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Volume Balance in Chronic Kidney Disease: Evaluation Methodologies and Innovation Opportunities

Edoardo La Porta[a, b] Luca Lanino[b] Marta Calatroni[c] Elena Caramella[d] Alessandro Avella[e] Caroline Quinn[f] Alessandro Faragli[g, h, i, j] Luca Estienne[k] Alessio Alogna[h, i, j] Pasquale Esposito[l]

[a]Department of Cardionephrology, Istituto Clinico Di Alta Specialità (ICLAS), Rapallo, Italy; [b]Department of Internal Medicine (DIMI), University of Genoa, Genoa, Italy; [c]Division of Nephrology, Humanitas Clinical and Research Center, Milan, Italy; [d]Division of Nephrology and Dialysis, Ospedale Sant'Anna, San Fermo della Battaglia, Como, Italy; [e]Division of Nephrology and Dialysis, Ospedale di Circolo e Fondazione Macchi, Varese, Italy; [f]Department of Biological Sciences, Rensselaer Polytechnic Institute, Troy, NY, USA; [g]Department of Internal Medicine and Cardiology, Deutsches Herzzentrum Berlin, Berlin, Germany; [h]Department of Internal Medicine and Cardiology, Campus Virchow-Klinikum, Charité – Universitätsmedizin Berlin, Berlin, Germany; [i]Berlin Institute of Health (BIH), Berlin, Germany; [j]DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany; [k]Department of Nephrology and Dialysis, SS. Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy; [l]Division of Nephrology, Department of Internal Medicine, Dialysis and Transplantation, University of Genoa and IRCCS Policlinico San Martino, Genoa, Italy

Keywords
Chronic kidney failure · Heart failure · Body water · Electric impedance · Telemedicine

Abstract
Background: Patients affected by chronic kidney disease are at a risk of cardiovascular morbidity and mortality. Body fluids unbalance is one of the main characteristics of this condition, as fluid overload is highly prevalent in patients affected by the cardiorenal syndrome. ***Summary:*** We describe the state of the art and new insights into body volume evaluation. The mechanisms behind fluid balance are often complex, mainly because of the interplay of multiple regulatory systems. Consequently, its management may be challenging in clinical practice and even more so out-of-hospital. Availability of novel technologies offer new opportunities to improve the quality of care and patients' outcome. Development and validation of new technologies could provide new tools to reduce costs for the healthcare system, promote personalized medicine, and boost home care. Due to the current COVID-19 pandemic, a proper monitoring of chronic patients suffering from fluid unbalances is extremely relevant. ***Key Message:*** We discuss the main mechanisms responsible for fluid overload in different clinical contexts, including hemodialysis, peritoneal dialysis, and heart failure, emphasizing the potential impact provided by the implementation of the new technologies.

Alessio Alogna and Pasquale Esposito are equally contributing last authors.

karger@karger.com
www.karger.com/kbr

Correspondence to:
Alessio Alogna, alessio.alogna@charite.de

Introduction

The body fluid balance has always represented a critical issue in medicine since chronic and acute volume unbalances are negative prognostic factors in many different settings and conditions. In current practice, the concept of fluid balance and management has replaced the old idea of "hydration," a term used in the past to improperly describe the complex mechanisms behind the regulation of water and solutes in the human body. In this review, we describe the state of the art and new insights in body volumes evaluation and management in patients with chronic kidney disease (CKD), underlying the innovation opportunities provided by the implementation of new technologies.

Fluid Volume Evaluation: An Overview

First, it is important to distinguish the fluid volumes in the human body. The major volume is the total body water (TBW) [1], which in physiologic conditions represents a fixed percentage of the body weight. This percentage progressively decreases with ageing, and it is markedly influenced by the percentage of body fat and sex [2]. TBW can be differentiated in sub-volumes (shown in Fig. 1): intracellular water (ICW) and extracellular water (ECW). In physiologic conditions, ICW accounts for around 2/3 of TBW and 1/3 of ECW.

ECW is more critical to define, representing the volume most exposed to fluid unbalance. It could be further subdivided into 2 volumes: intravascular (IV) and interstitial volume, the latter accounting for 3–4 times more fluid than the former in physiological conditions [3]. Finally, IV or plasma volume (PV) can also be partitioned in more specific sub-volumes, that is, arterial (30–40%) and capacitance vessels (60–70%) [4], while the interstitium can be divided in extracellular matrix and mesothelium (pleura, peritoneum, and tunica albuginea). Otherwise, in specific pathological conditions, other human compartments can accumulate an important amount of fluid, including the bowels, bladder, lungs, and pathologic cavities in soft tissue or parenchyma. In Table 1, we reported changes in fluid volumes distribution between physiological condition and kidney disease (shown in Fig. 1). Red blood cell volume is part of ICW in the description given above, but its analysis and evaluation, together with PV, is of interest in the evaluation of the IV compartment [5].

Physiological and pathological values of volumes can be evaluated by different methods. The first approach historically used to measure the dimension and distribution of fluids in the human body is the indicator-dilution method. It is possible to calculate the volume of distribution of a specific substance starting from a basic correlation between mass volume and concentration: volume = mass/concentration. Injecting the human body with a known mass of a substance and then taking a sample of blood and measuring its concentration after equilibration, allows for volume of distribution of that specific substance to be calculated.

