FLUID ASSESSMENT BY OBJECTIVE MEASURES IN END STAGE KIDNEY DISEASE

Ph.D. Thesis

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1. THE LIST OF ABBREVIATIONS

ANP	Atrial Natriuretic Peptide
BP	Blood Pressure
BCM	Body Composition Measurement a.k.a. bioimpedance
BNP	B-type Natriuretic Peptide
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
CNP	C-type Natriuretic Peptide
CPT	Current Procedural Terminology
DOPPS	Dialysis Outcomes and Practice Pattern Study
ECW	Extracellular Water
ENaC	Epithelial Na^+ Channels
ESRD	End Stage Renal Disease
IDWG	Interdialytic Weight Gain
HD	Hemodialysis
HDF	Hemodiafiltration
HJR	Hepato Jugular Reflux
ICW	Intracellular Water
IDWG	Interdialytic Weight Gain
LVEDP	Left Ventricular End Diastolic Pressure
MI	myocardial infarction
OH	Overhydration
OH%	Percent overhydration

PCWP	Pulmonary Capillary Wedge Pressure
RAS	Renin-Angiotensin-Aldosterone System
ROC	Receiver Operating Characteristic
UF	Ultrafiltration

2. INTRODUCTION

Maintaining intravascular volume and blood pressure is essentially equivalent to maintaining life. Organisms that cannot maintain their fluid status within the narrow ranges of homeostatic balance are at their last moments of life; the mechanism of death in most mammalians is essentially equivalent to losing perfusion pressure to vital organs and the cessation of organized function as a whole even though individual cells, tissues and organs may persist for minutes, hours even days. Blood pressure is thus a critical vital sign that organisms try to preserve at all cost.

Maintaining blood pressure is a particularly difficult task with multiple factors that interplay but the two central components of blood pressure is maintaining vascular tone and maintaining intravascular volume. As with any biological system there must be a decision loop whose parts include sensing or status assessment, evaluation of the data and adjustment. These parts of the decision loop are analogous to computer coding while every part is a component of the maintenance of biological systems. Therefore, maintaining blood pressure and maintaining intravascular volume need to be sensed, assessed, evaluated and adjusted for maintaining a homeostatic state. Biological systems, however, are well-prepared to this task and there are several mechanisms to regulate fluid status.

While regulation of the fluid status has been studied and explored in the last century extensively and we seem to have some good grasp on how this may be achieved. The assessment part of the decision loop seems to have been a more difficult element of fluid status maintenance.

2.1. Physiological volume sensors

2.1.1. Renal fluid flow sensors

Essentially all tubular epithelial cells in the nephron are endowed with a single sensory cilia to sense the amount and direction of fluid flow (1). Unlike cilia in the bronchial epithelium or the oviduct these cilia do not beat but are designed to deflect and the inner microtubules through the signaling of intraflagellar transport proteins – such as polycystin-1 - process the information. Abnormalities of the various component proteins of the ciliary system present as various clinical syndromes, most notably cystic diseases although the exact mechanisms of these developments are not fully understood. Flow-related deflections of these cilia activate various ion channels – for example calcium channels – and modulate ion currents. The intraflagellar transport proteins

also sense chemical compositions, calcium concentration or pH in addition to their primary function of detecting and measuring flow rate. The mechanical bending of a cilia is the first step in a cascade of autocrine chemical signaling. This cascade eventually affects sodium uptake which is an ATP-dependent process and thus the rate of luminal fluid flow is regulated in addition to the other endocrine and paracrine processes in the body. These are the chemically induced renin-angiotensin-aldosterone hormones that are stimulated when there is a low blood flow taking signals from receptors in the macula densa. The macula densa is capable of processing fluid volume-related succinate, adenylate cyclase 3, chloride concentration and finally effect the blood pressure by the RAS axis. The distal tubule and collecting tubules also has a role in sensing the volume status via the sensing of bicarbonate through various sensor proteins. The kidney thus has both a chemical and a mechanical means of assessing fluid status and fluid flow.

2.1.2. Carotid volume sensors

Another mechanism through which the human body is capable assessing its own fluid status is through the pressure sensors in the carotid body; the aortic baroreceptors and other vascular bodies that send afferent information on vascular stretch by volume status. A network of branching nerve fibers enmesh these vascular sites where they act as baroreceptors as well as some act as chemoreceptors. These vascular receptors are found in the lungs and subclavian arteries. The osmotic assessment in the carotid bodies have long been known (2) through the studies of Verney who injected hypertonic then hypotonic saline into the carotid sinus and found that diuresis followed if the saline was hypotonic or fluid retention ensued depending on the sodium concentration. Better yet, Peters (3) in 1937 recognized that the fullness of the vascular bed without changes in osmolality he could induce diuresis simply by producing graded hemorrhage or by transfusion; this through the release of antidiuretic hormone or vasopressin. Schrier in fact, remarks (4) that “since these earlier studies the role of blood volume as a regulator of renal water excretion has been recognized in numerous other investigations.” It was also observed that changes in the peripheral pressure, thus redistributing fluid from the thorax to the lower body through tilt tables or negative lower body pressure will induce diuresis or water retention depending on whether the intrathoracic pressure increases or decreases (5). Decreasing the intrathoracic stretch of these receptors for example by increasing the pressure in the lungs via positive pressure breathing on mechanical ventilation the urine flow will decrease and using negative pressure will actually increase urine flow (6) as the stretch receptors can in the lungs sense the pressure milieu. This same author, Goetz, found that the receptor for

measuring intravascular volume may be in the atrium that sends the signal to various hormonal pathways including to the renin-angiotensin axis as well as the vasopressin pathway. These vascular receptors mostly detect pressure and through a complex pathway send their signals to the medullary and hypothalamic areas to process and influence vascular tone, cardiac function and ultimately blood pressure, end-organ perfusion.

2.1.3. Cardiac volume sensor

Cardiac sensory receptors have long been known from the early studies noted above. The heart can readily sense intravascular volume as "inflation of a balloon in the left atrium of the conscious dog produces a composite response consisting of alterations in cardiovascular function, renal function, and circulating hormones" (7). Increasing the left atrial pressure by balloon inflation the ensuing hormonal changes included a decrease in the anti-diuretic hormone (ADH) as well as renin value. This resulted in increased urine flow. Interestingly, however, cardiac denervated dogs (8) had essentially the same response! This indicates that there must be another mechanism of volume assessment than the simple neural reflex arc. In fact there may be another, perhaps more important mediator of volume measurement – initiation of graded response to graded sensory input – through volume expansion and cardiac muscular stretching. This mediator could be the hormone implicated by de Bold when he injected rats with myocardial extracts and observed a rapid diuretic response. This mediator was later found to be the circulating atrial natriuretic peptide (ANP). This is not only a signal molecule for the organism but in the clinical arena it also acts as a circulating biochemical marker that we will discuss later. The teleological purpose of this hormone is to adjust intravascular filling and cardiac stretch. An increased vascular volume can eventually be detrimental and this vascular expansion the body is capable to reset a normovolemic state by increasing diuresis, decreasing blood pressure and volume removal. ANP is a hormone recognized in the early 1980's both as a hormone and as a clinical tool for diagnosing a congestive heart failure which is the equivalent of fluid excess.

