The art of balance
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CHAPTER 1
- GENERAL INTRODUCTION
Challenges are all around us in everyday living and stress helps us to cope with changes in our surroundings, as well as with internal stressors. The response to stress is an elaborate mechanism that has evolved over millions of years and exists in all animals. Although it is an important and basal mechanism, it is not yet fully understood. Throughout history, many scientists have tried to get a better understanding of the concept and mechanisms of stress.

In the 19th century, Claude Bernard introduced the concept of a milieu intérieur (a stable internal environment) where animal cells are kept constant through bodily compensatory mechanisms [1]. He stated that the constancy of the intracellular environment was an essential condition for life and should be restored rapidly to survive serious derangements. This concept evolved further by the work of Walter Bradford Cannon who named it homeostasis. Illness would occur when homeostatic systems failed to keep physiology within normal values [2].

David Cuthbertson observed loss of lean body mass in patients after trauma. These patients had a higher urinary excretion of intracellular components, such as nitrogen, potassium and creatinine [3]. Cuthbertson hypothesized that trauma patients used the protein derived from their lean body mass as an energy source. He later described the metabolic response to severe stress as three phases, i.e., the ebb phase, the initial flow phase and the late flow phase. The ebb (shock) phase starts with a decrease in metabolic activity, increases in blood glucose and sodium retention. The flow (post-shock) phase starts after 3 to 10 days when an increased catabolic state leads to a negative nitrogen balance, proteolysis and decrease in fat stores. The excretion of intracellular components is markedly increased during this phase. When patients start to improve, the flow phase ends and the catabolic state is reverted to an anabolic state [4]. Later, other scientists have defined these three phases differently, but they can all be summarized as an acute phase, an established phase and a recovery phase with the goal to restore homeostasis [5].

**HUMAN BODY COMPOSITION**

Homeostasis is maintained by keeping a relatively constant volume and composition of body fluids. Two compartments can be distinguished to where the key electrolytes are distributed: the extracellular volume (ECV) and the intracellular volume (ICV). The ECV can be further divided into the interstitial compartment and the plasma volume. The ECV covers around 43% of the body fluids, whilst the ICV makes up around 57% of the total body fluid [6].

The percentage total body fluid or total body water (TBW) varies per person [6-8]. In an average man, the TBW is about 60 percent of his body weight. Skeletal muscle mass accounts for a large part of TBW and makes up 40 to 50% of TBW. The percentage of TBW depends on age, gender and degree of obesity [6]. Total body water normally decreases with age, mainly because of an increase in fat percentage and a decrease in skeletal muscle mass. As women usually have a greater fat percentage as well, their TBW is lower and is around 50 percent of their total body weight. Babies on the contrary have a higher TBW, which is around 70 percent of their body weight [9,10](Figure 1).
Total body water is depicted in blue and in percentages. All values are depicted for Caucasian subjects [7,9,10]. Infants have a considerably higher TBW percentage. Men also have a higher TBW percentage compared to women, mainly because they have more muscle mass and less body fat. As a person gets older, the TBW decreases.
Figure 2. Fluid compartments and electrolyte distribution.

In red the ICV is depicted, with its major cation potassium. In yellow the ECV (including plasma and interstitium) is depicted, with its major cation sodium. Water, potassium and sodium can be exchanged between the ICV and ECV.

The left image depicts the normal distribution of water, potassium and sodium among the compartments. In an average man, the ECV is around 43% of the TBW and the ICV is around 57% of the TBW. The ICV is mainly skeletal muscle mass.

The right image depicts the loss of muscle mass as it occurs in critically ill patients. As skeletal muscle mass makes up 75% of all cells, this leads to a reduction of the ICV. At the same time, the ECV increases, due to sodium and fluid retention. Adapted from Guyton, et al. [11].

The ECV and ICV are separated by cellular membranes and have a different composition of electrolytes. The major cation of the ECV is sodium. Almost 98% of total body sodium resides in this compartment. Potassium is the major cation of the ICV and mirrors sodium with around 95% of total body potassium located in the ICV (Figure 2). Both are the principal determinant of the osmolality in their respective compartment and both are related to the volume of water in their compartment.