Since the first half of the last century, many substances with different distribution properties have been used to measure the various body fluid volumes. For example, deuterium oxide (heavy water), tritiated water [6, 7], sodium bromide [8], and more recently radiosulfate have been used to measure TBW and ECW [9]. Dilution methods have also been used to quantify IV, by studying the volume distribution of plasma or red cells dyes, such as Evans blue, indocyanine green, iodine-131 (for plasma),

Table 1. Percentage changes in fluid distribution among body volumes in kidney disease [1–4, 80–82, 121–123]

	TBW, % of BW	ICW, % of TBW	ECW, % of TBW	IV, % of ECW	Interstitial fluid, % of ECW	Reference
Healthy man	60	55	45	20	80	[1–4]
Healthy woman	50	55	45	20	80	[1–4]
Nephrotic syndrome	65–70	40	60	15	85	[121]
CKD early stage 1–3	60	55	45	20	80	[122]
CKD advanced stage 4–5	65	50	50	15	85	[123]
CKD in dialysis	70	40	60	15	85	[80–82]

CKD, chronic kidney disease; TBW, total body water; ECW, extracellular water; ICW intracellular water; IV, intravascular volume.

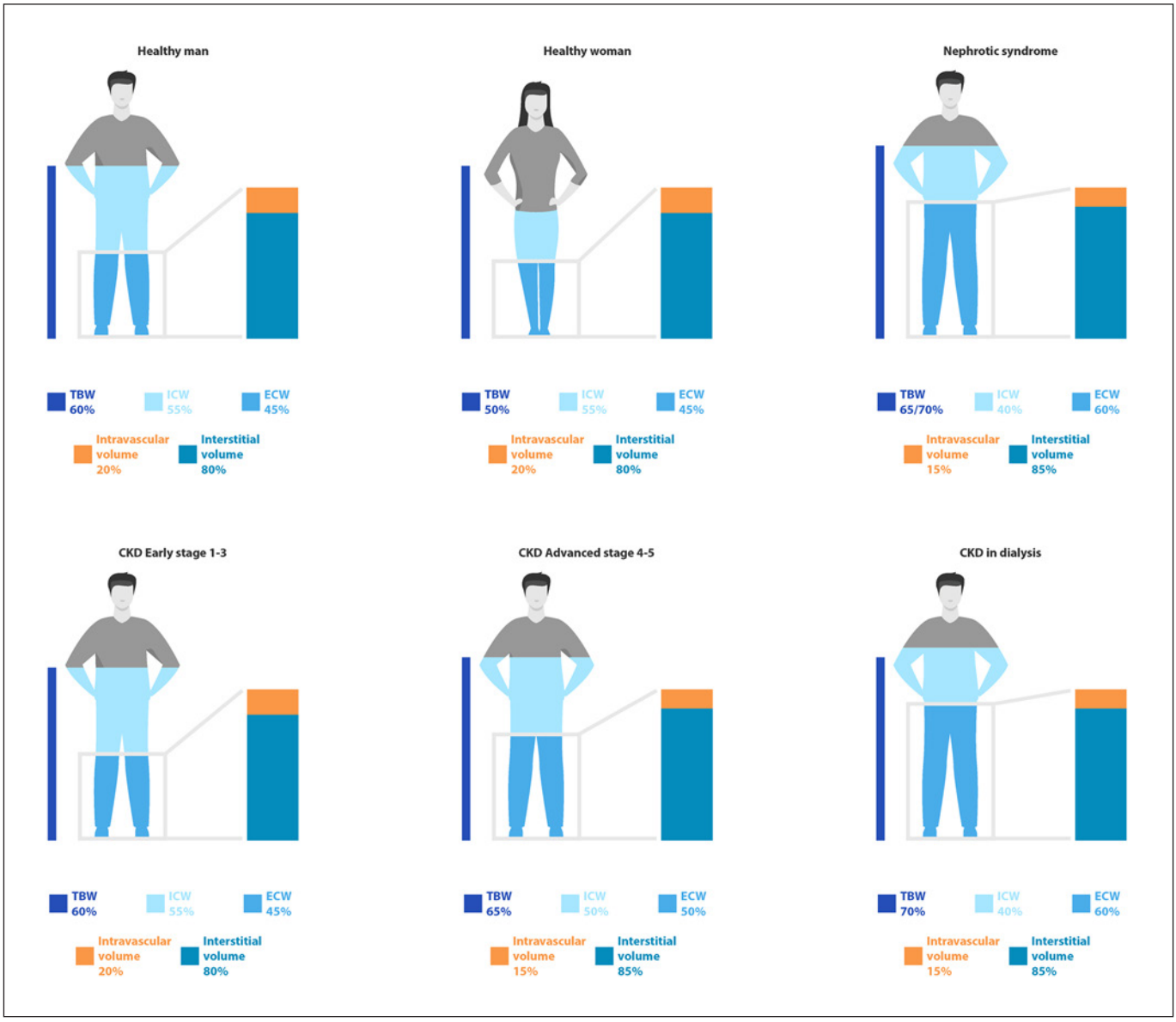

Fig. 1. Body fluids distribution in physiological condition and kidney disease. Graphic representation of different percentages of fluid distribution among CKD stages and nephrotic syndrome, with respect to physiological condition. CKD, chronic kidney disease.

carbon monoxide, and chromium-labelled red blood cells [10, 11]. Anyway, dilution methods, despite their high accuracy, are limited to specific research uses, since they are invasive, expensive, and not easy to perform. Other methods have been developed to evaluate fluid volumes status that we can categorize in 2 groups: techniques of quantification and evaluation, that we listed in Table 2.

Quantification techniques, like dilution methods, measure one or more of the fluid volumes previously described and include noninvasive technologies, such as bioimpedance and magnetic resonance spectroscopy (MRS). Instead, evaluation techniques are heuristic methods that can help physicians in the clinical setting for the evaluation of the fluid volume status. They can include physical examination, blood pressure, central venous pressure (CVP) measurements, ultrasonography, biomarkers, etc. This distinction is not strict, but it is useful to facilitate the understanding of this topic.