These examples how the mammalian body is capable to assess its own fluid and volume status are only some examples and only serve to illustrate that fluid assessment is a serious matter in the Created World and that the constant assessment and re-assessment its status is critical in maintaining vital function and in fact life itself. This is not an exhaustive list nor do I want to target the discussion to detailing the physiology of fluid volume assessment. Rather, the ensuing discussion will focus on how clinicians can assess the fluid status in those whose vital functions

depend on both the preservation of adequate effective circulating volume and avoidance of excessive fluid overload.

2.2. Clinical relevance

One of the most vulnerable patient populations is that with renal dysfunction. As the renal function declines in its capacity to clear toxins and waste product, in its clearance function of creatinine and other substances additional renal functions decline as well. Such examples are the endocrine function to hydroxylate pro-vitamin D or to produce erythropoietin necessary to maintain a normal or adequate hematocrit. (9) As the kidney loses its physiological function chronic bone disease and anemia develop with the decline of the clearance. At the same time the kidneys develop a progressive loss of ability to remove excess fluid (10) which in turn may be the progenitor of further decline not only of the cardiac dysfunction seen in chronic kidney failure patients but also of the declining renal function. Loss of the ability to remove fluid is a critical point in the development of renal decline because this translates to the deterioration of cardiac function. (11)

2.3. The pathological environment

It has been well recognized that renal dysfunction is a risk factor for cardiac disease and cardio-vascular mortality (12). There may be many reasons for this decline such as the diminished clearance of cardio-toxic substances, decreased hematocrit thus an increase in left ventricular mass due to the anemic environment and perhaps the worsening of soft tissue calcification. This calcification may be compounded by the atherosclerotic progression that has many components such as uric acid whose clearance declines with the clearance of all else, or diminished phosphate clearance which exacerbates the calcium-phosphate precipitation or the vascular calcification. Further exacerbates the calcium deposition the diminished production of osteocalcin production by the osteoblasts which are inhibited by the complex cascade of increased PTH (parathyroid hormone) which is elevated by the rising phosphate level because of the diminished renal clearance thereof. Increased cardiovascular mortality is also associated with the abnormally high aldosterone levels which is in turn stimulated by the high potassium level. In turn, high potassium values are not only due the diminishing clearance of potassium itself but also a consequence of the acidosis due to the lower ability of the kidney to reclaim bicarbonate in the proximal tubule and excrete titratable acids in the distal tubules. There is a host of reasons why the declining renal function is a risk factor for ever increasing cardiovascular risk. The diminishing ability to excrete salt and water is also a factor as the

retention of water is a major determinant of blood pressure which is also another factor that can hasten the decline of renal failure and increase the cardiac damage. Hung et al. found in a combined animal and prospective observational study that "volume overload contributes to CKD progression and cardiovascular diseases" (11). They followed a group of patients with chronic kidney disease (CKD) for 2.1 years and measured their fluid status using a bioimpedance apparatus. They found that fluid overload gets worse with time and progression of CKD but also found fluid overload to be a risk factor.

Therefore, it is important to conclude that one the most vulnerable population in which fluid overload should be assessed and monitored is perhaps the population with diminished ability to adjust its own volume status, those with CKD. A sub-population of these patients, perhaps should be the CKD5-D dialysis population who may have no ability on their own to adjust their fluid status. As we have seen the first part of the decision loop is to assess the volume status and the population where it may be the most critical to do so is the CKD population. We will therefor investigate how best to assess fluid status in the end-stage renal disease (ESRD) population and we will offer two options for this.

2.4. Background:

2.4.1 The Problem

The clinical task of accurately ascertaining patients' volume status seems quite easy. This may come as a self-evident part of medical practice that all physicians should be able to diagnose volume-overload in a large variety of patients. Nothing seems to be more evident than the simple fact that physicians can auscultate patients' lungs and listen patients' hearts and determine the volume status. After all, congestive heart failure is the classic and prime example of volume overload and diagnosing congestive heart failure seems to be a simple diagnostic challenge. Perhaps the most specific finding of these are related to the elevated neck veins that indicate an increased left ventricular pressure transmitted to the right side of the heart and thus presenting as a jugular venous distention (JVD) or transmitting from a congested liver and being detectible as hepato-jugular reflux (HJR) (13). These physical findings are often absent unless the patient is seriously in a decompensated life-threatening state. Waiting for this state of life-threatening situation is not an ideal situation to assess the fluid status of any patients. Their specificity is also tainted by other physical confounders such as a tricuspid regurgitation, a fast beating tachycardia or neck anomalies. In the dialysis population this problem is further exacerbated by the fact that many dialysis patients have had or do have internal jugular venous

devices as vascular accesses. Patients with a dialysis catheter in the jugular vein cannot be simply assessed based on their JVD or HJR because the catheter is in the way. If they have had dialysis or any other venous catheters in the past then there is a 50% chance of having a subclavian venous stenosis (14) but the jugular vein too has a very high rate of stenosis. (15)

Physical exam is a necessary and integral part of the medical arts, without physical exam physicians cannot make their first impression to guide them for further investigation and testing. Physical exam is the part of medical practice that will initiate a process after the medical history is obtained and the work-up process will be started. HK Walker and co-workers remark:

> "Physical examination is the process of evaluating objective anatomic findings through the use of observation, palpation, percussion, and auscultation. The information obtained must be thoughtfully integrated with the patient's history and pathophysiology. Moreover, it is a unique situation in which both patient and physician understand that the interaction is intended to be diagnostic and therapeutic. The physical examination, thoughtfully performed, should yield 20% of the data necessary for patient diagnosis and management" (16).

However, this is the part of the medical evaluation that may be most problematic. While 20% of the information may be obtained through the physical exam these 20% may be the critical parts that will determine the direction of the investigation and may in fact determine to some degree the outcome of investigation.

2.4.2. Medical error: bias

Physical exam can not only guide diagnostic considerations but determine and misguide the clinicians and perpetuate clinical bias and thus lead to catastrophic consequences. The medical literature is rife of this problem and we are cautioned not to overly rely on the "good old habits" and practices that we were taught in the beginnings of our medical careers. Medical errors are often based on errors of various forms of bias, such as the so called availability error which represents a form of decision-making error where recent experience – missed or discovered – will guide further decision making. Error of representation is a form of error when a clinician makes an erroneous decision based on how well a clinical or physical presentation fits the classic presentation of an illness. If a patient has shortness of breath, cough and crackles on physical examination one thinks of congestive heart failure even though a picture of pneumonia

or pneumonitis caused by toxic fumes are just as plausible. Another form of medical error making is the anchoring error when a clinician clings steadfastly to her or his initial clinical impression and all available evidence is dismissed in favor of the first impression to which he is "anchored" and he thinks is the right diagnosis. "Attribution errors involve negative stereotypes that lead clinicians to ignore or minimize the possibility of serious disease. (17)" Patients' complaints may be dismissed as "just another drunk" or as those of a psychiatric patient and yet a serious illness may be overlooked. Finally, there are medical errors that emanate from the fact that the physician feels compassion or sympathy with the patient and thus certain painful or uncomfortable tests such as a pelvic exam or multiple venipunctures for blood cultures are waived when affective errors are committed. The basis of these medical errors are often the initial physical exam that will lead down an erroneous – or correct – path. (18) Physical exam thus ought to be regarded as just part of the decision making and subject to errors not only the detection errors but may contaminate further decision making.

