Critical illness is accompanied by changes in body composition, such as an increase of the extracellular volume and a contraction of the intracellular volume. The research described in this thesis aimed to address a better understanding of these changes and corresponding biochemical derangements that critically ill patients experience during their illness.

In Chapter 2, we evaluated the association between derangements in circulating potassium levels and outcome and described the effect of the introduction of a computerized potassium regulation protocol (GRIP-II, Glucose and potassium Regulation in Intensive Care Patients). A before-after analysis was performed in more than 10,000 patients of whom 45% were regulated by GRIP-II. We found that hypokalemia, hyperkalemia and potassium variability were all independently associated with increased in-hospital mortality. Implementation of GRIP-II was effective and led to a significant decrease in potassium derangements.

Chapter 3 describes the results of the GRIP-COMPASS trial. In this trial, we compared the effect of two different potassium targets - that were both within the normal range - on the postoperative incidence of atrial fibrillation and flutter. Potassium levels in both arms were regulated by the GRIP-II computer algorithm. The normal-low target was 4.0 mmol/L, the normal-high target was 4.5 mmol/L. Patients assigned to the high-normal target received significantly (73%) more potassium, mean potassium concentrations were only marginally different (4.22 mmol/L vs. 4.33 mmol/L, \( P < 0.001 \), respectively). There was no significant difference in the incidence of atrium fibrillation or flutter between the two groups (38% vs. 41% respectively).

In Chapter 4 we further explored the remarkable intransigence of potassium levels despite the strongly different doses of potassium that were administered. In this chapter we performed comprehensive fluid and electrolyte balance studies in cardiothoracic surgery patients. Daily water, sodium and potassium balances were separately determined. The electrolyte free water (EFW) component of the water balance was also calculated. We found that rapid and profound volume and electrolyte administration resulted in a strongly positive fluid and sodium balance (4.0 ±0.6L and 814 ±75 mmol), but in a negative potassium and EFW balances (-101 ±14 mmol and -1.1 ±0.2L) over the first 4 days of ICU admission. This observation suggests that in contrast to conventional theory, the ICV remains constant or even decreases in critically ill patients, while the ECV rapidly expands.

In Chapter 5, we applied the same balance methodology to measure potassium and sodium shifts in human liver grafts and the relation of these shifts with graft viability. If potassium derangements occur after reperfusion during conventional liver transplantation, i.e., without an ex vivo perfusion phase, hyperkalemia is expected. Ex vivo perfusion with dual hypothermic oxygenated machine perfusion (DHOPE) improves graft function. We studied the effect of DHOPE on potassium and sodium shifts in ex situ and in vivo models. In both models, we observed increased potassium uptake by hypothermic machine perfused livers after reperfusion, which led to a decrease in blood potassium levels. Conversely, DHOPE-preserved livers showed a higher sodium output compared to conventional preserved livers. High potassium uptake was associated with a better viability of the liver graft.
Preservation of intracellular potassium may also be important to maintain skeletal muscle mass. Muscle wasting is an important complication of several chronic diseases, such as heart failure, and independently related to lower survival. The addition of angiotensin and aldosterone inhibitors to standard therapy has led to a profound increase in survival in heart failure patients. In Chapter 6 we stated our hypothesis that the potassium sparing nature of these inhibitors may lead to an increase in total body potassium and therefore to a preservation of skeletal muscle mass. If this medication does indeed lead to an increase in total body potassium has to be demonstrated by either potassium balance studies or 40K scintigraphy.

We described long-term changes in the incidence of dysnatremia in the intensive care and its association with mortality in Chapter 7. In this chapter, we studied all sodium measurements of two university hospital ICUs over a 21-year period. We observed a striking shift in the pattern of ICU-acquired dysnatremias: the incidence of hyponatremia almost halved (47% to 25%, \( P < 0.001 \)), whereas the incidence of hypernatremia almost doubled (13% to 24%, \( P < 0.001 \)). Severe dysnatremia was significantly associated with higher mortality. We concluded that the higher incidence of hypernatremia is probably due to changes in therapy and therefore often ICU-acquired. ICU-acquired hypernatremia should thus be preventable and its incidence may therefore be considered as indicator of quality of care.

There is some evidence that sodium can be stored without expansion of the extracellular volume (ECV) (i.e., nonosmotically). This phenomenon has been described in various patient groups, but has not yet been demonstrated in critically ill patients. In Chapter 8 we aimed to identify the possibility of nonosmotic sodium and chloride storage with balance studies. We used meticulously recorded fluid, sodium and chloride balances of the first 4 ICU days. The balances could not account for 296 mmol (111 to 566 mmol) of sodium and 243 mmol (62 to 471 mmol) of chloride during this period. We were the first to describe missing osmotically active chloride in humans. We suggest that the apparent disappearance of both considerable amounts of sodium and chloride from the extracellular space, might result from movement into the ICV, without invoking non-osmotic storage. The exact mechanism behind the disappearance of sodium and chloride certainly requires further study.

Muscle mass is an important determinant to survive critical illness and is associated with morbidity and mortality in critically ill patients, but it is difficult to quantify in ICU patients. Many methods, such as MRI, CT or anthropometric measures, are not suitable for usage in the ICU. Urinary creatinine excretion (UCE) as a surrogate for muscle mass, has been shown to be strongly associated with mortality in various patients groups. However, it has not been evaluated in the critical ill. In Chapter 9 we studied the relation of baseline UCE excretion with short-term and long-term mortality in critically ill patients. We included 6,151 patients with 11,198 UCE measurements. We found that in ICU patients without severe renal dysfunction, low urinary creatinine excretion at ICU admission is strongly and independently associated with both short-term and long-term mortality. This underscores the importance of low muscle mass as risk factor in ICU patients and the relevance of UCE as a possible biomarker.
Critical illness induces loss of muscle mass, which can add up to more than 10% in the first week of ICU admission. It has been observed earlier that prolonged ICU admission leads to a decrease in both UCE and serum creatinine. However, the time course of UCE during ICU admission has not been described in detail. Also the time courses of estimated renal function as calculated by various frequently used formulas, that often use serum creatinine as input variable, have not been described. In Chapter 10 we studied the time courses of UCE, measured creatinine clearance, estimated creatinine clearance and estimated glomerular filtration rate (according to the Modification of Diet in Renal Disease (MDRD), Chronic Kidney-Epidemiology Collaboration (CKD-EPI), and Cockcroft-Gault equations). We included a total of 248 ICU patients, with 5,143 UCE and 7,170 serum creatinine measurements. Over 30 days, the relative decrease in UCE was similar for male, female, survivors and non-survivors (1.3, 1.4, 1.2, and 0.9%/d, respectively, $P = 0.39$). We also observed that both the eGFR and estimated creatinine clearance equations became progressively more unreliable during ICU stay. Our findings underscore the intransigent nature of muscle wasting in critically ill patients. The use of UCE may improve assessment of muscle mass and might be superior in monitoring renal function.