Table 2. Advantages and disadvantages of methods of volume quantification and evaluation [6–34]

Methods	Advantages	Disadvantages
Quantification methods		
Dilution methods (e.g., radioisotopes) [6–11]	Very high accuracy and reproducibility	Not suitable in the clinical setting. Time spending. Invasive. High costs
Magnetic resonance spectroscopy [12–13]	Accurate, noninvasive	Not suitable in the clinical setting. Expensive. Time spending
Bioimpedance analysis [14–16]	Fast, reproducible, noninvasive, and cost-effective	Available equations are not validated in different clinical settings
Evaluation methods		
Physical examination (vital signs, edema, and dryness) [17]	Inexpensive and available in every clinical setting	Very poor sensitivity, operator-dependent
Catheterization (e.g., CVP, PCWP) [18–20]	Sensitive, fast, and reproducible	Invasive; susceptible to errors due to acute HF; risk of complications related to the procedure
Imaging: chest X-ray [17]	Fast, reproducible	Radiation exposition, poor sensitivity
Imaging: US vena cava [21–24]	Sensitive, fast, cost-effective, and noninvasive	Operator-dependent, training needed; limited feasibility in overweighted patients
Imaging: lung US [25–30]	Sensitive, fast, cost-effective, and noninvasive	Operator-dependent, training needed
Biomarkers (e.g., BNP and NT-proBNP) [31–34]	Sensitive, reproducible, and cost-effective	Influenced by kidney and HF, inflammation, sepsis, and other conditions

CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; US, ultrasound; BNP, brain natriuretic peptide; NT-proBNP, N-terminal-pro-b-type natriuretic peptide; HF, heart failure.

Techniques of Fluid Volume Quantification

All methods that are able to quantify body fluid volumes belong to this group. The most well-known and used, in addition to dilution techniques, are MRS and bioimpedance analysis (BIA). MRS can be used both in vivo and in vitro studies, and it has a very wide scope of application in research, ranging from the study of organ metabolism and tissues to the measurement of body fluids, obtaining functional data together with anatomical evaluation [12]. Unlike magnetic resonance (MR), MRS can detect signals from atoms other than hydrogen such as phosphorus, carbon, and sodium providing information about adenosine triphosphate, glycolysis, and many other metabolites and metabolic pathways. Interestingly, a new MR technique has been described, the sodium MR that uses strong magnetic fields, magnetic field gradients, and radio waves to generate images of the distribution of sodium in the body. Coupled with conventional MRI, sodium MRI allows the absolute quantification of tissue sodium concentration and water content [13]. However, MRS and MR-based approaches are not suitable for clinical practice. On the other hand, techniques based on BIA are cost-effective, simple, and widely used in the clinical setting. BIA is based on the analysis of bioelectrical information obtained by the passage of an electrical impulse through the body to measure fat mass, fat-free mass, TBW, ECW, and ICW. Body water evaluation using BIA is based on the inverse correlation between resistance and the amount of fluids (water and electrolytes) [14]. Different BIA techniques and methods have been developed: whole-body tetrapolar or localized, single frequency or multifrequency, bioimpedance vectorial analysis, and bioimpedance spectroscopy.

These techniques usually work by using regressive equations built comparing collected data from their measurements with reference methods, such as dilution methods. The accuracy of these equations mainly depends on certain assumptions made during the "model building" phase and the statistical significance of the analyzed samples. For example, BIA equations developed in a setting of healthy and young subjects could give very inaccurate results when applied to elderly patients with sarcopenia

[15]. Bioimpedance methods are also very helpful in the nutritional assessment in the clinical setting and the follow-up of the outpatients [16], especially in hemodialysis (HD) patients, as recently demonstrated by Battaglia et al. [17], that showed a high correlation between BIVA and muscle mass, measured with US technique.

Techniques of Fluid Volume Evaluation

These methods are not able to quantify body fluid volumes, but they provide information about volume status or hemodynamic assessment of patients. Depending on the clinical setting, invasive or noninvasive techniques can be used, including physical examination, measurement of blood pressure and the heart rate, X-ray, ultrasonography, and invasive hemodynamic monitoring or biomarkers. Physical evaluation and basic clinical parameters have lower specificity and sensitivity compared to more sophisticated methods, but represent a good starting point for further evaluations [18].

Invasive techniques do not provide a direct evaluation of volume status, but they are accurate methods for hemodynamic monitoring. Indeed, the measurements of CVP and pulmonary capillary wedge pressure agree with right and left atrial pressure are extremely useful for the hemodynamic assessment of critically ill patients [19]. Nevertheless, while central venous and arterial catheterization remain the most used for this method [20], other noninvasive hemodynamic markers, such as pulse pressure, systolic pressure variation, and stroke volume variation, can detect early phases of fluid unbalance [21]. Nonetheless, the evaluation of hemodynamic assessment should be interpreted together with the global clinical status and represents only an indication for the evaluation of the body volume status.

Ultrasonography is widely applied in the study of the inferior vena cava (IVC) size, which changes consistently with CVP and IV. Ultrasound evaluation of IVC is a bedside and noninvasive method of CVP estimation that provides quite a good correlation with the invasive measurement of CVP [22]. Physiologically, during inspiration, intrathoracic pressure becomes negative and intra-abdominal pressure increases, leading to increased venous return and a decreased IVC size (collapsibility index). Instead, in patients with fluid overload and venous congestion, the IVC size is frequently increased, and its physiological collapse decreased [23]. In 2015, the American Society of Echocardiography published a recommendation about ultrasound evaluation of IVC: the measurement should be taken with the patient in the supine position, from the subcostal view, with the IVC displayed along its long axis. No recommendations were given about the phase of the respiration to measure the maximum and the minimum diameter during the breathing. Moreover, the measurement of IVC collapsibility index (IVCCI) was recommended, where IVCCI = (IVC max − IVC min)/IVC max [24]. However, despite its routine use, this technique displays a significant inter-operator variability, that could be partially overcome simplifying the IVC measurements and performing short training sessions [25].