2.4.3. Evidence for physical exam's utility

Physical exam to assess volume status is an interesting undertaking. Studies that investigate fluid assessments in patients are typically in the clinical situation of congestive heart failure (CHF). Assessment of congestive heart failure is essentially the assessment of fluid status as all fluid accumulation with elevated cardiac filling pressures and pulmonary edema with inadequate fluid excretion essentially define CHF. Thus evaluating studies that assess fluids in congestive heart failure fall in the realm of fluid assessment (19). However, studies that compared physical exam to other means of assessing fluid overload or fluid status have all showed a sorry picture as the physical exam was not at all diagnostic. In a well renowned study that aimed at prospectively differentiating shortness of breath etiology from cardiac failure from other etiologies such as pulmonary etiology the diagnostic yield was rather low. This included both the sensitivities and the specificities of physical examination.

This was a prospective study of Breathing Not Properly Multinational Study (19) patients were serially examined in the emergency room as they were identified in the emergency rooms with the chief complaint of shortness of breath. A total of 1586 patients were enrolled in seven sites including five in the United States, one in France and one in Norway. In this study specific efforts were made to differentiate between fluid overload, CHF and its diagnosis based on physical findings and an alternative method using the biomarker B-type Natriuretic Peptide (BNP). While this was a validation study for the use of BNP to diagnose CHF the study had

other relevant findings and conclusions namely that physical exam alone was a poor discriminator between fluid overload from CHF and dyspnea not caused by fluid overload.

Forty nine percent of patients were confirmed CHF by physical exam alone. In clinical practice we use lung crackles as the most reliable sign of CHF yet when examined by an emergency room physician and the examination data were reviewed by 2 blinded (to the actual confirmed diagnosis) cardiologist, only 43% had such rales. The physical findings of CHF could not make the right cardiac diagnosis when two independent cardiologists assessed the available data on the patients. This is less than the fifty-fifty result of a coin toss! The classic third (S_3) heart sound was not even present more than 7% of the patients (n: 1586).

Table 1. 1586 patients' baseline data having shortness of breath. Patients were examined by two independent and blinded cardiologists to assess their status whether they had CHF or not. Maisel AS et al. N Engl J Med 2002;347:161-167. (19)

TABLE 1. BASE-LINE CHARACTERISTICS OF 1586 PATIENTS WITH DYSPNEA.

CHARACTERISTIC	VALUE
Age (yr)*	64±17
Sex (%)	
Male	56
Female	44
History (%)	
Congestive heart failure	33
Myocardial infarction	27
Chronic obstructive pulmonary disease	41
Diabetes	25
Symptoms (%)	
Shortness of breath	
Slight hill	92
Level ground	78
Own pace	76
Orthopnea	53
Paroxysmal nocturnal dyspnea	46
Nocturnal cough	44
Signs (%)	
Elevated jugular venous pressure	22
Rales	
Lower lung fields	43
Upper lung fields	12
Wheezing	28
S_3 gallop	7
Murmurs	19
Lower-extremity edema	42

*Plus–minus value is the mean ±SD.

Similarly, a study by Dao and colleagues (20) who examined the percent accuracy of making the right diagnosis of CHF based on physical findings, patient history or BNP value. Physical findings, again came out as a low predictor of the actual diagnosis, had a low sensitivity though better specificity. The diagnosis of fluid overload in the 250 patients whom they examined could not be determined very accurately; the presence of pulmonary crackles had a sensitivity of 56%, S_3 third heart sound 20%, jugular venous distention 39% and edema 67%. In evaluating these patients the associated specificities were better ranging from 68% for the presence of edema and 99% for S_3 heart sound.

While the disease process of CHF for fluid overload and its detection for assessing fluid status is a good model these two studies outlined above were not conducted on renal failure patients, in fact the Breathing Not Properly study excluded patients with kidney disease. In a subproject (21) of the ongoing Lung Water by Ultra-Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk ESRD Patients with Cardiomyopathy Trial (20) the reliability of physical findings were tested against lung ultrasound to differentiate between fluid overloaded dialysis patients and euvolemic patients. They tested peripheral edema and lung crackles by auscultation, alone or in combination were tested against lung comets on the ultrasound imaging. Over one thousand paired measurements were performed in 79 patients with poor results. The sensitivities of peripheral edema detecting fluid overload – as determined by lung ultrasound comets – ranged from 1-10% while lung crackles indicated instrument detected pulmonary fluid overload 9-27% depending whether the pulmonary edema was deemed mild, moderate or severe. When pulmonary crackles and peripheral edema were combined the sensitivities improved slightly to 13-31%. Specificities were again much better, ranging from 88% to 100%. It is thus clear that physical exam in the dialysis patient population was similarly unable to give appropriate assessment for fluid status.

2.5. The biomarker: B-type Natriuretic Peptide (BNP)

2.5.1. Biology of BNP

As the name implies, this is a polypeptide whose physiological function is natriuresis, that is, sodium excretion. This 32 amino-acid polypeptide is synthesized by the heart ventricles in response to volume-related stretch. First it is synthesized as pre-pro-BNP which is then further processed to pro-BNP as a glycoprotein which then is further processed by the cardio-myocytes to a 76 amino acid N-terminal-pro-BNP (NT-pro-BNP) and the biologically active 32 amino acid molecule BNP (22); its half-life is 18 minutes and molecular weight 3464. BNP is closely related to the atrial natriuretic peptide (ANP) as well as a similar structure CNP. BNP is similar not only in structure to ANP but also in physiology. BNP as well as ANP have similar actions in the kidney, in the collecting ducts and on specific natriuretic peptide receptors. ANP causes renal vascular vasodilation and increased urine flow within 2 minutes after its appearance in circulation in experimental laboratory animals (23), likely through the epithelial Na^+ channel (ENaC). ANP and BNP also cause peripheral vasodilation as well as they block the sympathetic nervous system and block the renin-angiotensin-aldosterone axis (24) essentially antagonizing aldosterone by inhibiting renin secretion. These cardiac hormones cause peripheral vasodilation through membrane-receptors (there are three types) and inhibit cardiac fibrosis and maladaptive hypertrophy (25). Ramnarian and Mehra (26) have reported "a case in which a large atrial myxoma induced overproduction of natriuretic peptides, causing clinically relevant hyponatremia, hypotension and polyuria".

These cardiac hormones are degraded through the neutral endopeptidase (NEP). NEP is expressed in a wide variety of tissues and is particularly abundantly expressed in the kidney which may explain its higher blood levels in renal failure. NEP is an enzyme responsible to degrade a host of other enzymes and it is frequently found on the surfaces of various lymphocytic leukemias. While both ANP and BNP can be measured clinically, ANP is often measured in experimental conditions only and its measuring kits are not as readily available for those in clinical practice as that for BNP or NT-pro-BNP. In clinical practice BNP is typically measured by commercially available kits such as a whole blood essay; Biosite Diagnostics Inc., using the Beckman Coulter Access 2 instrument.

