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Subcutaneous interstitial pressure and volume characteristics in renal impairment associated with edema

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The kidneys and the interstitial compartment play a vital role in body fluid regulation. The latter may be significantly altered in renal dysfunction, but experimental studies are lacking. To help define this we measured the subcutaneous interstitial pressure, bioimpedance volumes, and edema characteristics in 10 healthy subjects and 21 patients with obvious edema and chronic kidney disease (CKD). Interstitial edema was quantified by the time taken for a medial malleolar thumb pit to refill and termed the edema refill time. Interstitial pressure was significantly raised in CKD compared to healthy subjects. Total body water (TBW), extracellular fluid volume (ECFV), interstitial fluid volume, the ratio of the ECFV to the TBW, and segmental extracellular fluid volume were raised in CKD. The ratio of the ECFV to the TBW and the interstitial fluid volume were the best predictors of interstitial pressure. Significantly higher interstitial pressures were noted in edema of 2 weeks or less duration. A significant nonlinear relationship defined interstitial pressure and interstitial fluid volume. Edema refill time was significantly inversely related to interstitial pressure, interstitial compartment volumes, and edema vintage. Elevated interstitial pressure in CKD with obvious edema is a combined function of accumulated interstitial compartment fluid volumes, edema vintage, and tissue mechanical properties. The edema refill time may represent an important parameter in the clinical assessment of edema, providing additional information about interstitial pathophysiology in patients with CKD and fluid retention.

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Patients with impaired kidney function gradually lose their ability to excrete salt and water, especially in the advanced stages of the disease. Impaired salt and water excretion, in combination with other factors such as hypoalbuminemia and cardiac failure, often result in chronic volume overload.[1–3] The prevalence of volume overload has been estimated as high as 63% in hemodialysis patients[4] and 84% in peritoneal dialysis patients.[5] Uncontrolled hypervolemia is often difficult to treat and has been associated with high blood pressure, left ventricular hypertrophy, heart failure, and increased cardiovascular mortality.[6,7] The excess volume, often exceeding several liters, is lodged mainly within the extracellular fluid space, which has two main compartments: plasma and the interstitial compartment (IC). As plasma and intracellular volume expansion are tightly regulated, the low-pressure IC principally acts as a 'buffer zone' for excess extracellular fluid, thus having a key role in plasma–interstitial fluid dynamics, both in 'steady states' and in dynamic states such as during dialysis and ultrafiltration. In accordance with Starling's hypothesis,[8] fluid accumulation within the IC occurs when the rate of fluid influx into the interstitium exceeds its return to the circulation through lymphatics. Despite its high prevalence, very few studies have investigated the pathophysiology of fluid accumulation in relation to the dynamic changes within the IC in chronic kidney disease (CKD).

Fluid exchange between the interstitium and plasma is governed by the various components of Starling's hypothesis, where the interstitial hydrostatic pressure (ISP) is a key physiological variable.[9,10] Animal experiments have demonstrated edema-preventing mechanisms opposing interstitial volume expansion, mainly rapid increase in ISP in the first instance.[9,11] When this has been surpassed, edema results, with interstitial volume expansion, followed by a plateau and an eventual compensatory reduction of ISP with increasing lymph flow.

Mobilization of fluid from the interstitial space to plasma, that is, plasma refilling, is an important dynamic shift during diuretic therapy or ultrafiltration.[11,12] Koomans *et al.*[13] demonstrated faster plasma refill rates during ultrafiltration

in patients with more pronounced edema. Interstitial volume and pressure may therefore be closely linked and key determinants of plasma refill rates, alongside other nonhydrostatic forces such as the plasma protein concentration and colloid osmotic pressure. Few studies have explored this volume–pressure relationship, particularly in patients with renal dysfunction. Fauchald *et al.*[14] measured subcutaneous interstitial fluid colloid osmotic pressure and interstitial volume in 11 nephrotic patients and studied the changes during ultrafiltration; however, concomitant ISPs were not measured. Fisher *et al.*[15] measured ISP in 25 healthy volunteers which correlated well with their clinical hydration status. Human studies of ISP have been mainly limited to healthy volunteers,[16,17] cancer patients with lymphedema,[18] or tumors.[19] These studies have confirmed a negative ISP in nonedematous human skin regardless of age or gender,[17,18,20] consistent with observations noted in several animal experiments conducted since its first description by Guyton *et al.* in 1963 (see refs. 21–24 and reviewed in Wiig[25]).