Lung ultrasound (LUS) has become, thanks to the possibility to identify pleural effusion and B-lines or "ring-down artefact," which are long, hyperechoic lines originating from the pleura, a bedside tool for the evaluation of central circulation congestion. In clinical practice and various scientific paper, B-lines are improperly associated to "comet-tail artefact," which instead are caused by different reflective interfaces [26].

Several LUS strategies to assess B-lines are used, based on the number of sectors examined and the B-lines count, and different scores have been proposed. The more B-lines are detected, the more significant the result of the examination becomes and the worse the severity of the extracellular volume (ECV) overload [27]. One of the most used approaches, in different studies, employs the exploration of 28 sectors and 5 B-lines as the threshold for a clinically significant pulmonary congestion [28]. Anyway, in the clinical routine, protocols with less sectors (e.g., 6–8 sectors) are usually preferred for point-of-care ultrasound [29, 30]. Different probes and frequencies can be used to perform LUS, but an ultrasound penetration between 4 and 8 cm is recommended [31]. In the last several years, thanks to the improvement of artificial intelligence (AI), new methods of automatic detection and quantification of B-lines have been developed. These kinds of approaches have shown the potentialities to be advantageous in terms of faster data analysis and applicability to large sets of data without increased costs [32], and they will be probably adopted in the clinical setting in the coming years. Finally, several biomarkers have been studied for the evaluation of fluid volume status (both for fluid overload and hypovolemia), yet only a few of them have entered the daily clinical routine.

In the field of nephrology, the most simple and reliable markers to estimate fluid volume are serum blood urea nitrogen to creatinine ratio and fractional excretion of sodium. In particular, in states of hypovolemia with intact tubular function, blood urea nitrogen is expected to rise out of proportion to plasma creatinine concentration (serum urea/serum creatinine >100) [33], while urinary sodium excretion decreases (urinary sodium <10–20

mmol/L or fractional excretion of sodium <1%) [34], due to avid urea and sodium reabsorption by the proximal tubule. These methods are not very specific, and they are affected by the underlying clinical conditions, such as in cases of concomitant renal and/or cardiac dysfunctions. Instead, biomarkers of heart failure (HF) such as B-type natriuretic peptide (BNP) or N-terminal-proBNP (NT-proBNP) were shown to be helpful in the diagnosis of fluid overload, particularly in correlation with HF [35]. The concentration of these biomarkers increases in the bloodstream when left ventricular cardiomyocytes are stretched by preload, and are highly reproducible and widely available. However, the value of these volume biomarkers in the specific setting of CKD patients has been questioned due to evidence showing that they can accumulate in patients with renal dysfunction [36].

Volume Balance and Evaluation in Different Clinical Settings of CKD Patients

Volume Balance in CKD and HF

Patients with cardiac and renal diseases frequently show shared elements in their clinical presentation [37]. So, HF patients often manifest a degree of renal dysfunction, while CKD patients, especially in the later stages, present an increasing prevalence of cardiac disorders [38, 39]. Due to the tight connection between heart and kidney diseases, the term "cardiorenal syndrome" has been proposed to facilitate the classification of these conditions [40]. Cardiorenal syndrome comprises of a complex pathophysiology involving renin-angiotensin system activation, the sympathetic nervous system, and hemodynamic alterations [41]. The spectrum of kidney and heart diseases is very wide, but alterations of water balance and sodium handling are common pathogenetic features and important prognostic factors, considering that the presence of volume unbalance in these conditions is a predictor of worse outcome.

In CKD patients, sodium retention occurs as the result of the relationship between the glomerular filtration rate, sodium excretion, and ECV [42]. Indeed, while in normal subjects, at a steady state, there is a linear relationship between ECV and sodium excretion, which regulates blood pressure, in CKD this system is impaired [43].In CKD patients, salt ingestion is followed by an increase in sodium excretion per residual nephron, as a part of the adaptive response to reduced nephron number, leading to increased sodium excretion [44]. This response should be mediated by some degree of subclinical volume expansion and elevation in the mean arterial blood pressure, and represents a protection against the development of continuous sodium retention and edema formation.

However, this response seems limited in CKD and, most importantly, CKD patients are unable to further adequate sodium excretion in the presence of rapid changes in salt ingestion, so they are prone to develop volume expansion or depletion [45, 46]. In addition, recent works by Titze [47] showed that sodium balance is more complex than previously thought, because of the presence of sodium storage in the skin. This finding is accentuated in CKD patients, and is correlated with left ventricular hypertrophy [48]. So, these pathophysiological alterations may create the conditions for a chronic ECV overload in CKD patients [49, 50].

Chronic fluid overload and LVH establish a vicious circle, as showed in recent study, fluid congestion evaluated with NT-proBNP and BIS measurements is strongly correlated to left ventricular mass index in patients with CKD [51]. To counteract fluid congestion in CKD, both diuretics and water restriction showed efficacy in reducing blood pressure and body fluids, evaluated with NT-proBNP and body weight, without worsening the renal function [52]. On the other hand, in HF patients, the myocardial dysfunction causes arterial underfilling and reduction of renal blood flow, with the consequent reduction of the renal function (forward mechanism) [53]. These events lead to a systematic, sympathetic, and neurohormonal receptor activation; and the net movement of fluid to the IV to preserve organs perfusion [54].

To preserve glomerular capillary pressure (and so the glomerular filtration rate), the kidney can autoregulate through different mechanisms: myogenic adaptation of the glomerular afferent artery, the tubuloglomerular feedback, and the activation of the renin-angiotensin-aldosterone system [55, 56]. On one hand, there is a continuous increase in fluids of the IV compartment, on the other hand, there is a net accumulation of interstitial fluid caused by an alteration in the capillary endothelial permeability [57]. The final effect of this pathway is the proportional increase of the IV and interstitium [58] (shown in Fig. 2). The consequent fluid overload, in turn, can determine the development of tissue hypertension and central venous congestion, which may lead to further worsening of the renal function, perpetuating a vicious circle (backward mechanism) [59].