2.5.2. Clinical use of BNP

The use of BNP as a marker of congestive heart failure has really been established in the clinical arena by the previously cited (19) Breathing Not Properly study. This study was able to select patients who had CHF versus those who had dyspnea due to another etiology. The study established that the cut-off value for BNP to diagnose CHF is above 100 pg/mL with a sensitivity of 90% and a specificity of 76%. The BNP study found that there was no other single or combined predictor of CHF more accurate than BNP. The value of BNP associated with New York Heart Association classification. Another study(27) found this blood value of 100 pg/mL to have a 100% sensitivity and 90% specificity with a 100% negative predictive value for "cardiac events" which were "fatal or non-fatal myocardial infarction (MI) in high risk vascular surgical patients". Thus using this marker for both a volume status diagnostic test in CHF as well as an outcome predictor has been investigated and validated.

While there have been multiple validation studies mostly with cardiac catheterization, one European study (28) was able to demonstrate a remarkably strong correlation between end diastolic pressure (LVEDP) (nonlinear regression analysis $r = 0.94$, $p < 0.001$, $n = 60$) as well as pulmonary capillary wedge pressure (PCWP) ($r = 0.73$, $p < 0.001$, $n = 30$). Another study (29) demonstrated this BNP correlation with right sided ventricular volume overload – due to ventricular septal defect – using right heart catheterization and again found the correlation between BNP (as well as ANP) and right ventricular end diastolic pressure to correlate strongly ($r = 0.76$, $p < 0.001$, $n = 44$). Importantly, however, it is not so much the (left or right ventricular) ejection fraction ($r = 0.58$) that determines BNP levels as the right ventricular volume, or its overload ($r = 0.88$, $p < 0.001$, $n = 41$)(30) when measured by cardiac magnetic resonance imaging.

2.5.3. Validation of BNP in renal failure

Validation of BNP utility in renal failure patients on chronic hemodialysis have also been done by many, including Antlanger (31) who correlated BNP values to bioimpedance values and found that NT-pro-BNP and the expansion of the Extracellular Water (ECW) space correlated strongly in a multivariate regression analysis ($r = 0.438$, $p < 0.001$, $n = 288$). Validation of BNP in ESRD patients has been done earlier by a Korean group (32) who ever so cautiously concluded that "BNP level seems to have a limited potential for assessment of overhydration in HD patients" even though they correlated BNP values to inferior vena cava diameter and body surface area ratios by 2-D Echocardiography as well as bioimpedance values. They found that

the area under the receiver operating curve (ROC) for overhydration by IVC Diameter was 0.819 and when this was measured by bioimpedance then the ECF/TBW ratio was 0.781 for pre-HD BNP level (n = 49 on HD and n = 723 controls). They also tested these measures of fluid overload against ANP and cGMP as well and found similar correlations though to a lesser degree with cGMP.

2.6. The device

Another method to assess fluid excess or perhaps deficit is through a device that is now becoming part of clinical practice. The use of this device is not entirely wide-spread for many reasons. The principal reason for this is perhaps is lack of experience but also because of finances. Clinical experience, for example in the United States is entirely lacking with bioimpedance. American clinicians do not and have not used bioimpedance results to adjust fluid removal or even fluid optimization in direct patient care. The device certainly has been around for a long time and we have known its clinical utility but bioimpedance measurements have not been translated to clinical practice, perhaps clinical research only. Most of the clinical research with bioimpedance has been done outside of the United States thus papers that reported their findings did not reach the American clinical practitioners as clinically applicable method to assess a patient's fluid status. These papers thus appeared but with less international impact than if the clinical research had been carried out in an American research or clinical environment. Furthermore, payment of performing bioimpedance measurement has not been set either. Because most Asian and European payers pay their clinicians by diagnosis related groups (DRG's) or most clinicians are on a salary introduction of a novel technology is not rewarded financially. In the American market there is no payment for the measurement in the fee-for-service insurance. The scenario is similar to the reimbursement of ambulatory blood pressure monitoring which only pays around $55 per procedure, the use of ABPM is not as wide-spread as its utility would dictate; at this time bioimpedance has no reimbursement schedule even though it already has a Current Procedural Terminology (CPT) code 0358T.

2.6.1. The mechanism of bioimpedance

The description below is not intended to explain the physics of bioimpedance measurements even though the basic understanding of how this device works is very important and perhaps has clinically relevant aspects. The thorough explanation and description of the physical workings of bioimpedance measurements is beyond the scope of this treatise. Furthermore, the discussion and clinical practice related to bioimpedance studies will refer to the device

manufactured by the Fresenius Gmbh Corporation in Bad Homburg, Germany as all of those clinical studies intended to be discussed here were done and performed by using this Fresenius device termed Body Composition Monitor, abbreviated as BCM. When using bioimpedance in the generic form we shall use the proprietary term BCM even though we really should use "bioimpedance" to discuss the procedure.

2.6.2. Physics

The physics of BCM is based on the conductivity of various body compartments at different rates and resistance values. The BCM generates alternating electric currents at a low voltage from 5 kHz through 1000 kHz at 50 different frequencies. High-frequency current can pass through most tissues and the total body water, while low-frequency, low energy current cannot "penetrate cell membranes and thus flows exclusively through the extracellular water"(33). The current is passed through the patient using conductive electrodes placed on the foot and the ipsi-lateral hand. The electrodes – similar to EKG electrodes – are to be placed at the level of the medial and lateral malleoli of the ankle, and the other foot electrode at the mid-metatarsal bones of the foot. The upper extremity electrodes are placed between the ulnar head and dorsal radial tubercle and the other at the level of the mid-metacarpals. This way there are two electrodes at the ankle and at the wrist. BCM "determines the electrical resistances of the total body water and the extracellular water" and it "enables clear separation between extracellular and intracellular water by the extremely wide range of measurement frequencies" (33).

2.6.3. Theoretical basis of BCM

The basics of body composition measurements the theory of Hanai (34) in which the fluid filled cylinders will conduct electricity differently, especially if they are of different composition. BCM measurements rely on the basic resistivity of tissues and the derivatives of these measurements. Resistivity is an intrinsic property of every material unlike resistance. Resistance increases and is inversely related to cross sectional area. Lean tissues contain about 70% water and the rest is protein and minerals. Fat tissue is no more than 20% water – the rest if lipids – and when excess fluid or overhydration is measured it is a compartment of 100% water.(35) Therefore, in lean tissue it is the intracellular fluid that is predominant while in the adipose tissue it is the extracellular fluid (36). This is the body composition model as opposed to the pure volume model which only takes intracellular water and extracellular water in account. This way excess fluid is calculated by the various tissue hydration status not only the ratio of intracellular water (ICW) and extracellular water (ECW).

2.6.4. Validation of bioimpedance-measured results

The classic methods for measuring total body water space (37) is based on isotope distribution estimation in the extracellular and intracellular water spaces with sodium bromide and potassium isotopes, respectively, deuterium or isotopes of oxygen (38), sucrose or even inulin-based volume measurements (39). These methods that we regard as the gold standard measurements of fluid compartments or that of various tissues such as the volume of fat tissue content are not conducive to daily practice. Fat tissue measurement for example is based on Dual Energy X-ray Adsorption (DEXA) (40) methods but fluid space measurements are based on hemoglobin concentration differences before and after ultrafiltration (41); in the latter study using inulin as well as urea as a marker. These studies mostly done in the 1950's are the classical methods to validate a new technology assessing fluid spaces but they are not practical for quotidian clinical use. It is also telling that some or many of the science relating to these measurements are published in papers dealing with engineering. Their replacement with a new technology such as the use of bioimpedance is a welcome change. On one hand the technology will preserve the ability to measure fluid spaces and on the other hand the cumbersome method of injecting isotopes, tracers or markers is supplanted.