Volume assessment in renal impairment *per se*, remains problematic, especially in end-stage renal disease. Agarwal *et al.*[26] detected clinical edema in 23% of 146 dialysis patients but found no correlation between edema and other determinants of volume overload. Clinical edema appears at the latter stages of volume overload, when at least 50% expansion of interstitial volume has taken place.[1,27] Other fluid assessment methods such as bioimpedance spectroscopy,[28–30] blood volume measurement,[31] echocardiographic parameters,[32] and biomarkers such as brain natriuretic peptide[33,34] and isotope dilution[3] have been trialed with varying success and limited clinical use. Most applied technologies tend to be based on blood compartment measurements or volume parameters alone, and therefore fail to take into account characteristic changes within the IC tissue bed. It is conceivable that renal dysfunction with fluid retention may lead to differential ISPs and IC mobilization rates. There is a distinct lack of published studies investigating these key physiological variables in patients with fluid retention and advanced renal impairment. Interstitial fluid kinetic parameters such as ISP may provide valuable insight into extracellular volume status and its assessment in renal dysfunction.

We designed clinical experiments to (1) study volume and pressure characteristics in the subcutaneous IC, (2) define their interrelationship with clinical parameters, and (3) characterize clinical edema states in the presence of renal dysfunction in relation to the changes in interstitial physiological characteristics.

RESULTS

Study participants

A total of 31 subjects were recruited in the study: 10 healthy volunteers (2 men, 8 women; mean age 38.3 ± 12 years (range 24–60 years)) and 21 CKD patients with edema ((12 men, 9 women; mean age 64 ± 16 years, (range 25–84 years)), with a considerable overlap in age between the two groups. A subgroup of seven controls (five women and two men) and seven patients (four women and three men) matched for age (± 5 years) allowed further comparison of measured ISP and volume parameters. There was no difference in the mean age of these paired groups of healthy controls and patients with renal dysfunction (40.0 ± 14 and 46.4 ± 11 years, respectively; $P = 0.33$). Of the 21 patients, 4 were in CKD stage 3 (estimated glomerular filtration rate (eGFR) 30–60 ml/min per 1.73 m^2), 7 in stage 4 (eGFR 16–29 ml/min per 1.73 m^2), and 10 in stage 5 (eGFR <15 ml/min per 1.73 m^2), of whom 7 were on dialysis. The mean serum albumin of the patients was 31.4 ± 7 g/l. The patients were predominantly hypertensive, with a median mean arterial pressure of 97 mm Hg, and 14 (66.7%) with blood pressures $>140/90$ mm Hg. Diabetes and/or hypertension were the most frequent primary renal diagnoses (9 patients, 42.9%), followed by glomerulonephritis (6 patients, 28.6%).

Clinical characteristics of edema

In all, 16 (80.9%) patients had 'grade 4' (thigh and beyond) edema, 3 (14.3%) patients had 'grade 3' (up to knees) edema, and 1 (4.8%) patient had 'grade 2' (mid-calf) edema. The duration of edema varied considerably (mean 182 days, median 14 days, range 4–1820 days). The edema was categorized clinically as 'very tense' in 7 (33.3%) patients, 'moderately tense' in 8 (38.1%) patients, and 'compliant' in 6 (28.6%) patients. Edema refill times (ERTs) were variable with a mean of 142 ± 98 s (median 123, range 17–340 s).

Bioimpedance-derived body fluid volumes

The total body water (TBW, 49.9 ± 14 vs. 34.5 ± 5 l, $P = 0.01$), extracellular fluid volume (ECFV, 23.96 ± 6.7 vs. 14.01 ± 1.5 l, $P = 0.0008$), interstitial fluid volume (IFV, 19.96 ± 6.1 vs. 11.1 ± 1.3 l, $P = 0.001$), and body weight (88.3 ± 21.4 vs. 70.1 ± 11.4 kg, $P = 0.04$) were significantly higher in the patients as compared with healthy volunteers, providing a distinct separation of the hydration status between study and control groups (Figure 1). These differences were maintained for the Bio-ratio (ECFV/TBW) and when TBW, ECFV, and IFV were adjusted for weight, height, and most significantly (after adjustment for multiple testing) the body mass index. This remained true in the age-matched subgroup of seven patients and seven controls. Table 1 shows the comparative adjusted body volumes of patients and healthy volunteers.

There was no significant difference between the intracellular fluid volume (ICFV) of patients and healthy volunteers (25.02 ± 7.3 vs. 21.61 ± 4.9 l, respectively, $P = 0.24$). The measured excess IFV (mean difference between patients and healthy volunteers 8.9 l) confirmed that the IC harbored the majority of the total extracellular fluid accumulation (mean difference 9.95 l) in the edematous subjects.

Gender, age, comorbidity, and body fluid volumes

IFV showed no correlation with age ($r = 0.15$, $P = 0.42$). However, interestingly, extracellular volume parameters ECFV (27.2 ± 5.8 vs. 19.5 ± 5.2, $P = 0.008$) and IFV