CHAPTER 12

GENERAL DISCUSSION
The maintenance of a constant volume and composition of body fluids is essential for homeostasis. Many mechanisms that allow the maintenance of homeostasis have been unraveled. However, there remains much to discover about the acute changes in the fluid and electrolyte compartments in critically ill patients.

In this thesis, we aimed to improve the understanding of the measured biochemical derangements and associated underlying changes in body composition during critical illness. This chapter discusses our main findings and identifies potential future research areas.

**CATABOLISM IN CRITICALLY ILL PATIENTS**

During the first week, a critically ill patient can lose up to 10% of his total lean body mass [1]. Muscle mass is the result of a balance between protein synthesis and breakdown. Critical illness induces marked proteolysis to guarantee a sufficient supply of amino acids to support the synthesis of acute phase proteins and other components of the systemic inflammatory response. This protein imbalance leads to rapid muscle wasting [1].

Due to the loss of muscle mass as well as muscle function, survivors of critical illness can experience significant muscle weakness, which can persist for years [2]. Although more information on the extent of muscle wasting has been gained over the last years, current methods to quantify and monitor and ultimately reduce muscle wasting are cumbersome or inaccurate.

**THE IMPORTANCE OF BASELINE MUSCLE MASS**

Most studies focus on the magnitude of the catabolism that accompanies critical illness, but the muscle mass itself at the onset of critical disease may be an important determinant of the ability of patients to overcome their ICU stay as well. Low muscle mass on ICU admission is independently associated with morbidity and mortality in critically ill patients [1,3]. However, it is still difficult to quantify muscle mass in this patient group, as measures to assess muscle mass are generally poorly suited for ICU patients [4,5]. Anthropometric measurements, such as BMI, waist circumference, mid-arm or mid-thigh muscle measurements are often hampered by the presence of edema, ascites or dehydration. More advanced techniques, such as computer tomography (CT) and magnetic resonance imaging (MRI) are invasive and expensive and not practical for routine use in ICU [6]. Repeated ultrasonography of well-defined muscle parts to measure baseline muscle mass and detect subsequent muscle wasting appears to be a more promising technique. However, this technique also has its limitations and there is no universal protocol yet to measure muscle mass with this method [7].

In various patient groups, urinary creatinine excretion (UCE) has shown to be an easy and inexpensive method to assess muscle mass [8-10]. We showed in Chapter 9 that baseline 24-h UCE, as a marker of muscle mass, is associated with both short-term mortality and long-term mortality in critically ill patients. Although we did not use other measures to assess muscle mass, and therefore could not verify the assumption that UCE solely reflects muscle mass, baseline UCE was a very strong predictor of outcome.

In Chapter 10 we subsequently show that UCE declines during ICU stay in patients who were admitted to the ICU for longer than 30 days. A decrease in UCE during ICU stay was suggested earlier [11]. In this earlier study, the UCE on the day of discharge was lower in long-stay ICU
patients (i.e., more than 7 days) compared to patients who stayed for a relatively short period in ICU. Unfortunately, this study did not have any data on the baseline UCE. Our study was therefore the first to actually show the gradual but very considerable decrease in UCE during ICU stay.

**IDENTIFYING THE ACUTE STRESS PHASE IN CRITICALLY ILL PATIENTS**

Loss of muscle mass and consequently muscle function is a major long-term consequence of critical illness and hugely affects quality of life after ICU admission. The metabolic stress response can be divided into a catabolic (acute) phase and an anabolic (post-acute) phase. The start and end of these phases are not embedded in stone and are different in every patient. Also the occurrence of a new derangement during critical illness, such as a second episode of sepsis, can induce the start of a new catabolic phase [12]. Identification of the current metabolic phase of a patient might be useful to successfully intervene. Interventions, such as nutrition, may be more helpful in the post-acute phase [13].

Over the last years, several studies have investigated the impact of the timing, dose, constitution and route of feeding in the critically ill [14,15]. However, to date there is no universally accepted standard of care defined. One of the challenges is to differentiate the acute phase from the post-acute phase and thus identify a phase in which a patient is possibly ready for enhanced feeding.

A dynamic marker that shows the catabolic rate from day to day could aid in developing nutritional strategies that are based on metabolic signals rather than on a predefined number of days [16,17]. The potassium balance in critically ill patients might be such a dynamic marker (Chapter 4).

Since the vast majority of potassium resides intracellularly, negative balances indicate the loss of ICV during catabolism. If the potassium balance becomes neutral or even positive, this may indicate that the patient is beyond the catabolic phase and may even be anabolic. This knowledge may be used to adapt feeding strategies.