Volume Evaluation in CKD and HF

The complexity of the physiopathology of the cardiorenal connections accounts for the difficulty of the fluid

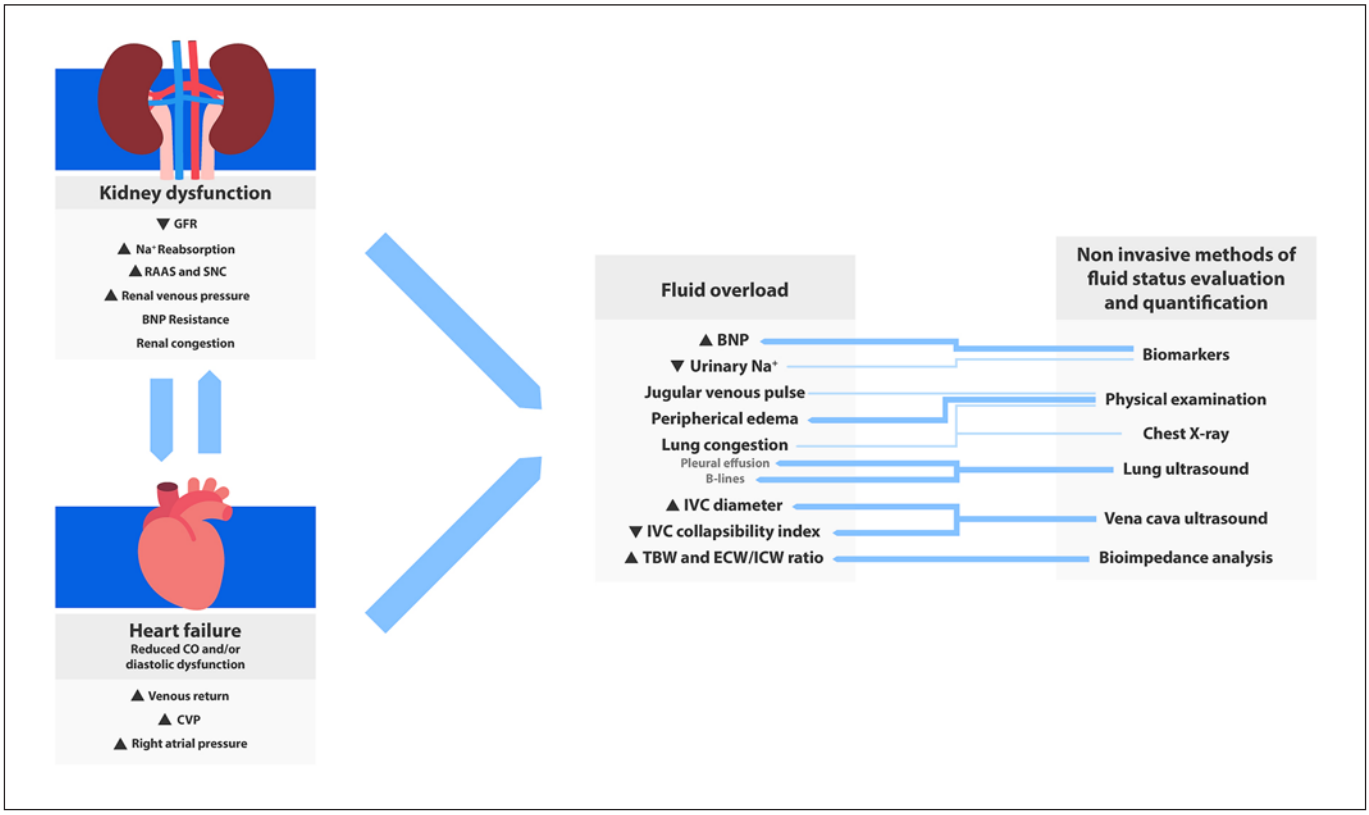

Fig. 2. Mechanisms underlying fluid overload in kidney dysfunction and HF, and noninvasive methods of fluid evaluation and quantification. HF and kidney dysfunction are strictly correlated and co-influenced and participate through various mechanism to establish and exacerbate fluid overload. Clinical and biochemical signs of fluid overload are heterogeneous, and fluid status evaluation is frequently challenging. A multiparametric approach using different noninvasive methods are the preferable approach in outpatients and not in critical patients to evaluate fluid status. Thick lines in the figure suggest most reliable methods. CVP, central venous pressure; ECW/ICW, extracellular and intracellular water; IVC, inferior vena cava; GFR, glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; TBW, total body water; HF, heart failure.

volume assessment in these conditions. Fluid volume assessments are made more challenging by the lack of sensitivity and specificity of physical signs and symptoms (edema and dyspnea). Indeed, edema becomes clinically evident only when it is significant, and it can be present without systemic fluid expansion (e.g., vasodilatory drugs), while shortness of breath leads to 10–20% of false positives [60]. Individually, several indices of HF severity, such as elevated filling pressures, jugular venous pressure, orthopnea, and echocardiographic filling patterns, anticipate higher cardiovascular event rates. Other strategies of noninvasive fluid status assessment include evaluation of the levels of cardiac biomarkers, including natriuretic peptides and cardiac troponins that may also anticipate readmission risk, particularly if they remain high at hospital discharge [61, 62]. In acute HF invasive methods for evaluation of the hemodynamic status, such as pulmonary capillary wedge pressure, CVP, and pulmonary artery resistance could be very useful, for a comprehensive evaluation of the fluid status of a patient [63].

BNP and NT-proBNP are established markers of HF but, as reported above, the coexistence of a concomitant renal dysfunction could considerably change their interpretation. In general, HF is very likely at BNP values >500 pg/mL and an NT-proBNP values >450 pg/mL, even if different cutoffs have been proposed, especially for patients with renal dysfunction [64]. The mechanisms underlying natriuretic peptides elevation in CKD patients are not fully understood. Cardiac wall stress, caused by fluid overload and subclinical ischemia is a tempting hypothesis, but the results from different studies are controversial [65].

