoperatively compared to baseline in both groups, however, no difference was observed between the groups.

**Respiratory parameters**

No differences were seen between the carbohydrate group and the controls in the relative dynamic respiratory parameters (POD 6 vs. baseline).

**Short term response to carbohydrate, gastric emptying**

The patients responded to the carbohydrate drink with a temporary increase in plasma glucose and serum insulin concentrations (figure 5). Plasma glucose concentration reached a peak above 10 mmol/L between 30 and 60 minutes after the carbohydrate load. The serum insulin concentration curve showed a similar profile. After 120 minutes the remaining activity in the stomach was 11±3%.

![Figure 5](image-url)  
**Figure 5.** Plasma glucose concentrations and serum insulin concentrations during the gastric emptying study. Values are given as mean ±SEM. The time scale is 0-120 minutes after ingestion of carbohydrate drink and before induction of anaesthesia.

In brief, the patients can be considered to have a decreased glucose tolerance. No adverse effects were seen with the carbohydrate drink. If glucose is administered during surgery there is no obvious advantage of preoperative carbohydrate loading neither in insulin resistance or stress hormone response.
Paper IV

In 63 out of 73 patients, enteral feeding was started within the first three days of their ICU-stay. The median duration of enterally administered nutrition was 13 days (range: 2-54). EN was discontinued in 34 patients because they were able to feed themselves, 19 patients were moved to another hospital and 11 patients died. Some of the patients had a small oral intake towards the end of the weaning period, although they still required assisted ventilation.

In 45 patients the nasogastric tube did not have to be changed. In 25 patients a change of the tube to a softer feeding tube (Kangaroo®) was performed, usually in connection with a coniotomy.

Vomiting or regurgitation beside the tube occurred in 13 patients during the ICU-stay. All episodes happened during the first days of enteral feeding.

No diarrhoea was observed in 52 patients, 11 had small diarrhoea, 13 moderate and two patients suffered from large diarrhoea. The frequency of diarrhoea co-varied with antibiotic treatment. During their ICU-stay patients were treated with a mean of three antibiotics (range: 1-6).

No gastric residual volume (GRV) was seen in 29 patients and 12 had small GRV during the time they were on enteral feeding. Seven patients had a moderate GRV which decreased in one patient when EN was started. Twenty-four patients had a large GRV, which subsequently decreased in 14 patients.

Aspiration pneumonia occurred in 7 patients.

In summary, early enteral nutrition is a feasible method to administer artificial nutrition in the cardiothoracic ICU. It is reasonably safe and well tolerated by patients when individually adjusted. However, it is often not possible to meet the entire nutritional requirement by this route, why some parenteral supplementation certainly is necessary.
Paper V

Demographic data are presented in Table 1.

Cardiac index
In the dopexamine group, CI increased with dopexamine infusion but not when EN was added. In the EN group, EN alone did not increase CI.

Splanchnic blood flow
SBF on the first postoperative day was 17±5 % of CO for the dopexamine group and 16±4 % for the EN group. In the dopexamine group, SBF1 increased at the beginning of the first phase. In the dopexamine group, SBF returned to baseline levels towards the end of the first phase and remained constant during the second phase. In the EN group, SBF did not differ from baseline during the first phase, but increased after the addition of dopexamine. Dopexamine alone thus did not increase SBF in our elderly patients.

Systemic and splanchnic oxygen consumption
There was no difference in systemic and splanchnic oxygen consumption (VO$_2$I). In both groups the oxygen delivery increased and the systemic vascular resistance index (SVRI) decreased over time. The splanchnic fraction of the systemic oxygen consumption did not differ between groups.

Splanchnic oxygen extraction ratio (OER) did not increase by EN or dopexamine. Systemic OER was higher in the dopexamine group as compared to the EN group.

The EN group had higher baseline concentrations of mixed venous and hepatic lactate. In the dopexamine group, arterial, mixed venous and hepatic lactate concentrations increased from baseline with no further increase when enteral nutrition was added. In the EN group, corresponding concentrations were unchanged throughout the investigation.
Discussion

Markers for nutritional status and outcome

BMI

The populations in paper I and IV contain a number of underweight subjects. In paper I, we show that low BMI and albumin correlate with adverse outcome in an elderly population, with 23% of subjects exhibiting a BMI ≤24 kg/m². Among the ICU patients in population IV, median BMI was 26 and 50% had a BMI <25. The ICU patients in paper IV have several complications, which may be related to low BMI. In the interventional studies II, III and V, average BMI was 25-27, with no overtly underweight subjects.

