

# Volume Overload in CKD

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# Subjects

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  - oldest theory of VO
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# Introduction

## **Fluid balance** ○

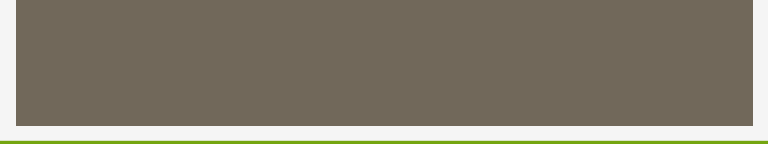
is generally defined by the difference ○  
between the daily fluid input and the  
daily fluid output and it should not be  
associated with weight and insensible  
losses, but it could be correlated with  
dialysis fluid removal if an individual is on  
renal replacement therapy

## **'Fluid overload' (FO)** ○

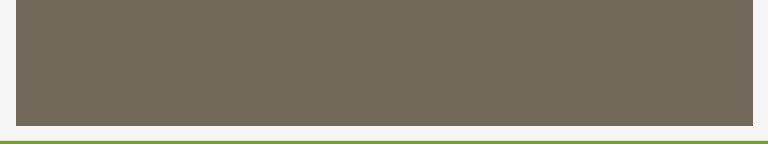
is defined by a percentage of body weight – ○  
a cut-off value of 10 % has been associated  
with increased mortality

Volume overload (VO) is a common scene ○  
for

patients on RRT but, also for those with pre-dialysis chronic kidney disease (CKD), even though only a limited number of studies have been conducted in these patients



All studies performed *until now in CKD* ●  
*patients described a significant* ●  
*proportion of overhydrated patients, even*  
*in the absence of*  
*clinically detectable signs of hypervolemia*



Chronic VO leads to hypertension ◉  
left ventricular hyper-trophy (LVH) ▪  
increased arterial stiffness ◉  
heart failure (HF), ◉  
and even an increased morbidity and ◉  
mortality, especially in dialysis patients



several studies shown ○

VO is considered to be an important contributor to an adverse prognosis, an effect modifier and an independent predictor of all-cause and cardiovascular (CV) mortality in ○

pre-dialysis CKD patients and end stage renal disease (ESRD) patients on RRT ○

One of those study : ●

Tsai et al. reported, in 472 non- dialysis ●  
patients with stage 4–5 CKD, a significant  
statistical association between the  
severity of VO and an increased risk of  
rapid decline in  
renal function and necessity of RRT ●  
initiation



VO was found to be a better predictor of renal dysfunction progression than the presence of diabetes (DM) in these patients ○

○  
Also, in non-renal clinical settings, VO is the primary cause of hospital admission and readmission of patients with HF and it is with associated with HF progression ○

# Sodium and Water

## Metabolism:

## The Importance of the Kidney

Pathophysiology ○

oldest theory of VO: ○

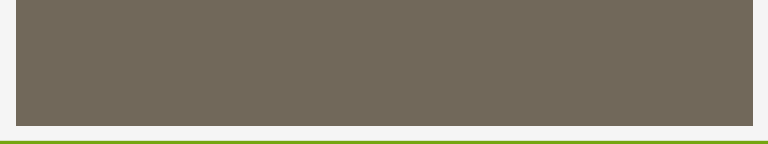
Tonicity is characterized by the movement of the osmoles on the interior and exterior of a cell causing, therefore, the movement of water. ○

The body fluids tonicity is maintained within normal range (280 mOsm) throughout homeostatic mechanisms that supervise the intake and excretion of water and sodium (Na) ○

Important for these processes are: ○

- the function of thirst and the secretion of the antidiuretic hormone (ADH), by activation of hypothalamic osmoreceptors in response to changes in tonicity; ○

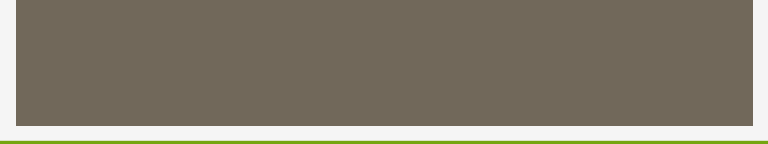
- the kidney – participating in the maintenance of normal water and Na balance, as it both preserves and removes water and Na (Na reabsorption, vasopressin release, the medullary gradient) ○



it is important to differentiate the mechanisms that control water balance (tonicity, osmoregulation) from the mechanisms that control Na balance (extracellular volume).