Valle et al. [66] investigated a clinical approach based on natriuretic peptides and several BIA measurements for the fluid volume management. Patients were catego-

Table 3. Telemedical trials in HF patients

Study/author	Study type	Patients no. and characteristics	Intervention	Outcomes and comments	References
TELE-HF Chaudhry et al. [74]	Multicenter randomized controlled trial	1,653 patients recently hospitalized for HF	Telephone-based interactive voice system	Readmission or death within 180 days. Not reached	[65]
BEAT-HF Ong et al. [76]	Multicenter randomized controlled trial	1,437 patients hospitalized for HF	Health coaching telephone call and telemonitoring	180 days all-cause readmission. Not reached	[67]
IN-TIME Hindricks et al. [77]	Randomized controlled trial	716 patients NYHA class II and III plus recent implant of dual chamber ICD or CRT-D with telemonitoring function	ICD or CRT-D telemonitoring	The composite clinical score: death, admission, and change of NYHA class. Significant improvement of clinical outcomes	[68]
TIM-HF2 Koehler et al. [75]	Multicenter randomized, controlled, parallel-group, unmasked trial	1,571 patients NYHA class II and III (EF <45% or EF >45% and oral diuretics)	Daily monitoring of body weight, blood pressure, the heart rate, EKG, SpO_2, and a self-rated health status	Reduce the percentage of days lost due to unplanned cardiovascular hospital admissions and all-cause mortality	[66]

NYHA, New York Heart Association; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization defibrillator; HF, heart failure.

rized as early responders, late responders, and nonresponders (based on the BNP fall after therapy), to allow physicians to identify high-risk patients. They report lower 6 months readmission rate in patients admitted to the hospital for acute HF and reduction of the health-care costs [66]. IVC diameter and IVCCI measured using point-of-care ultrasound are reliable indirect parameters of the right atrial pressure and volume status in HF [67]. A recent systematic review of the literature performed by Ciozda et al. [22] reports consistent findings in support of the use of IVC size for the estimation of CVP in non-mechanically ventilated patients. In particular, the IVC size was directly correlated to CVP, while IVCCI was shown to have a negative correlation. Anyway, IVC diameter measurement differences can exist between users. Moreover, other limitations consist of possible alterations to IVC measurement in the presence of diastolic dysfunction and the lack of normal values [68].

In recent years, LUS has been widely used and investigated in HF and CKD settings. In different studies, it has been demonstrated that lung ultrasonography has higher accuracy in detecting pleural effusion than bedside chest X-rays (96–93 vs. 65–47%) [69]. Chest X-rays can detect pleural effusion only if the volume is at least 200 mL, and the sensitivity of this method decreases in the supine position, whereas ultrasound can detect effusions as small as 20 mL [70]. A multidisciplinary panel of 28 experts has developed a consensus paper for LUS, based on those recommendations. B-lines show a very high correlation with the more established parameters of HF [71].

Anyway, LUS has several limitations in the evaluation of volume status. For instance, some conditions (e.g., pulmonary fibrosis) cannot be differentiated from pulmonary congestion, and B-lines due to HF cannot be distinguished from acute respiratory distress syndrome of other origins. Finally, LUS cannot be used to evaluate volume depletion [72].

The importance of the follow-up in CKD and HF patients is crucial considering the high rate of rehospitalizations. The COVID-19 pandemic has made this even more challenging. In this new scenario, vulnerable populations, such as patients with multiple chronic conditions or immunosuppression, will face the difficult choice between risking iatrogenic COVID-19 exposure during a clinician visit and postponing needed care [73]. Different methods of remote monitoring of CHF and CKD patients were studied, and some methods have now become part of the clinical routine with a large disparity between one hospital and another. In Table 3, we reported a brief list of the main significant trials of the last decade. Noninvasive methods, however, have not been fully proven to be associated with a better outcome [74, 75]. Concerning noninvasive methods, the most widespread involves regular telephone support to monitor the symptoms, the body weight measurement changes, and the psychological status of the patients [76]. The results of such remote monitoring are controversial, displaying both positive and negative results, the negative ones being mainly due to the low sensitivity of body weight changes [76]. However, the results of the TIM-HF2 trial published in 2018 suggest

that a structured remote patient management intervention could reduce the days lost due to unplanned cardiovascular hospital admissions and all-cause mortality [75].

One of the most effective approaches seems to be the use of invasive implanted devices, such as implantable cardioverter defibrillators and cardiac resynchronization therapy devices, which are able to detect potential arrhythmias and changes in thoracic congestion [77]. The IN-TIME trial which used automatic implant-based multiparameter telemonitoring (namely Biotronik Home Monitoring) controlling rhythmic, technical, and vital parameters was shown to decrease the mortality of HF patients [77]. Another extremely accurate way to predict decompensation events in HF patients is represented by the cardioMEMS, invasively implanted in the pulmonary artery to measure its pressure [78]. CardioMEMS has already been shown to decrease mortality and rehospitalizations, however, its utilization is still limited to end-stage HF patients [78]. For both invasive and noninvasive solutions, what emerged clearly is not just one parameter, but multiple parameters should be used to detect patients at higher risk [76, 77].

Alternative approaches have also been reported. Recently, a multicentric research team tested different algorithms, using weight scale measurements and transthoracic bioimpedance data to predict HF decompensation events [79]. They demonstrated that, differently from weight scale measurements alone, the use of transthoracic BIA and weight scale in combination with trend algorithms, improved the detection of HF. BIA technology, more broadly, can also be very well miniaturized and embedded in wearable devices, increasing the range of opportunities to optimally mitigate CKD progression speed and maximizing the quality of life [80].