There have been other methods of assessing fluid overload in clinical practices such as the study we already mentioned by Lee (32) who correlated findings of elevated BNP as a biomarker and the ultrasonographic (2D Echo) measurement of the inferior vena cava (IVC) diameter as well as BCM results. When volume-overload was measured by IVC he found the correlation to be so strong that the area under the ROC curve was 0.766. While his study was primarily a study to correlate BNP with other measurements he found a good correspondence among IVC diameter measurement, BNP and BCM results (ECW/TBW ratios). This study by Lee was carried out among 49 dialysis patients and 723 controls. Such validation is important because it proved the accuracy of the bioimpedance technology not only in physiological circumstances but also in disease states, most notably in the dialysis population.

There had been other methods of validation or observed correspondence between the results of BCM measurements such as vascular pedicle width on chest X-ray and BCM results (42). Some have found a correlation (43) between BCM-directed ultrafiltration results and the decrease of blood pressure together with the successful decrease of antihypertensive medications; a validation on clinical grounds. Validation for the use of the bioimpedance method in hemodialysis patients (44) was performed using the BCM measurement results of 1,540

disease-free adults and “back calculating” the body weight, resistance values, age, and height in the hemodialysis population of 483 dialysis patients. The prediction model was thus gained from the healthy individuals and the model was tested to be valid and similarly reliable in the hemodialysis population. The study concluded that “Multiple regression analysis showed a significant relationship among body weight, R, age, and height in 739 men ($r^2 = 0.82$, $p < 0.0001$) and among body weight, R, and height in 724 women ($r^2 = 0.68$, $p < 0.0001$)” where R denoted resistance.

3. OBJECTIVES

We have thus seen that health care providers practicing their art of medicine to assess the physiologically important fluid status, physical exam fails to give guidance. Physical exam is an inadequate method of assessing fluid overload as well as fluid deficit. In addition to this failure to detect fluid overload physical exam is unable to quantitate fluid excess. The degree of abnormality can be estimated with an even lower degree of accuracy. Hence, a method more reliable, more sensitive and more capable to measure the degree of deviation from normal is needed in clinical practice. This dissertation will thus propose two methods to do just that, one using a biomarker and one using an instrumental examination that should satisfy the requirements alluded to in the above discussion.

The dissertation will examine the following interrelated problems and questions:

- What is the clinical importance of measuring fluid excess in the dialysis population?
- What is the clinical utility of using the volume-related biomarker, BNP? What is the clinical relevance of elevated BNP in patients on dialysis?
- What is the clinical utility of using a device such as bioimpedance in assessing fluid status in dialysis patients?
- How does the use of BNP relate to other methods of volume estimation, such as the bioimpedance measurements?

4. METHODS

4.1. Patient population of BNP studies:

This study (45) was "approved by the institutional review board of the Louisiana State University Health Sciences Center in Shreveport. This is a prospective observational feasibility pilot study of 19 consecutively admitted veteran patients who were acutely hospitalized in the Veterans' Administration Hospital in Shreveport, LA, and were determined during their hospitalization to need dialysis. The purpose of this study was to evaluate the clinical utility of making clinical decisions for ultrafiltration based on patients' BNP values. Eleven patients were prevalent ESRD dialysis patients and 8 were incident dialysis patients. Two of the 19 patients had temporary femoral dialysis catheters, while others had a tunneled dialysis catheter or an arteriovenous fistula or graft. They were evaluated by us as nephrology consultants. These patients were admitted for various indications to the general medical or surgical wards such as pneumonias, cardiac arrhythmias, bone fracture, CHF, chest pain, alcohol withdrawal, gastrointestinal bleeds, and other indications. Their indications for hospital admission varied and their symptoms were often unrelated to the concurrent presence of volume overload." The characterization of this population best described by Table 2, below.

These are essentially all African American male military veterans from the Viet Nam era though there were a few patients from World War II. who served in various military theaters. Their socio-economic status was determined by their historical status as living in the "Deep" South and their schooling which was rarely ever higher than high school degree and their body mass index (BMI) was close to 30 kg/m^2 indicating that they were obese.

Table 2: Demographic, clinical and laboratory characteristics of the BNP study population

CHF: Congestive Heart Failure (after reference #(45)

DEMOGRAPHICS n=19	
Age [years]	68 ± 11
Gender [male/ female]	19/0
Body Mass Index [kg/m^2]	29.6 ± 9.6
Diabetes Mellitus [%]	14/5 (73/27)
Incident/ Prevalent ESRD [%]	8/11 (42/58)
CHF diagnosed on admission	8/11 (42/58)
Chest pain on admission [%]	3/16 (15/85)
Ejection Fraction [%] n=16	43.8 ± 15.5
Dialysis access: Fistula/Graft/Tunneled Catheter/Temporary Catheter [%]	9/1/7/2 (47/5/37/11)
Blood Urea Nitrogen [mg/dL]	60.9 ± 38
Creatinine]mg/dL]	7.06 ± 4.50
Albumin [g/dL]	3.1 ± 0.6
C-Reactive Protein [mg/L]	7.06 ± 4.5
Hematocrit [%]	35 ± 9.2
Intact Parathyroid Hormone [pg/mL]	361 ± 363
Calcium [mg/dL]	8.5 ± 0.8
Erythropoetin dose [units/ week]	14,839 ± 1,479
Length of hospital stay [days]	17.2 ± 15.7

4.2. BNP-Study design

This (45) was a prospective observational feasibility pilot study of 19 consecutively admitted veteran patients who were acutely hospitalized in the Veterans' Administration.

"After conventional hemodialysis was started in the hospital, UF was commenced based on the admission BNP value. The UF was targeted to achieve a BNP goal of 500 pg⁄mL. UF was limited to 5 L per session. A descending UF profiling was used in every patient's treatment, and sodium profiling was avoided considering that these were volume-overloaded patients. UF was halted if the patient's systolic BP dropped suddenly or below 100 mm Hg. Dialysis was delivered thrice weekly with UF, and isolated UF was delivered thrice weekly between dialysis days, achieving a 6-times-a-week treatment schedule. Hemodialysis was delivered using a Fresenius 2008K (Fresenius AG, Bad Homburg, Germany) volumetrically controlled hemodialysis machine with Fresenius Optiflux 160 dialyzers. BNP values were measured before dialysis; immediate post-dialysis values were not measured. The decision to continue UF was based on the next-day predialysis BNP value. The patients' indication for UF was evaluated based on the morning BNP value. Since the target BNP was 500 pg⁄mL, patients were deemed volume-overloaded if the BNP was >500 pg⁄mL.

The decision to discharge these patients were made by the primary medical or surgical team after considering the patients' medical, financial, and social realities, which were admittedly less than ideal. We used the nonparametric Wilcoxon matched pairs test for BNP, body weight, and BP and the Student t test for the other continuous data to calculate significance." Although we designed this as a pilot study we did not change the level of significance, that is, we left the p value at 0.05.