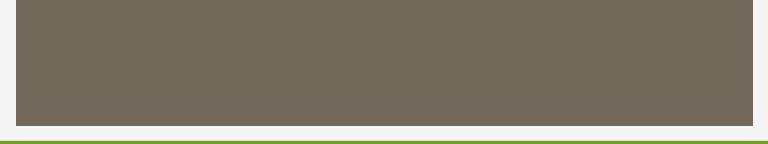
Anomalies of water balance determine modifications of serum Na concentration, leading to hypo/hyponatremia,

whereas anomalies of sodium balance determine modifications of the extracellular volume (ECV), leading to volume depletion/volume overload.



Water balance is primarily controlled by thirst and the ability of the kidney to produce more concentrated urine when osmolality increases or more diluted urine when osmolality decreases

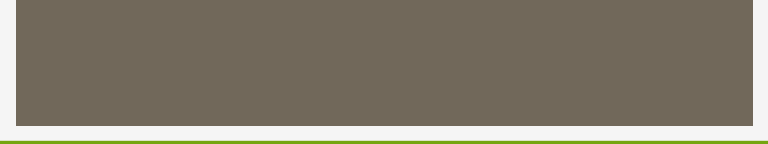
The most important inductor of thirst is hypertonicity, with a sensitivity of only 2–3 % increase in the plasma osmolality.



In normal individuals, the osmotic threshold of thirst is approximately 290–295 mOsm/kg H<sub>2</sub>O

ADH secretion is stimulated primarily by hyperosmolality and by arterial volume decrease (HF, cirrhosis, vomiting)

The osmotic threshold for ADH release is 288–290 mOsm/kg



if ADH levels are very high (like in chronic HF), water channel remains permanently in the plasma membrane leading to continuous water reabsorption, leading to interstitial water excess and edema ○

# New Insights on the Pathophysiology of Volume Overload

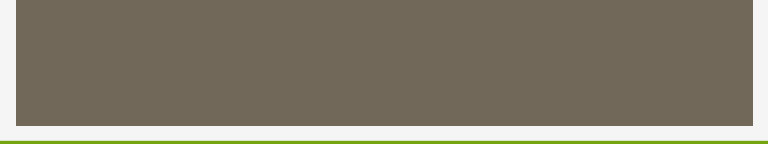
## **Role of Interstitial Fluid Compartment in Fluid Homeostasis**

Recently, an essential role of the interstitium in the underlying mechanisms involved in fluid homeostasis was

recognized

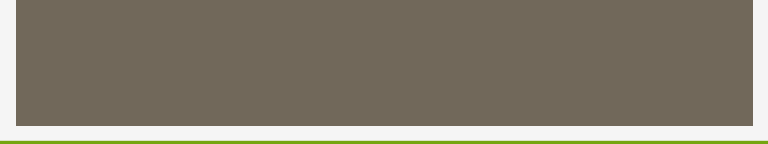
Interstitial fluid pressure is determined by a complex interplay between the fluid influx (blood capillary filtration), the fluid outflow (lymph flow), and the compartment's ability to expand (tissue compliance)






The interstitial fluid pressures are negative in healthy subjects and positive in CKD patients, but with no association between body fluid volumes and blood pressure

Moreover, it seems that the increase in the interstitial fluid pressure observed in CKD compensatory changes in the local microcirculation and this could further lead to either reduced trans capillary filtration in the interstitial , or to an increased lymph flow



Acute interstitial VO is associated with  relatively quick boosts of interstitial fluid pressures, while interstitial fluid excess in chronic edematous state cause only moderate escalation of interstitial fluid pressure



relative fluid shift from the interstitial into the intravascular space is induced by a high sodium intake. ○

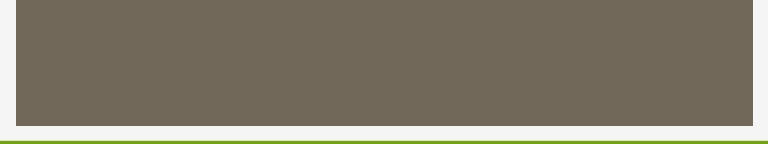
In the Heer et al.'s study 50–550 mmol of Na were given to normal men in order to sodium balance evaluate ○