Another opportunity to increase the quality of life of chronic patients is given by voice-enabled technology and AI. Recently, a feasibility study was conducted to evaluate the quality of the data collection of a voice-enabled automated platform called CardioCube [81]. The use of AI, in particular machine learning (ML), to track the clinical status of HF outpatients has been evaluated in another recent study, using a wearable electrocardiogram with sensing patches. They developed an algorithm enabled to assess compensated and decompensated HF patients by analyzing cardiac response to submaximal exercise [82].

Volume Balance in HD

Despite medical improvements, the risk of mortality in HD patients remains approximately 30 times higher than the general population and 10–20 times higher after stratification for age, gender, and presence of diabetes [83]. Fluid volume management is an important component of cardiovascular risk [84] and several studies have reported that around 30% of dialysis patients are in chronic volume overload [85]. In extracorporeal dialysis, fluid removal is obtained by ultrafiltration (UF), a fluid transport from blood to dialysate, generated by the hydrostatic pressure gradient across the membrane. The optimal volume status of dialytic patients is usually described as dry weight, defined as the lowest tolerated post-dialysis weight with minimal sign and symptoms of hypovolemia or hypervolemia [86]. Instead, interdialytic weight gain (IDWG) indicates the volume of fluids accumulated by the patient during the interdialytic period and that is necessary to remove during the single HD session by UF. When IDWG is excessive and consequently the UF rate is rapid, complications such as intradialytic hypotension, muscle cramps, nausea, or vomiting occur more frequently. The plasma refilling rate is a key factor during UF in hemodynamic balance. It has a very wide intraindividual and interindividual variability and can overcome 10 mL/kg/min [87]. In the dry-weight reduction in hypertensive HD patient trial, extreme IDWG was associated with adverse outcomes, while chronic volume overload was strongly correlated with mortality [88]. So, normalizing the ECV and avoiding a large IDWG should be primary clinical goals in the management of HD patients. Minimization of dietary sodium intake (<1,500 mg/day), an increase of dialysis time, and the reduction of dialysate sodium [89] have been described as valid methods to achieve these objectives. Moreover, in the HD setting, it should be considered that additionally a residual renal function (RRF) can be of significant help in maintaining the volume balance. Indeed, the presence of residual diuresis with loss of water and sodium with urine allows to reduce intradialytic fluid removal, decreasing the risk of intradialytic hypotension, chronic hypervolemia, HF, and consequently improves patient survival [90].

Volume Evaluation

Volume evaluation is challenging in HD patients since clinical examination and patient history are not always reliable. For example, hypertension may be a sign of volume overload, but it can also depend on sympathetic overactivity and/or increased arterial stiffness. Also, blood pressure is often influenced by lower left ventricular ejection fraction, cardiac valvular disease, malnutrition, and chronic wasting disease. Thus, hypertension is an important element guiding the assessment of dry

weight, whereas the absence of hypertension does not necessarily indicate optimal fluid volume [91]. A HD-specific method to evaluate patient ECV is the relative PV monitoring, that, by use of photo-optical technology applied through a transparent chamber affixed to the arterial end of the dialyzer, allows measurement of the absolute changes of hematocrit during HD sessions.

Moreover, the assessment of IVC diameter, BNP and, in recent years, LUS has been studied as candidate indicators of volume status in HD patients [92, 93]. LUS was deeply investigated in this clinical setting and the relationship between B-lines and UF; or IDWG and its prognostic value in the prediction of mortality; or CV events has been confirmed in different studies [94]. Furthermore, BIA methods are used to noninvasively measure TBW, ECW, and ICW; and to calculate lean mass and fat mass exploiting empirical equations. BIA is highly reproducible and operator independent. For this reason, it has been widely introduced in the HD setting [95]. Fluid overload measured with BIA (defined as overhydration/ECW ratio >7–15%) [96] has shown a significant correlation with mortality, confirmed in different studies and metanalysis [97, 98]. However, in a recent study, Mitsides et al. [99] speculated the possible influence of the subcutaneous sodium accumulation in reducing the predictive value and accuracy of BIA. A BIA-guided-HD approach has also been investigated in many trials and summarized in systematic reviews and meta-analyses. Studies have in general been successful in achieving secondary outcomes such as control of hypertension, as well as reducing fluid overload and hypotensive events, but there is still inconclusive evidence on hard outcomes such as mortality and hospitalization [100, 101]. Further studies should be performed to better describe the effect of BIA-based strategies on survival in HD patients [50, 102]. Nowadays, due to the limitation of the UF rate, reaching a real improvement in volume management is still challenging without enhancing sodium water restriction or frequency of HD sessions. The fluid removal during adherent renal monitoring study, a prospective, nonrandomized trial, examined the performance of a noninvasive, multisensor fluid monitoring system, applied to the chest, to determine its performance and reliability during HD. Compared with body weight, bioimpedance showed a more sensitive detection of changes in the body fluid [103]. Even with these new approaches, achieving the optimal balance between UF and the risk of intradialytic hypotensive events is a complex task in clinical practice. ML may help to personalize the multiple dialysis-related prescriptions affecting patients' intradialytic hemodynamics. One of the progenitors of this approach is the automatic control of blood volume [104], such as the hemocontrol biofeedback system (Hemocontrol™, Hospal, Italy) that modifies sodium concentration of dialysate and regulates the UF rate through a biofeedback mechanism, based on relative PV [105]. Successively, different predictive models for session-specific endpoints (such as Kt/V, fluid volume removal, and blood pressure) have been proposed, with encouraging results, based on patient characteristics, historic hemodynamic responses, and dialysis-related prescriptions [106]. ML works using interconnected processing units organized, inspired by the neurons in the human brain. ML learns to compute a specific input-output mapping by tuning a set of parameters in response to being exposed to a sufficiently large set of data [107]. The results of a ML analysis can assist physicians in decision-making via early detection of vital parameters such as blood pressure, the heart rate, the respiration rate, and body temperature, available through the artificial kidney [108]. This kind of online monitoring systems with automatic biofeedback in combination with progress in nanotechnology has made possible the implementation of home HD [109], as well as the development of the wearable artificial kidney and implantable bioartificial kidney, still in the preclinical study stage [110]. The clinical setting is complex and requires a multiparameter approach. In this scenario, AI and new technologies may improve the diagnosis and treatment under medical surveillance.