4.2.1. BNP-studies' population behavior

Parenthetically, we characterized this population in another, cross sectional study (46) when we evaluated their degree of adherence to the prescribed dialysis schedule. This population was the basis of three studies with BNP. These patients (n = 97) were in the exact same city - Shreveport, LA; USA – living under the exact same condition, perhaps being disadvantaged over the veteran population in that their health care finance was not taken care of and they only received Medicare coverage (US elderly patients' retirement fund financed though the Federal Government) and maybe public assistance. Otherwise this patient population was taken from the same social, genetic and geographic pool. These two cohorts, the veterans and the

community dialysis patients are representative samples of the same population. These patients in this study of compliance had an average achieved Kt/V of 1.4 ± 0.28, a dialysis vintage 5.7 ±4.7 years. The focus of our study was to assess their behavior with respect to adherence to medical advice. We compared them to the findings of non-adherence indicators established by the Dialysis Outcomes and Practice Patterns Study (DOPPS Study).(47) We found that "Most (95.8%) patients were of African American ancestry and had a longer vintage on dialysis."

4.3. Patient population for BCM studies

The patient population of seven studies (48) we performed using the bioimpedance apparatus was decidedly different from that of the BNP studies previously described. This was an East European population of all White people in Budapest, Hungary at Semmelweis University in a single chronic dialysis facility operated by a for-profit chain provider (Fresenius Medical Care) as a contractor for the universal health care system paid by a single, state payer. Patients were treated at this facility from a single territory of no more than 50 miles radius and were all provided free transportation to and from the dialysis facility. The facility treated an average of about 120 patients with end stage renal disease with thrice weekly hemodialfiltration. The patients' target hemodiafiltration achieved Kt/V was targeted to be above 1.3 and the replacement fluid for the treatment to be greater than 21 liters. All hemodiafiltration treatments were performed using on-line generated replacement fluid and all dialysis membranes were of polysulfone manufactured by the same provider. The indices of our patient population is described by one of our publication where we were able to their behavior regarding their interdialytic fluid gain. Table 3 describes some of their dialysis-related characteristics.

Patient characteristics of BCM study population

Table 3. Patient population (n = 100) characteristics after data in reference number " (48)

Age (years)	60.9 ±14.7
Gender, male (%)	56
Diabetes (%)	27
Target weight (kg)	69 ±1.3
Dialysis Access (Arterio-Venous Fistula, %)	82
Delivered Clearance (Kt/V)	1.40 ±0.25
Residual urine volume (mL/day)	362 ±493
Median [25-75%] Residual urine output (mL/day)	100
Hematocrit (%)	36 ±4
Serum albumin (g/L)	40.1 ±3.9
Serum total protein (g/L)	68 ±5

4.4. BCM-population patient behavior

Just as we characterized our patient population for the BNP studies by their behavior relating to their dialytic, renal replacement therapy we also attempted to characterize the patient population that was the basis of our bioimpedance studies. This population of Hungarian patients could be described in many aspects and many respect, however, one behavior that we can examine is also listed in the Dialysis Outcomes and Practice Pattern Study (DOPPS) as an outcome determinant behavior and that is the interdialytic weight gain (IDWG). As we have already seen in the Saran (47) article the non-adherence measures are phosphate level, IDWG, cutting dialysis session by >10 minutes and skipping >1 dialysis sessions a month. Their study concludes that "Nonadherence was associated with increased mortality risk (skipping treatment, excessive IDWG, and high phosphate) and with hospitalization risk (skipping, high phosphate)". The relative risk (RR) of death compared to the adherent patient was 1.12 for increased IDWG, 1.30 for skipping HD and 1.11 for shortening treatment time and phosphate had a RR of death of 1.17. Hyperkalemia, just as in other studies has the lowest RR, 1.04. The greatest risk factor for abnormally high IDWG is dialysis facility size (>125 patients).

Interestingly enough the DOPPS study found that the Japanese patients were the most non-adherent with IDWG (34.5%) compared to the American (16.8%) or European (11.0%) patients.

4.5. The clinical utility of using a device for fluid space estimation: bioimpedance

4.5.1. Methods of BCM studies for fluid overload, antihypertensive medications and obesity

This (49) was a cross sectional study of prevalent hemodialysis patients of the same data base as mentioned above involving 79 patients. "Patients with edema, or ulceration, or those who declined participation were excluded from the study. We collected their monthly laboratory data and their demographic data (Table 3) from the medical records. We prospectively measured their predialysis fluid volumes and degree of OH by a portable whole body, ankle-to-wrist bioimpedance monitor (BCM—Body Composition Monitor; Software version 3.2; Fresenius Medical Care Ag., Bad Homburg, Germany). The instrument calibration was checked and verified monthly as prescribed by the manufacturer. The patients were asked to lay flat just prior to their hemodialysis session in their reclining dialysis chair. Disposable electrode strips provided by the manufacturer were placed on the dorsal surfaces of the hand and foot, at the wrist and distal metacarpal bones over the knuckles, and at the mid-ankle and distal metatarsal bones, respectively. The patients' age, gender, height, weight, and blood pressure were fed into the BCM and then assuring that no contacts were made between the patient and conductive surfaces and far from any potential instruments with an electric field—such as dialysis machines, electrocardiogram (EKG) monitors, and television sets—in a room separate from the place where their dialysis session was to be delivered, the measurements were recorded. BCM measurements were performed in a separate room, purely for our convenience; to perform accurate BCM measurements, it is not necessary to use a separate room. The BCM instrument returns measurements on OH in liters (L), total body water (TBW) in liters, extracellular water (ECW) in liters, urea distribution volume (V) in liters, intracellular water (ICW) in liters, lean tissue mass (LTM) in kg/%, and body mass index (BMI) in kg/m2. Overhydration is a part of the extracellular volume, measured by a model developed by Hanai; the OH is calculated on measurement values, using a model of two conductive fluids (33, 34). Body fat is calculated by the BCM instrument based on the internal algorithms set by the manufacturer. Prior to initiating a clinical study with the use of BCM hydration, blood pressure and antihypertensive medications were only managed based on clinical impression and the clinical signs and symptoms of volume excess or deficit. Laboratory testing was performed in the clinical laboratory of Semmelweis University School of Medicine (Budapest, Hungary) accredited

laboratory meeting all clinical and scientific standards and calibrations required by the State. These laboratory tests were collected midweek for the dialysis patients' monthly laboratory monitoring. The blood pressure measurements included in the study were collected at the beginning of the dialysis session. Calculations were performed by mathematicians at the Louisiana State University Shreveport, Louisiana. Correspondence of clinical data was performed using GraphPad Prism (GraphPad Software, Inc.) software using linear regression analysis, Student's t test as appropriate. Multivariate regression analysis was also performed using SPSS (IBM Corporation, Somers, NY)."

4.6. Whence doth the ultrafiltrate come?

Considering that we are discussing the accurate measure or at least the estimation of fluid status of dialysis patients the question where the ultrafiltrate comes is the next logical step. Do we know when we remove fluid from patients where this fluid is removed from, which fluid compartment is affected by ultrafiltration the most? In order to investigate this question and to assess what we are really doing to patients we devised a cross sectional study of the same patient population described before.