Plasma volume increased by about 330 ml when Na intake was 550 mmol/ day, but without modifications of TBW or body weight even ○

when Na intake was as high as 1,700 mmol. ○



It is noticed that Na storage does not determine body weight modifications



Another important cohort study enrolled  hypertensive patients and normotensive control subjects and showed that patients with refractory hypertension had increased tissue Na content, assessed by Na-MRI measurements, in comparison to control subjects

# Cardiotonic Steroids (CTS): Involvement in CKD

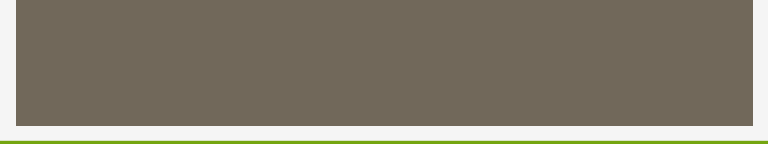
CTS are also called 'digoxin-like' ●  
endogenous substances found in the  
serum and urine of uremic and  
overhydrated patients and, also, in other  
clinic conditions, such CHF ,hypertension,  
renal ischemia and preeclampsia



They represent a relatively new   
discovered

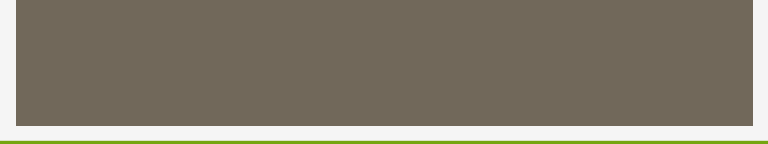
class of endogenous cardio tonic steroid  
hormones that act as a specific ligand for  
the Na/K-ATPase Tran membrane protein  
on


the surface of cardiomyocytes



It has previously been reported that ○  
marinobufagenin (MBG), an endogenous  
bufadienolide CTS, is elevated in  
both in clinical and experimental renal ○  
failure  
(MBG), has a greater importance in the ○  
pathogenesis of renal failure





It appears, therefore, that CTS and  especially MBG might become the new therapeutic targets in the management of uremic

Cardiomyopathy and over load diseases

.

Haller et al. found that in experimental ○  
chronic renal failure, increased levels of ○  
MBG contribute to hypertension and  
cardiac fibrosis through suppression of this  
transcription factor and suggested that  
this could represent a new potential  
therapeutic target

# Malnutrition-Inflammation and VO in CKD

Protein-energy malnutrition (PEM) ◉ develops when the diet cannot satisfy the body's need for protein and/or energy – a frequent status in dialysis patients

PEM is accountable for a poor quality of life and increased all-cause mortality in ESRD patients ◉ [



In renal patients, there is an important pro-inflammatory status

Inflammation promotes atherosclerosis ,

The term of 'malnutrition-inflammation-atherosclerosis' (MIA) syndrome or 'malnutrition- inflammation complex syndrome'

(MICS) has been adopted. MIA syndrome is considered as one of the main cause of mortality in ESRD patients

New recent studies are associating to a greater degree malnutrition and inflammation with VO

Hung et al. found in 338 pre dialysis CKD patients the volume overload was positively correlated with IL-6 and TNFa and the only parameter that was strongly associated with all components of the MICS syndrome.

At the same time, the presence of MICS had additive deleterious effects to VO.



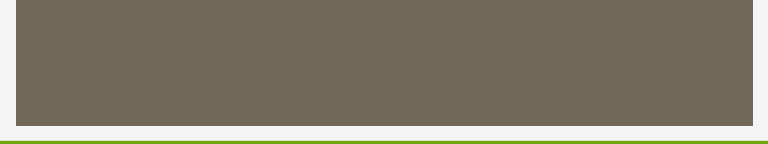
Lately, endotoxemia appears to become   
a new piece in the puzzle of systemic  
inflammation of renal patients with VO.


# Assessment of Fluid Status in CKD

One of the most important tasks for a nephrologist is the correct assessment of fluid status.

ESRD patients, treated by a standard dialysis prescription, are affected by chronic volume overload and by intermittent inter dialytic weight gain (IDWG).