Volume Balance in Peritoneal Dialysis

Peritoneal dialysis (PD) is performed by the patient or the caregiver at their own home and presents some peculiarities in respect to HD in the mechanisms regulating fluid management. Indeed, in PD, the water is removed mainly by osmosis and is regulated by Starling forces through the peritoneum. Therefore, the rate of water removal is dependent on the osmolality of the intraperitoneal solutions, which induce an osmotic gradient between the peritoneal cavity and the peritoneal vessels with the consequent transfer of water into the peritoneal cavity through a crystalidosmosis process [111]. The commonly used solutions contain glucose at different concentrations (1.36, 2.27, and 3.86%) and UF is increased by increasing the concentration of glucose in the peritoneal dialysate [111]. Because of the absorption of glucose from the peritoneal cavity into the capillaries, the osmotic efficiency of the glucose-containing solutions is reduced during the dwell. Icodextrin, a glucose polymer, is reabsorbed only to a small extent by the peritoneum, and therefore induces UF that lasts over time through a col-

loid osmosis mechanism [112]. The choice of peritoneal solution usage depends on the clinical needs of each patient, allowing for personalization of the treatment. Moreover, PD is associated with better preservation of the RRF than HD, because of a lower frequency of volume depletion episodes [113]. However, despite these advantageous factors, volume unbalance is also common in PD patients. A recent prospective study by Van Biesen et al. [114] found a significant amount of volume unbalances in a cohort of 1,054 incidental PD patients. In particular, a relative volume overload of >7%, detected with BIA was present in 57% of the participants before the start of PD and persisted after 1, 2, and 3 years of follow-up (48, 49, and 53% of the patients, respectively). As for HD, in PD, volume excess can be harmful as well and it is associated with left ventricular dysfunction and hypertension, that in turn correlates with worse survival, also considering that cardiovascular complications are responsible for 40–60% of deaths in PD patients [115].

Volume Evaluation

Fluid volume assessment in PD is carried out exploiting the same techniques described before. Physical examination is part of the routine evaluation of PD patients and can be used together with blood pressure measurements, imaging, and natriuretic peptides. However, clinical examination often proves to be imprecise and incapable of guiding practicing nephrologists to more appropriate PD prescriptions. BIA has been increasingly employed in the evaluation of volume status in PD patients, as it can be easily performed by patients themselves at home. However, even if it might be theoretically useful, it should be also admitted that available data do not strongly support the claim that BIA is useful in the management of volume status. A prospective trial by Tan et al. [116] tried to determine the clinical impact of the longitudinal plot of the BIA analysis vector (i.e., the direction in which fluid status is changing). Unfortunately, the authors found that the intervention did not result in further improvement in fluid analysis measurements [116]. The COMPASS study evaluated the usefulness of BIA in preserving RRF and CV function in non-anuric PD patients [117]. The authors found that when compared with the control group receiving only clinical evaluation, patients receiving BIA-guided fluid management did not present significant clinical benefits. Although not generalizable, these results at the least indicate that further research is warranted to investigate the role of BIA in PD patient volume management. One of the most peculiar aspects of PD is that the treatment is delivered at patient's home, both in the case of use of manual (i.e., continuous ambulatory-PD) and automated exchanges (i.e., automated-PD). So, this technique is suitable for the widespread adoption of telemedicine platforms, which could be of great support for the patients.

A prototypical PD-telemedicine platform would allow for fast communication between patients and health-care providers while remaining nonintrusive and portable. Notably, in the telemonitoring systems, many important parameters could be considered, including peritoneal volumes, blood pressure, body weight, and BIA [118]. So, the adoption of this strategy can provide useful real-life information on volume status and control. Interestingly, recent studies performed in Europe [119] and Asia [120] found that telemonitored PD patients presented low rates of technique failures and hospitalizations, as well as reduced overall costs.

Conclusions

Body fluid management is one of the most important issues in the clinical practice. The first step to improve the quality of care provided to our patients and clinical outcomes is to understand the physiopathology behind body fluid unbalances. This challenging task should take advantage of basic research and clinical trials to achieve a better knowledge of the relationship between the heart and kidney, molecular signal pathways, and adaptive response in kidney disease. The second step is refining our diagnostic methods and remote monitoring techniques, to allow real-time evaluation of the fluid status of a patient in and out of the hospital. This will be possible thanks to the application of new technologies, like telemedicine, wearable devices, nanotechnologies, the AI-medical support system, and bioengineering. In particular, progress in AI will likely allow us to overcome the human diagnostic threshold, leading to a quality of care that is unconceivable nowadays. The need to develop these tools comes from the necessity to reduce costs for the health-care system, incentive personalized medicine, provide health assistance to a wide number of people, and it has been further exacerbated by the recent emerging necessity to monitor chronic patients in the midst of the COVID-19 pandemic. Once regulatory and ethic barriers are removed, and as soon as AI-based techniques prove to be effective, we will be probably seeing an exponential spread of automated medical support systems for real personalized healthcare, without any increase in workload for medical personnel and reduced admissions to hospitals and the related costs.

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Conflict of Interest Statement

Alessandro Faragli and Edoardo La Porta are shareholders of the company BOCA health-care GmbH. Other authors declare no conflicts of interest.

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Author Contributions

E.L.P. provided the idea, collected the literature, and wrote the manuscript; L.L., M.C., E.C., L.E., A.A.V., and A.F. collected the literature and wrote the manuscript; A.A.L., C.Q., and P.E. revised the manuscript.

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