4.6.1. Methods of fluid space determination in dialysis patients

We randomly selected 40 prevalent stable dialysis patients (50) on chronic HD for at least 3 months preceding the BCM measurements in order to assess which fluid space was affected by ultrafiltration. All patients signed an informed consent for the study. All patient were selected from the same dialysis unit we already described before, “patients with known heart disease, absent limbs, acute renal failure, those with a pacemaker or with a skin disease, as well as hemodynamically unstable patients were excluded from the study.” “All measurements took place in connection with the same mid-week dialysis session. After patients consented to the study, their height was recorded and they were carefully weighed and their when undressed to their underwear. Body mass index (BMI) was calculated as weight (kilograms)/(height in meters)^2.They were asked to lay flat in an examination room at the dialysis unit.” …”We measured the various fluid spaces using a portable, whole-body ankle-to-wrist bioimpedance apparatus” the previously described (49). The multichannel, total body BCM instrument using 50 different frequencies “returns values of measurements on overhydration (OH) in liters (L), total body water (TBW) in liters, extracellular water in liters, urea distribution volume (V) in liters, intracellular water (ICW) in liters, lean tissue mass in kilograms”. OH is a calculated value, it is part of the ECV which is greater than the anticipated value based on the previously described validation studies. “Blood pressure recordings were obtained by the dialysis unit staff in a sitting position with the arm supported, 5 minutes after being seated in the dialysis unit, using aneroid sphygmomanometers by the auscultatory technique. All BPs readings were obtained in duplicate, and the average of these two readings was recorded. After the first BCM measurement, patients walked to their dialysis chairs and started their HD sessions. Ultrafiltration was carried out using the interdialytic weight gain based on their previous post-dialysis body weight corrected to the value to remove the amount shown as OH. The maximum UF value was set to be 12 mL/kg/h. The dialysis unit’s Fresenius 5008 dialysis machines (Fresenius AG) were programmed, as part of the unit’s protocol, to deliver a decrescendo linear UF profile, removing the maximum amount of fluid in the beginning and least at the end. No sodium profiling was performed, the dialysate sodium concentration was set at 138 mmol/L, the dialysate temperature at 36 °C. Immediately after the completion of the dialysis session, patients were asked to return to the examination room where the BCM measurement was repeated within 15 minutes of the end of dialysis”. “Data were then tabulated using Microsoft Excel (Microsoft Office 2010, Redmond, WA, USA) and reported as mean ± standard deviation. Statistical analysis was performed with InStat Prism® (GraphPad Software, Inc., La

Jolla, CA, USA) and Statistical Package for the Social Sciences 19 (IBM Corporation, Armonck, NY, USA). We utilized Wilcoxon matched pairs signed-rank to test the significance of differences between predialysis and postdialysis values. Association between BMI and EC volume expansion was examined using correlation coefficients." Considering that we used the very same patient population as described before the description of this cohort (n = 40) will only be expanded or specified by the extra information that the pre-dialysis body weight was 71.0 ±15.5 kg and the population serum albumin level was 3.85 ±0.43 mg/dL.

4.7. Confirmatory study for changes in fluid spaces due to diuretics in hypertensive patients

In a cohort of 60 hypertensive patients referred to hypertension specialty clinic we examined (51) what diuretics can do to fluid spaces using the same bioimpedance technology previously described (49, 50). This was a retrospective study of "60 consecutive patients in the hypertension clinic… referred for undergoing bioimpedance fluid space measurements in order to elucidate an underlying fluid excess contributing to difficult-to-control hypertension. All patients had been screened for underlying metabolic, hormonal, and renal abnormalities as the etiology of their hypertension, and, by exclusion, were found to have essential hypertension. In this particular cohort, normal renal function was defined as serum creatinine <1.4 mg/dL and no underlying renal pathology by a comprehensive laboratory and imaging evaluation. They were all stable on their chronic medical therapy (no interval antihypertensive medication changes >3 months). BP was measured in accordance with the 2013 European Society of Hypertension/ European Society of Cardiology Clinical Practice Guidelines1 in a sitting position at rest by a nurse using an oscillometric automated BP meter (Omron M4-I; Omron Healthcare B.V., Hoofddrop, The Netherlands). Patients' bioimpedance indices were measured using a regularly calibrated BCM multifrequency bioimpedance apparatus… in a manner previously described". "Statistical comparisons between variables were calculated with t test for continuous variables and with nonparametric testing (chi-square) for categorical variables. Linear regression analysis was performed with dependent variables of age, sex, presence of diabetes mellitus, number of antihypertensive medications, BMI, presence of (thiazide-type) diuretics, percentage of OH of ECV, fat mass (percentage of body weight), and creatinine clearance (according to Cockroft-Gault) to examine predictors of ICV:ECV ratio."

"The study population included 60 patients, aged 62.1±13.2 years, with 63.3% men and 30% diabetic (Table 9). Serum creatinine for the cohort was 1.08 ±0.24 mg/dL, with a calculated creatinine clearance according to the Cockcroft-Gault equation of 82.3 ±32.5 mL/min. Fourteen

(23.3%) of the patients had calculated creatinine clearance <60 mL/min, with a mean of 52.3 ±5 mL/min. Serum potassium was well preserved at 4.3 ±0.4 mEq/L."

4.8 Putting the marker (BNP) and the device (BCM) together; synthesis

Now that we have examined how the biomarker BNP fares in clinical practice when assessing fluid status and we have seen how the bioimpedance apparatus is used to establish patients' overhydrated status both in the dialysis population and in the non-dialysis, hypertensive population the question arises how these methods may relate to each other. The question is whether assessing the fluid status of a patient with BNP or BCM result the same assessment and whether establishing a patient's fluid status by one method can be concluded by the other. We have also seen that physical examination falls short of the correct assessment and when the physical exam is compared either to BCM or to BNP the results can be quite surprising and contrary to the established wisdom of correct assessment by the physical exam.

4.8.1. Study design: BNP vs. BCM

Thus, we designed a study (52) to establish the above concordance between the two measurements by this observational cohort study that evaluated the correspondence between bioimpedance-measured overhydration percentage (OH%) and BNP. We measured predialysis OH% by bioimpedance apparatus and BNP by microparticle enzyme-linked immunoassay in 41 prevalent stable hemodialysis patients, 19 (46%) women, aged 58.9 ±14.5 years." The cohort, where we took our sample for this study was from the same previously described and discussed. The cohort's characteristics are listed in table 4. The BCM measurements were taken the exact same manner as previously described using electrodes at the mid-metatarsals and between the medial and lateral malleoli on the foot and also between the radial and ulnar tuberosities in the wrist and mid-metacarpals. Patients were lying on an examination table away from conducting materials before their dialysis sessions. "Venous blood samples for BNP were taken after the bioimpedance measurements but prior to the dialysis session; they were processed by the state-certified laboratory without delay using a microparticle enzyme-linked immunoassay (Abbot, Abbot Park, IL, USA)."