In cardiac conditions, low BMI can be caused by hypo- as well as hypermetabolism (32, 57). A low BMI increases the risk for complications such as infection, reintubation and mortality (60, 127, 134) as well as an increased length-of-stay (LOS) (148).

Cardiac disease often coexists with other chronic conditions, which may lead to weight loss. Unintentional weight loss is a predictor of mortality, independent of low BMI for patients of any age (14, 57, 148, 181).

A normal BMI does not exclude the presence of malnutrition. In patients with heart failure (57), cardiac surgery patients (169) and ICU-patients (135), a low BMI is an obvious risk factor although it may be masked by fluid retention. Thus, body composition is not always correctly reflected by BMI (71). This can be one plausible explanation as to why we found relatively few patients with a low BMI in our investigation.

High BMI does not necessarily increase the mortality risk (141). Five-year-survival was higher in patients with BMI between 24 and 30, as well as for those with mild obesity (BMI 30-34) (148). BMI is thus an imprecise measure. Its sensitivity as a marker is high but its specificity may be low.
Obese patients may be classified as not being at risk if BMI or percentage of weight loss are used (40).

Changes in fat-free mass (FFM) and fat mass (FM) in age and disease may be more adequate markers of risk. In a study by Kyle et al, patients had lower FFM and showed greater age-related decrease in FFM than healthy controls (94). Low FFM, high FM and low FFM/FM ratio all increase LOS (93).

Nevertheless, BMI should be used in nutritional assessment. It is easily calculated and although it identifies only a minor proportion of the patients nutritionally at risk, a low BMI definitely indicates increased risk of mortality and morbidity (123, 129). However, in case of a normal BMI, care should anyhow be taken to evaluate weight development for each patient both pre- and postoperatively.

Albumin

Albumin remains widely used in cohort studies as a biochemical measure of nutritional status (37, 90). A low S-Albumin is thought to be prognostic for poor outcome, especially in the elderly. Among complications predicted by low albumin concentrations are extubation failure after cardiac surgery (130) and air leak or pneumonia after thoracic surgery (59). Albumin is affected not only by malnutrition, but also by infection, inflammation, oedema or dilution (116). Furthermore, a normal albumin concentration does not exclude malnutrition (38, 81).

In study I, we found that patients with low preoperative S-Albumin were more frequently infected than patients with normal concentrations. Preoperative CRP was normal in over 90% of the patients in study I, indicating that the great majority did not suffer from inflammatory or infectious conditions. Thus we find it plausible that S-Albumin reflects these patients’ nutritional status. In contrast to other authors (50, 61, 131, 138), we did not observe any relation between low S-Albumin and mortality in multivariate analysis.

In our population I, S-Albumin decreased with age. This is in accordance with findings by Omran (116). Similarly to other authors (121, 131), we observed an increased frequency of infections with increasing age. It has been shown in healthy elderly, that a low S-Albumin indicates a weak response to influenza vaccine (97). An age-related, increased frequency of sternal wound infections has previously been described (156). This may be due to a combined effect of an ageing immune system and a poor nutritional status, indicated by low S-Albumin.
Energy requirements and intake

In our studies II and IV, we found that oral intake as well as enteral nutrition can be improved when attention is paid to the circumstances in which the treatment is administered.

Resting energy expenditure (REE)

Actual energy requirements are difficult to calculate. We therefore measured REE pre- and postoperatively. Preoperative REE was 20-21 kcal kg⁻¹ d⁻¹. REE was increased emergency surgery to a higher level than by planned surgery.

All our patients had an increased REE postoperatively, even if their body temperature was normal. A possible reason for the latter could be an attenuated febrile reaction in the elderly (56). The increased REE in the patients in paper II lies within the ordinary postoperative range for surgery in general (48, 99) as well as for CABG (73).

In the unstable, supplemented group in study II, we observed a higher increase in REE postoperatively than in the elective controls. This could in part be due to the supplementation, since nutrition in itself increases metabolism (48, 56). No difference between the two control groups was seen in REE before and after surgery.

The Harris-Benedict equation was a good approximation of REE as measured by indirect calorimetry. This is not always the case. Underweight patients may have an increased REE (5, 32). In critically ill, measured REE may differ widely (70-140%) from the predicted (179).