Recently, balances from other intracellular elements have been studied. It has been argued that next to potassium, also phosphate balances may provide information on the presence of catabolism [12,18]. In critically ill children, phosphate balances were shown to be even more accurate than potassium balances [18]. Phosphate balances have not been investigated in critically ill adults and thus have to be studied in this population.

Nitrogen balances are traditionally used to assess the protein balance [19]. They have the disadvantage that total urinary nitrogen has to be calculated from urinary urea nitrogen. Urinary urea nitrogen is assumed to constitute 80 to 90% of the total urinary nitrogen and this can lead to underestimation of the nitrogen excretion in situations with increased excretion of non-urea forms of nitrogen, such as ammonium. This might lead to a false-positive nitrogen balance. Total urinary potassium and phosphate on the other hand can be directly measured. Potassium and potentially phosphate balances could serve as an easy obtainable marker to get more insight in the current phase of the metabolic stress response of a critically ill patient.

Balance studies themselves have other disadvantages [20-22]. They represent events in the preceding 24 hours, causing a delay in information. However, this can be overcome by performing balance studies covering a shorter time period. Possible shorter time periods could be 12
hours, 6 hours or even 2 hours. Covering shorter time periods could lead to a more “real-time” assessment of (new) catabolic events. A requirement to conduct such shorter balance studies is adequately timed urine sampling.

THE CONSTANCY OF THE INTRACELLULAR COMPARTMENT

General physiology models depict the ICV and the ECV as two compartments that are both quite flexible in size. Free water and electrolytes are distributed among the two compartments, leading to an equilibrium. Maintaining a constant ICV, however, is critical for cellular homeostasis [23,24]. Cellular volume changes affect many critical metabolic and signaling processes. Many life forms have developed mechanisms to stabilize the ICV. One of these mechanisms is to rapidly adjust the concentration of osmoles inside the ICV with the help of so-called osmoles [23,26]. These are intracellular molecules, can be generated on short notice to avoid shrinking or swelling by adjusting to intracellular osmolarity to that of the environment. In Chapter 4, a relative constancy or even immediate shrinkage of the ICV in critically ill patients was observed. It was already known that critically ill patients who receive large amounts of fluid retain water and sodium in the ECV. However, this detailed balance study showed that there was a negative potassium balance next to fluid and sodium retention. Although the water balance was strongly positive, the electrolyte-free water (EFW) balance was negative. A decrease of the ICV has been earlier reported in patients after trauma [27]. In these patients, a reduction of TBK and intracellular water was observed, but intracellular potassium concentration remained similar. The loss of body potassium in parallel with the reduction of the ICV is the result of muscle mass loss. An important clinical consequence is that the assumption that administered electrolyte free water (e.g. glucose 5%) does distribute equally over the ECV and ICV in proportion to their relative volumes is not correct.

VIABILITY OF LIVER GRAFTS

The liver serves as an important physiological buffer for enteral potassium loads. The cellular uptake of a potassium load requires active transport by Na+/K+-ATPase [28]. During procurement of liver grafts, lower temperatures are used to reduce the graft’s metabolic requirements and its need for oxygen. Reduced active transport of sodium and potassium then occurs, but passive transport of potassium is facilitated [29]. As a consequence the reperfusion of a liver graft is typically accompanied by hyperkalemia in the recipient. However, a new technique to preserve the liver graft (DHOPE), led to hypokalemia in recipients after reperfusion. During DHOPE liver grafts undergo hypothermic oxygenated perfusion [30]. Liver grafts show increased intrahepatic ATP-levels during DHOPE through the oxygenation of the perfusion fluid whilst they have been ATP-depleted because of previous ischemia. The low temperature during perfusion assists in this restoration of ATP levels [30].

In Chapter 5 we compared potassium and sodium shifts in liver grafts transplanted after the liver graft was preserved by the conventional and the DHOPE technique. We observed significantly higher ATP-levels in DHOPE livers after reperfusion. High ATP-levels significantly correlated with a decrease in recipient serum potassium levels upon reperfusion. Also, increased recipient potassium levels correlated with high peak ALT. A decrease in serum potassium might therefore be an useful marker of early function of liver grafts. The observed decrease in serum potassium was mirrored by an increase in serum sodium, which emphasizes the proper early function of the Na+/K+ pump.
SODIUM DERANGEMENTS IN THE CRITICALLY ILL

In Chapter 7 we showed that hypernatremia is often iatrogenic and associated with mortality. Infusion with sodium-based fluids, although used on a routine basis, are thus not without danger. Sodium-based fluids are commonly used in clinical practice as it is believed that only these fluids will expand the ECV, without significant and unwanted expansion of the ICV [31]. Other fluids, such as glucose/saline mixtures, are believed to distribute among both compartments. However, in Chapter 4, we were not able to demonstrate any increase in the ICV by rapid infusion of large fluid volumes. As homeostasis aims for a constant ICV, the conventional theory that fluid will distribute evenly among the compartments until equilibrium is to be questioned. Further studies are needed to investigate if different fluid regimens, such as sodium-free solutions, do indeed have the same effect as sodium-based infusion fluids.