**CHANGES IN HUMAN BODY COMPOSITION**

As Cuthbertson already observed, the stress response accompanying critical illness leads to loss of lean body mass, especially of skeletal muscle mass [12]. Lean body mass can be defined as the fat free mass of the body. Critically ill patients can lose more than 10% of lean body mass in the first week of intensive care unit (ICU) admission. ICU survivors consequently often experience significant skeletal muscle weakness, which can persist for more than 5 years [13]. It is therefore not surprising that muscle wasting in critically ill patients is associated with increased morbidity and mortality [13,14].

Muscle mass is maintained by a balance between protein synthesis and breakdown. Wasting or catabolism occurs when there is a net loss of protein, as occurs in times of stress such as critical illness, under the influence of stress hormones and inflammatory mediators. Immobility and systemic inflammation lead to a decreased protein synthesis [13]. In critically ill patients the severity of injury, increase of pro-inflammatory cytokines, oxidative stress and exogenous glucocorticoids all contribute to muscle wasting [15].
The increase in protein turnover during critical illness is coupled to an increase in gluconeogenesis and loss of nitrogen. Nitrogen balances are therefore often used as a reflection of protein balance [16]. However nitrogen balances also have shortcomings and will generally result in an overly positive balance, which leads to an underestimation of protein requirements [17].

Catabolism, and thus changes in the body composition, could possibly also be assessed by another technique. Muscle wasting leads to a decrease in body cell mass (BCM). BCM is the totality of all cells in the body and the metabolic active compartment of lean body mass [18]. BCM is larger in males compared to females, again because males usually have a larger skeletal muscle mass. BCM is proportional to total body potassium. Therefore, the golden standard to measure BCM is the measurement of total body potassium (TBK) with 40K scintigraphy [18,19].

**POTASSIUM**

The ease of measurement of the extracellular sodium concentration, is the exact opposite of that of intracellular potassium [20]. Although, TBK can be assessed by 40K scintigraphy [18], it is a cumbersome method that is not very suitable for bedside measurements. TBK and thus BCM is known to decline during muscle wasting. However, one can argue that in order to detect or quantify a decrease in BCM, which in critically ill patients will often be due to catabolism, only measuring the change in BCM and thus the change in TBK is sufficient. A method to identify such changes is to perform balance studies. Balances are defined as the difference between the total output and the total intake. A negative balance indicates a loss. Net potassium loss under a constant serum concentration can only originate from the ICV [21]. In various patient groups experiencing loss of BCM, such as surgical, burn and pediatric patients, negative potassium balances have been observed [22-26]. Balance studies could therefore be a feasible approach to determine changes in TBK and thus BCM [20].

**SODIUM**

The most notable and rapid change during the catabolic state that accompanies acute critical illness is an increase of the ECV because of sodium and fluid retention [6, 27]. During treatment in the ICU, patients receive large amounts of sodium-based fluids as part of their resuscitation therapy to minimize vascular leakage. This can lead to sodium accumulation and iatrogenic hypernatremia. Hypernatremia may result in increased morbidity and mortality and this complication of the intravenous therapy is thus not without risks. Moreover, the generally accepted model on sodium homeostasis, which states that sodium is distributed among only two compartments (i.e., the ECV and the ICV) has been challenged. Recent studies have suggested that sodium can also accumulate without weight gain or hypernatremia in a sub-compartment of the extracellular compartment [28]. Whether this also occurs in critically ill patients and if this sub-compartment is altered by critical illness has not yet been studied.

**CREATININE**

Creatinine is the stable end product of creatine, which is predominantly present in muscle where it is converted to creatinine in a steady rate. After creatinine is released into the circulation, it is almost completely excreted in the urine [29]. In steady state conditions, urinary creatinine excretion will therefore be equal to creatinine production, irrespective of circulating creatinine. Twenty-four hour urinary creatinine excretion is almost perfectly correlated with lean body mass, as assessed by 40K studies [30].
In stable outpatients, measurement of creatinine excretion in 24-hour urine collections is a widely accepted method for muscle mass estimation and creatinine clearance [24, 31-33]. Although it has not been well studied in critically ill patients, a decrease in creatinine excretion has been observed in ICU patients after seven and fourteen days of ICU stay [34], which may be a reflection of the muscle loss these patients experience. In other patient groups, such as chronic kidney disease patients, it has been proposed that UCE might be a suitable marker to quantify the decline in muscle mass [32].