Voluntary food intake (VFI)

Nutritional deficiency influences the reaction to trauma and surgery (143, 161, 182). Healthy elderly who have an energy intake lower than recommended during a 10-year period have higher rates of mortality and morbidity (49, 180). Patients’ energy intake after hospitalisation is not dependent on requirements, but rather on the nutritional habits before hospitalisation (68, 84). Intestinal oedema (64) and loss of appetite caused by side effects of medication (e.g. nausea or loss of taste) (64) can result in anorexia and cardiac cachexia. A nutritional intake of less than 50% of the calculated need increases the risk of complications during the hospital stay (161). An early-acquired energy deficit worsens the outcome, in ICU patients (182) as well as in regular ward patients (68, 172). This adverse effect can not be compensated for later.
Furthermore, it has been shown that the deterioration of nutritional status in CABG patients continues four to six weeks after discharge (64). The weight loss occurring during hospital stay and after discharge correlates with lower self-reported physical health (44). On the other hand, early and sufficient feeding improves outcome (108) and quality of life (13) after surgery.

Supplementation can compensate for inadequate energy and micronutrient intake (132) and improve function (23, 128, 168). Postoperative artificial nutrition is not superior to oral support in postoperative, malnourished patients (78). In patients, who are not malnourished, routine supplementation does not show any beneficial effect, although an effect of micronutrient supplementation may be seen (100, 183). It is therefore important to identify the patients at risk and treat them accordingly (158).

We found that voluntary food intake in the early postoperative period was low. If the patients were left on their own they would not have met their energy requirements. In response to our active program of stimulating the patients to eat, the intake increased. Consequently, the energy deficit in the two control groups was considerable (2400 - 3000 kcal), while the supplemented group was in balance or had a minor deficit (800 ± 1200 kcal), figure 3. Nevertheless, we could not show any difference in the biochemical parameters.

Enteral nutrition (EN)

Even in the critically ill, the most physiological means to provide nutrition, whenever possible, is by the enteral route. Intestinal absorption is close to normal even in low cardiac output syndrome, although a decrease due to opiates may be seen on the first postoperative days (15). Hepatic lipid metabolism is maintained, which might decrease the risk for postoperative cholestasis (41). Gastrointestinal integrity is preserved as well as immunologic function (75). EN is feasible even in severe haemodynamic failure, but usually results in hypocaloric feeding (16).

Even though it has been shown that gastric emptying after CPB is significantly reduced (63), this presented no major problem in our clinical setting. Most of our patients had no or little GRV at the start of enteral feeding. Occasionally it was necessary to decrease the infusion rate temporarily or to administer prokinetic medication i.e. metoclopramide or cisapride, in accordance with others (21, 101, 125). In our view, the results indicate that a balanced enteral diet, in itself, could have a prokinetic effect.
Diarrhoea is thought to be a frequent side effect of EN. We observed diarrhoea during treatment with antibiotics, especially with broad spectrum antibiotics. The problem was however small in the majority of the patients in our investigation and no specific treatment for diarrhoea was necessary. In some cases the infusion rate was temporarily decreased or the formula was changed. Anti-diarrhoeic medication (loperamid) was needed in only one case.

Other factors than enteral nutrition in itself may cause diarrhoea, i.e. hypertonic EN, high infusion rates, electrolytes, or sorbitol in liquid medicine mixtures. The occurrence should be carefully evaluated and treated by administration of probiotics, reduction of hypertonic solutions and reduction of laxatives (17). It can also be argued that EN maintains a more normal gastrointestinal flora and thereby decreases the risk of diarrhoea.

Frequently, EN is started through a nasogastric tube, since the latter is easily available. Nasogastric tube change was rarely needed in our patients. This is partly due to the fact that the patients were mechanically ventilated and therefore sedated. However, even after tracheotomy and weaning from the ventilator only a few of the tubes were dislocated. No clinical problems were caused by regurgitation or vomiting, that occurred infrequently and only early in the enteral feeding period.

Pneumonia is more common after EN, regardless of other complicating factors (30). In our material, aspiration pneumonia occurred in 10%. The incidence was lower than in other studies (20, 80), that have reported pneumonia in 17% and 54%, respectively. In this context, postpyloric feeding is advocated, since regurgitation is decreased and there is a trend towards less microaspiration. The gastroesophageal reflux is nevertheless not completely abolished (74, 86). It has been suggested that a resting period from enteral feeding would increase the gastric acidity (80) thereby decreasing the risk for ventilator associated pneumonia. Others observed no difference (20). Time on ventilator is also of importance, as well as the patients being in the supine position (47).