Statistical analyses demonstrate an association between these two conditions and mortality



An inaccurate assessment of dry weight  leads to hypertension/hypotension,  
cardiac and vascular dysfunction,  
omission of small changes in nutritional  
status, and intradialytic morbidity and  
mortality



# Clinical Assessment of Fluid Status in Chronic Kidney Disease

This was the first method used for the estimation of a patient's water status, but its use as a unique assessment tool has been plagued by its lack of sensibility and specificity.

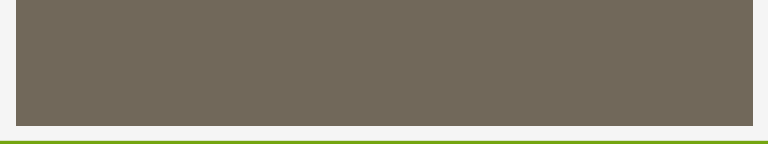
It comprises the evaluation of: BP, pedal edema, pulmonary congestion rales, turgid jugular veins, dyspnea, weight increase, history of previously excessive salt and water intake and the maximum ultrafiltration tolerated by the patient



There are several important shortcomings: ●

- a patient can present ECV excess ●  
without displaying signs/symptoms of VO
- high BP levels are not a reliable tool for assessment of VO as there is a proportion of patients that are normotensive despite VO and other patients that are hypertensive but normovolemic.

- pedal edema cannot account only for V<sub>O</sub>, being, also, present in cases of vascular stasis, use of calcium channel blockers or venous insufficiency; in contrast, a large proportion of volume overloaded patients does not present edema



• weight changes can occur, also due to nutritional diet modifications or poor nutritional status and cannot be judge only on ECV variations

clinical evaluation remains an important

fluid status assessment tool in the hands of well-trained, experienced nephrologists.

## **Echocardiography and Inferior Vena Cava Measurements**

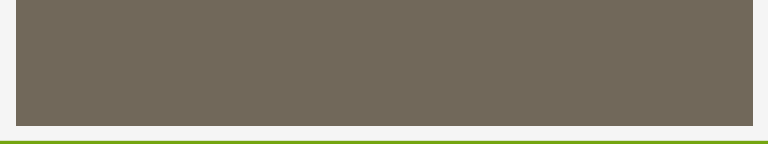
In early CKD stages, LVH develops as a physiological response to pressure and VO, but its prevalence and severity increases with progressive loss of renal function leading to structural changes due to chronic overload and CKD-associated factors.



In dialysis ●

patients, LV volumes fluctuates due to ●  
chronic VO, and the presence of  
associated cardiac impairment, so,  
echocardiography

should be performed at an achieved DW, ●  
for reliable results



Measurement of IVC is a simple, rapid and non-invasive method of fluid status assessment

In dialysis patients, LV volumes fluctuates due to chronic VO

A 2010 study, performed in 160 HD patients, could not correlate VO with an IVC augmentation, measured before the midweek HD session, and concluded that IVC has a positive predictive value of VO of only 18 %, with an important proportion of false negative cases (45 %)

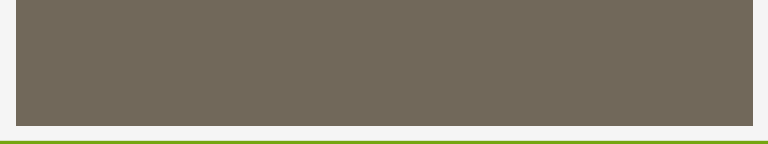
## **Biomarkers of Volume Overload in CKD** ○

In CKD patients, BNPB-type natriuretic peptide (BNP) and NT proBNP were correlated with renal function decline ○



## **Bioimpedance Analysis (BIA) in CKD**

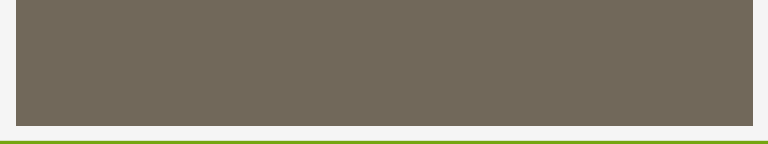
This represents a non-invasive, volume measurement technique based on the electrical principle that the body is a circuit with a given resistance (opposition of high and low frequency current flow between intracellular and extracellular compartments) and a given reactance (the ability of cells to store energy)



BIA is a useful tool for fluid management in pre-dialysis CKD patients. There are several studies that are suggesting the importance of BIA in these patients for a better estimation of over hydration and improvement in clinical management