A SUB-COMPARTMENT IN THE EXTRACELLULAR COMPARTMENT?

Recently, the accumulation of hypertonic sodium in peripheral tissues such as the skin has been reported [32,33]. This remarkable claim challenges the conventional assumption on the distribution of sodium. A sub-compartment of the extracellular compartment, in which sodium is stored non-osmotically, was postulated. In this “sub-compartment”, sodium is presumably bound to glycosaminoglycans in the skin. The role of chloride, the major circulating anion, in this postulated mechanism is unclear. Although the exact clinical significance of such a possible non-osmotic storage mechanism has not been verified, it might be related with hypertension [34,35]. The existence of non-osmotic sodium storage has been studied in varied patient groups, but not in critically ill patients.

In Chapter 8 we demonstrated with balance studies a significant disappearance of both sodium and chloride in critically ill patients. We were the first to demonstrate this phenomenon in this patient group. However, our study was not designed to identify the location of the missing sodium and chloride. One of the possibilities is that this missing sodium and chloride is indeed stored non-osmotically in tissues such as the skin and muscle. A major problem with this explanation is that no plausible mechanism for non-osmotic chloride storage exists. However, another key alternative is movement of sodium and chloride into the ICV [36]. Patients in Chapter 8 were known to have a negative potassium balance, which might point towards the possibility of sodium redistribution toward the ICV. In healthy volunteers, it has been demonstrated that muscle damage can lead to accumulation of sodium and chloride in the intracellular compartment [37]. As critically ill patients often suffer from critical illness myopathy, this might also be a possible scenario.
FUTURE PERSPECTIVES
CATABOLISM IN CRITICALLY ILL PATIENTS
This thesis provides several new potential markers to gain more insight into the changes in body composition during critical illness.

As it remains difficult to assess muscle mass and therefore to assess the impact of muscle mass wasting on survival, UCE could serve as an adequate surrogate. It is possibly an easy assessment of muscle mass to accurately identify low muscle mass at baseline. UCE provides important prognostic information and might possibly improve prognostic scores. Validation of our findings should be performed in large multicenter studies. Ideally, adequate adjustments for renal function and other techniques to assess muscle mass should be compared.

Potassium balances, and potentially phosphate balances as well, could aid the intensivist in providing nutritional or other support. This could be adjusted to the corresponding metabolic phase of the patient and therefore tailored support can be provided. A combination with UCE might even provide more information on nutritional success [18]. Balances could also serve as a secondary endpoint in nutrition trials. Balances are an relatively easy method, with the only challenge that urine samples have to be adequately collected.

THE CONSTANCY OF THE INTRACELLULAR COMPARTMENT
New techniques to adequately preserve, and to even enhance, the function of the liver graft before transplantation are being developed. A decrease in potassium levels upon reperfusion might be a good marker of ATP function in liver grafts. Future studies are necessary to confirm the utility of potassium levels as an early marker of liver function.

The water and salt homeostasis in critically ill patients remains a very challenging topic. The existence of a possible non-osmotic storage should be further studied, with more thorough techniques such as $^{23}$Na and $^{39}$Cl MRI or skin biopsies. However, even with these advanced techniques, it is difficult to differentiate signals from the intracellular and extracellular compartment. MRI is now unfortunately only able to detect the total $^{23}$Na signal and does not differentiate between fluid compartments. Nonetheless, regardless of the existence of a sub-compartment, the need to explore the increased use of infusion fluids that contain less or no sodium is obvious.
CONCLUSION

Changes in body composition due to critical illness remain intriguing. We showed that urinary creatinine excretion provides important prognostic information. Potassium balances are possibly a good marker to immediately demonstrate and quantify loss of ICV and may provide assistance in guiding nutritional therapy. More than 150 years after Claude Bernard introduced the concept of the milieu intérieur, we can still conclude that the constancy of the intracellular compartment is of utmost importance. The ability of the liver graft to retain its potassium intracellularly might be a good early marker of liver graft function. The postulated existence of a sub-compartment in which sodium (and chloride) are nonosmotically stored requires further proof. Increased use of infusion fluids such as glucose 5% may not be as detrimental for volume resuscitation in critical disease as previously assumed.
REFERENCES