Most of our patients covered 60-70% of their energy requirements enterally by the end of their ICU-stay, a similar figure to that reported by others (16). We made the clinical observation, that patients on either partial or total enteral nutrition tended to resume and tolerate oral intake more easily. There are difficulties that must be addressed and monitored. Side effects are avoided by ensuring proper tube position, choose proper feed and avoiding medication that might contribute to intolerance (17).
Parenteral supplementation is necessary in order to meet the energy requirements. We believe that in order to benefit from both parenteral nutrition (adequate intake) and enteral nutrition (fewer septic complications and maintenance of the gastrointestinal integrity (117)) in the severely ill, both routes should be used. The delivery of enteral nutrition to critically ill patients is greatly improved by guidelines considering all possible routes of feeding (4, 22, 83, 155, 184).

Metabolic function

Protein turnover

The 3-methylhistidine excretion in urine in our patients was half of that in patients after gastrointestinal surgery (136). The calculated muscle protein loss and urine urea excretion was lower in our patients than in other surgical patients or healthy individuals (85, 95, 106). A possible explanation may be a relatively low muscle mass and a significant comorbidity in a population of elderly undergoing CABG, compared to the younger patients after gastrointestinal surgery (mean age 57 years) (136). 3-methylhistidine excretion did not differ between the different groups in paper II, indicating that the intervention was too short in duration, that energy intake had not been sufficient or that there was no difference.

Loss of muscle mass means a decreased muscle strength. Both may last for a prolonged period of time after abdominal surgery (122, 178). Decreased muscle strength and secondary pulmonary changes after cardiac surgery are known to affect lung function (151). It seems plausible that preoperative carbohydrate loading improves postoperative muscle strength. We however saw no effect of preoperative carbohydrate loading on lung function as a marker of muscle strength.

Plasma appearance rate of $\alpha_1$-antitrypsin may be considered an indicator of the visceral protein synthesis (85). We have developed a new model for the fractional appearance rate of $\alpha_1$-antitrypsin. This gives us a better tool for further studies. We could not demonstrate any increased visceral protein synthesis in response to the present simple supplementation of nutrition. The fractional appearance rate in our patients peaks at approximately half the value of the patients in Karlssons study (85). This is in accordance with the fact that protein synthesis may be lower in the elderly.
Insulin resistance

Insulin resistance is common in patients who are elderly, suffer from IHD and undergo major surgery. Low whole body insulin sensitivity is associated with impaired myocardial glucose uptake and poor outcome after revascularisation (91).

Insulin resistance is often measured by the clamp technique, which can be rather strenuous for the patient. HOMA (see Methods) is easily obtainable and has been effectively used to evaluate insulin resistance in different populations, i.e. cardiovascular disease (70), after coronary stent placement (150) and in adolescents (88). Insulin resistance calculated by HOMA correlates with results from the euglycaemic clamp, hyperglycaemic clamp and fasting insulin concentration (104). The estimate of β-cell function obtained by the HOMA correlates with the hyperglycaemic clamp and oral glucose tolerance test (175).

The relatively high levels of glucose and insulin in study III suggest a high insulin resistance. We obtain similar results by calculating HOMA and applying cutoff levels as defined by Hanley et al (70) or Sekiguchi et al (150).

Preoperative oral carbohydrate administration

A positive effect of oral carbohydrate loading on insulin resistance has been described (112). We did not observe any such beneficial effect. Similarly, Breuer et al did not find an effect on postoperative insulin resistance after preoperative oral carbohydrate administration (29). A possible positive effect in study III may have been counteracted by increased stress hormone levels. All the patients had preoperatively high levels of insulin, glucagon and cortisol. The values still had not reached the baseline six days after surgery. The high levels of stress hormones, as compared to abdominal surgery (27, 72), may be due to the fact that our patients were elderly and suffered from a chronic disease.

The perioperative administration of glucose intravenously could possibly also have attenuated the effect of oral carbohydrate loading. We have several reasons for perioperative administration of glucose in the present patient group. Glucose is the preferred substrate for the ischemic heart (43, 124). Hypothermic cardioplegic arrest increases uptake and oxidation of glucose in the immediate reperfusion phase (96, 124). Small amounts of glucose decrease amino acid oxidation during surgery, thus diminishing catabolism (146).
Gastric emptying
The residual gastric activity of 11% after ingestion of oral carbohydrate in study III is higher than what has been reported in younger patients after surgery (114). It is, however, a low value compared to the healthy controls in a study by Delgado-Aros (42). The magnitude is modest and, taken together, these investigations suggest that it is safe to ingest a clear carbohydrate fluid two hours before pre-medication. Elevated plasma glucose is associated with decreased gastric emptying both in healthy subjects and diabetic patients (149). This can be the cause of the slightly higher gastric retention in our patients compared to the patients reported by Nygren (114).