## **Blood Volume Monitoring (BVM) ○ and Volume Overload ○**

This technique uses relative blood volume ○ (RBV) monitoring devices incorporated in the dialysis machine that allow non-invasive, real-time assessment of intra-dialysis changes of hemoglobin/hematocrit concentrations (by optical absorbance) or of the concentration of total plasma protein (by ultrasound recorded blood waves velocities)



The BVM method has been proposed for predicting DW but was, initially, conceived for a better management of intra-dialysis hypotension

## Heart Rate Variability (HRV) and Volume Overload in CKD

HRV is a simple, non-invasive technique used to evaluate cardiac dysautonomy in healthy individuals as well as in pathological settings

The HRV measurement provides data about the sympathetic and parasympathetic activity and reflects the ability of the sinoatrial node to modify the heart rate

In a simple manner, it measures the periodic variations in R-R interval from beat to beat

# VO and CKD Progression

Tsai et al. published in 2014 the ●  
results of a prospective cohort study

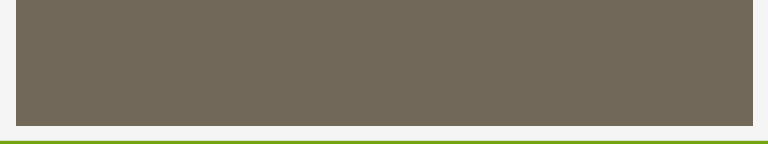
The study showed that VO was ●  
independently associated with an  
increased risk of rapid GFR decline  
and that the severity of VO was  
associated with an increased risk of  
RRT initiation

# Volume Overload Treatment: Sodium Plays the 'Leading Role

## **Pre-dialysis CKD Patients** ●

In pre-dialysis CKD patients, excess Na intake ●  
– as a risk factor determines VO increased BP  
and proteinuria.

Therefore, controlling salt intake could ●  
account for a simple, modifiable measure for  
reduction of VO, BP and proteinuria,  
the principal conditions leading to CKD ●  
progression

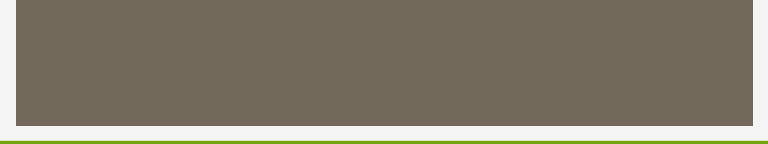


Reports show that 80–89 % of CKD patients ingest >100 mmol Na/day, a higher amount than what the guidelines are recommending



## **Renal Replacement Therapy Patients** ○

Volume control and sodium restriction is ○  
associated with improved BP values and  
increased survival rates in dialysis patients. ○  
lower Na intake leads to a reduction in BP ○  
and LVH and higher Na levels are  
associated with both elevated BP and  
IDWG



A number of proposed strategies were created over time for a better control of fluid status and BP: (1) Na profiling (modeling);

- (2) Na individualization;
- (3) UF profiling;
- (4) different HD techniques

# VO and Survival

- Poor volume control is ●
- mainly related to at least three factors ●
  - (i) weight gain (IDWG); ●
  - (ii) high ultrafiltration rate (UFR) ●  
causing as a consequence hypotension ●  
and (
  - iii) chronic volume over load. ●
- high inter dialytic ●

Comorbidities and lower dialysis ●

dose were also associated with higher ●  
mortality risk

High UFR could induce hemodynamics ●  
instability, intradialytic hypotension (IDH)  
and increased mortality risk ●

Hypotension during HD and aggressive ●  
UFR increase the risk for intra dialytic  
recurrent myocardial stunning and could  
determine, over time, irreversible fibrotic  
changes and chronic heart failure,  
arrhythmias and sudden cardiac death

# Summary

Progressive loss of renal function causes reduced sodium filtration and inappropriate suppression of tubular reabsorption that ultimately lead to volume expansion

Fluid overload frequently manifests in patients with moderate to particularly late stages of CKD and has been associated with hypertension, congestive heart failure (CHF), left ventricular hypertrophy (LVH) as well as

Edema

Volume overload is related to CVD<sup>3,4</sup> and is a predictor of outcome in hemodialysis and peritoneal dialysis.



**Thank you**