OUTLINE OF THESIS
This thesis focuses on acute changes in the composition of the fluid and electrolyte compartments in critically ill patients and aims to get a better understanding of the biochemical derangements in critically ill patients during these changes.

Potassium homeostasis is often disturbed during critical illness and such disturbances can induce severe complications such as cardiac arrhythmias and death [35]. After the observation of a potential beneficial effect of tight glucose control [36], our ICU introduced a nurse-centered, computerized decision support glucose regulation protocol (GRIP, glucose regulation in intensive care patients) in 2004 [37, 38]. As potassium regulation has many similarities with glucose control, a potassium regulation algorithm was integrated within GRIP (GRIP-II, glucose and potassium regulation in intensive care patients) [39].

In Chapter 2, we evaluated the relation between serum potassium, potassium variability and in hospital mortality during ICU admission as well as the effect of computer-driven potassium regulation.

As previously stated, potassium derangements can induce cardiac arrhythmias [35]. However, it is unknown if subtle changes within the normal range can also affect the incidence of atrial fibrillation. The GRIP-COMPASS trial compared the incidence of atrial fibrillation between two serum potassium targets that were both within the normal range in cardiac surgery patients. The results of this prospective study are described in Chapter 3.

After we discovered consistent negative potassium balances in GRIP-COMPASS patients which we did not fully understand, we further explored this in Chapter 4. In this chapter, we closely examined the fluid, sodium and potassium balances in cardiothoracic ICU patients. It is known that the initial days of ICU admission are accompanied by sodium and water retention and thus an expansion of the ECV [40]. However, the potassium balance and thus the change in the ICV of critically ill patients has not yet been studied.

The stability of the ICV is likely to be important for all organs of the body and the ability to maintain or regain stability of the ICV probably also influences the viability of an organ after transplantation. In Chapter 5 we evaluated potassium and sodium shifts during reperfusion of transplanted livers in both ex vivo and in vivo models and its relation with the viability of the liver graft.

Cachexia as a comorbidity is not only seen in critical illness. Heart failure patients constitute only one of the many patient groups that also suffer from this comorbidity. Survival of heart failure patients has greatly improved after the addition of potassium-sparing agents, such as
ACE inhibitors and spironolactone, to conventional treatment [41,42]. In Chapter 6, we postulate that the beneficial effects of these agents partly result from preserved total body potassium with consequent muscle mass preservation.

Critical patients are at risk of developing both hyponatremia and hypernatremia. Both can be caused by factors associated with critical illness, such as reduced urinary concentrating ability, increased insensible losses and increased activity of antidiuretic hormone. However, iatrogenic causes such as fluid administration and drugs are also associated with the development of sodium derangements. Both hyponatremia and hypernatremia are associated with a higher morbidity and mortality in critically ill patients. In Chapter 7 we analysed long-term changes in the incidences of sodium derangements and their association with therapy shifts over the course of twenty years.

Conventionally, sodium homeostasis is explained by a two-compartment model with intracellular and extracellular compartments where ions are completely dissolved, i.e., osmotically active. Recently, a sub-compartment of the extracellular compartment has been proposed [28] over which sodium is stored nonosmotically active without causing a volume expansion of the extracellular compartment. As critically ill patients receive large amounts of sodium-based fluid, we studied in Chapter 8 whether sodium is stored in such a compartment in critically ill patients.

Muscle mass plays an important role in the ability of critically ill patients to overcome their disease. A low muscle mass is associated with morbidity and mortality in critically ill patients [13,43]. However, muscle mass is difficult to quantify in ICU patients. In Chapter 9 we investigated the relation between baseline urinary creatinine excretion, as marker of muscle mass, with short- and long term outcome in ICU patients.

Although a decrease in UCE has been observed in ICU patients after prolonged ICU admission [34], the time course of UCE has not been described in detail in this patient group. Muscle wasting may be expected to lead to decreases in serum creatinine as well. Therefore, eGFR and creatinine clearance equations that use serum creatinine as input variable may become unreliable during ICU admission. In Chapter 10 we described the time course of urinary creatinine excretion, measured creatinine clearance and estimated glomerular filtration rate over the course of 30 days of ICU admission.