Splanchnic blood flow
The splanchnic blood flow (SBF) is autoregulated, however to a lesser degree than renal blood flow (163). Normally, the former is 20-30% of cardiac output and splanchnic oxygen consumption is 20-35% of whole body oxygen consumption. Feeding enhances the autoregulation of intestinal blood flow. Blood flow is better maintained in response to a decrease in perfusion pressure with intraluminal food present than in the starved condition (163). Also digestion produces postprandial hyperaemia.

In study V, SBF on the first postoperative day was somewhat lower than described by other investigators (82, 163). The higher age of our population might be a contributing reason (188). We did not find any signs of insufficiency in oxygen or substrate delivery caused by this seemingly low SBF. EN alone did not increase SBF in our patients, as opposed to the studies by Marla and van Brandt (103, 176). EN or dopexamine did not affect oxygen extraction ratio, systemic or splanchnic oxygen consumption. We did not observe any problems from the early use of EN.

Dopexamine is a β-adrenergic-receptor stimulator with mainly vasodilating properties (β2-effect) rather than inotropic β1-effect and is considered to enhance splanchnic blood flow. In the literature results of administration of SBF-enhancing inotropes are contradictory (11, 82, 111, 119, 162, 164, 167, 173, 174).

In study V, dopexamine alone had only a transient effect SBF in the elderly patients. This is in analogy with the case dopamine and renal blood flow, where effects seen in young, healthy subjects could not be reproduced in the elderly (58). We saw an increased SBF when dopexamine was added to EN. Addition of EN to dopexamine did however not result in increased SBF. The latter is in agreement with the findings in critically ill patients by Revelly (137), but in contrast to the younger patients studied by Bartsch (12).
In study V, arterial, mixed venous and hepatic lactate concentrations increased (although within the normal range), after dopexamine, with no further increase when EN was added. When delivering enteral nutrition, lactate concentrations did not differ over time, even when dopexamine was added. A possible explanation for these findings is a potentially more ischaemic situation during dopexamine infusion, resulting in an increased lactate production. This pattern may have been attenuated by an initial administration of EN.

Our results do not imply routine use of dopexamine infusion or EN in otherwise healthy patients undergoing CPB to improve splanchnic blood flow. On the contrary it seems as if dopexamine infusion leads to an increased lactate concentration, possibly indicating a more ischaemic condition. Based on our study, the clinician can however safely employ early EN, which is a physiological mean of delivering energy substrates and that might have additional beneficial effects.
Conclusions and summary

- Nutritional parameters should be taken into consideration when evaluating patients before surgery. BMI and S-albumin are important parameters in this context, in spite of their low sensitivity.
- Surgery in elderly results in a higher postoperative REE by 10-12% and makes the patients more susceptible to a decreased energy intake postoperatively.
- It is important to consider nutritional needs throughout the perioperative period. The energy intake is increased with motivated and active staff.
- The patients exhibited insulin resistance on the first postoperative days. Glucose should be administered during surgery and our patients received an adequate glucose infusion. This may however be the reason, why we did not observe any clearly adverse or beneficial effects of oral carbohydrate drink on insulin resistance or stress hormone response.
- Early enteral nutrition is a feasible method to administer artificial nutrition in the cardiothoracic ICU. It is reasonably safe and well tolerated by patients, when individually adjusted. However, it is often not possible to meet the entire nutritional requirement by this route, a reason why parenteral supplementation is necessary.
- No effect on protein synthesis and degradation was seen.
- Dopexamine and enteral nutrition by themselves did not increase systemic or splanchnic blood flow in the elderly patients.

Clinical implications

- In order to improve outcome, it is desirable to improve preoperative nutritional screening and assessment
- Nutritional treatment has to take into account the special demands of the elderly by implementing of routines from diagnosis until discharge with follow up in primary care.
- Meeting the patients’ nutritional requirements, regardless of the route of administration, is greatly improved by protocols and guidelines. An ongoing educational program has to be implemented to accomplish this.
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