Demographics for the BNP vs. BCM study population

Table 4. (after Table 1. in reference #(52) Demographics and groupings for volume estimation in dialysis patients: The concordance of Brain-Type Natriuretic Peptide measurements and bioimpedance values. Data are expressed as percents (%) for categorical variables and means ±SD for continuous variables. The division of the entire cohort based on BCM OH% is depicted in the third and fourth columns. P-values are denoted when significant or borderline. BCM = Body Composition Monitor; NS = not significant; OH = overhydration; SD = standard deviation. ACE-i = Angiotensin Converting Enzyme inhibitor; ARB = Angiotensin Receptor Blocker

	Overall cohort demographics	BCM-Assessed hydration subgroups		
	(n = 41)	OH <15% (n = 15)	OH >15% (n = 26)	*p*
Variables		Means ± SD or percents		
Age (years)	58.8 ±14.5	57.6 ±13.8	59.6 ±15.1	NS
Gender, male (%)	22 (53.6)	46	60	NS
Pre-dialysis weight (kg)	78.48 ±20.1	85.7 ±18.6	74.2 ±19.9	0.07
Body Mass Index (kg/m^2)	28.5 ±5.5	31.5 ±4.7	26.7 ±5.2	0.006
Residual urine (mL/day)	241.5 ±384.7	283.3 ±425.8	217.3 ±365.4	NS
Systolic blood pressure (mmHg)	142.9 ±28.2	141.8 ±25.4	143.6 ±30	NS
Diastolic blood pressure (mmHg)	82.4 ±17.3	81.2 ±13.1	83.1 ±19.5	NS
Mean arterial pressure (mmHg)	102.6 ±19.4	101.4 ±16.3	83.1 ±19.5	NS
Hematocrit (%)	33.8 ±5.1	35.8 ±5.3	32.6 ±4.6	0.05
Albumin (g/dL)	3.9 ±0.4	4.0 ±0.4	3.8 ±0.4	NS
Antihypertensive medication class (%):				
Beta-blockers	34.1	40	30.7	NS
Calcium channel-blockers (%)	14.6	6	19.2	NS
ACE-i or ARB (%)	19.5	13.3	23	NS
Diuretics (%)	4.8	0	7.6	NS
Vasodilators (%)	2.4	0	3.8	NS

5. RESULTS

5.1 Results of the BNP studies' population behavior and adherence study

Most patients were non-adherent as assessed by 2 of 4 measures of dialysis adherence: 29.2% of patients did not attend at least 1 dialysis session per month, and 86.4% shortened their dialysis session by 10 minutes or more at least 1 per month (46).

These parameters were identified as major risk factors for adverse outcome in the DOPPS study. While we found this patient population rather non-adherent there was an interesting pattern of their non-adherence. Patients would be more adherent in aspects they could help, diet, that is and less adherent that was out of their control: cutting the dialysis session short and missing dialysis sessions. This was a poor cohort who would regularly miss dialysis sessions or short treatment time but this they did because they could only get county transportation (free bus ride through the county's social services) and when the bus came they get off dialysis at once so as not to miss their ride. If they missed the ride from home to the dialysis they would miss dialysis. At the same time, when compared to the general American DOPPS population their interdialytic weight gain and their phosphate control was better. To "watch their diet" no extra resources were necessary and they did show that they made an effort even though the difference between the DOPPS cohort and the Louisiana cohort did not reach statistical significance due to the number (97) of Louisiana patients (46).

5.2. BCM-study population behavior results

We investigated (48) the interdialytic fluid excess in our patient population in a retrospective study of a sample size of 100 patients which was effectively all of our patients considering that we had about 16 peritoneal dialysis patients and some were either hospitalized or away the facility. This and all studies presented herein conformed to the ethical principles for medical research involving human subjects in the Declaration of Helsinki (as revised in Tokyo 2004) and was formally reviewed and approved by the Hungarian Ministry of Health, Independent Review Board. In this particular study we sought to find out "whether ambient temperature and relative air humidity had any effect on IDWG in our ESRD patients. Our study hypothesis was that excessive variation of outside temperature and/or humidity may have explained some of the session-to-session variations in weight gains observed between sessions of renal replacement therapy". This was a retrospective, cross sectional study, a chart review of existing data. We chose 3 different days to assess the climatic effect on IDWG; Weekend_1 was humid

(93 % humidity) and warm (24 °C); Weekend_2 was dry (38 % humidity) and hot (33 °C), and Weekend_3 was dry (30 % humidity) and warm (24 °C). These temperature and humidity values refer to the highest values on both of the week-end days preceding the first dialysis of the week. All patients received hemodiafiltration using a dialysate with a sodium content of 138 mEqu/L at 36 °C temperature.

The results of the study showed little effect or influence of the weather on patient's IDWG. The results are summarized by the plot graph in Figure 1 below.

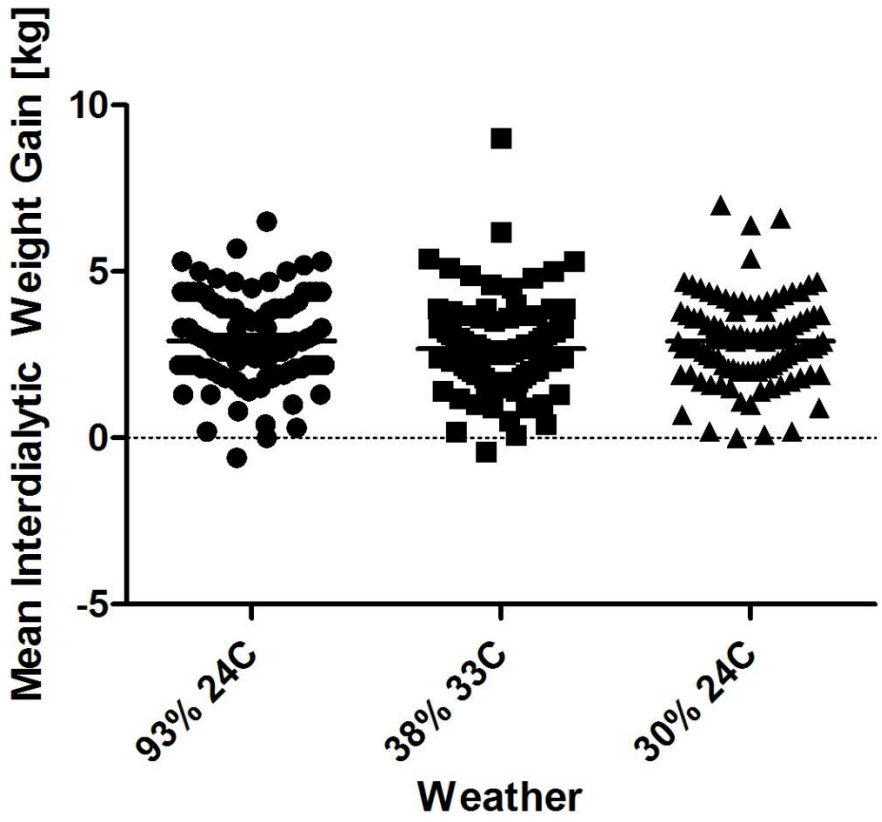

Figure 1. (After reference #48) **Weather conditions and interdialytic weight gain.** Individual and mean interdialytic weight gains under three different climatic conditions. The difference among the three week-ends Friedman one-way ANOVA test could not find an overall difference among the three groups (r = −0.178; p = 0.098). *IDWG:* interdialytic weight gain, *C:* temperature in Celsius grade

The results of the study (Table 5. and Figure 1.) showed that these patients consume about the same amount of liquid or fluid or water or, to be more precise, the gain about the same fluid weight no matter the weather. The "Mean IDWGs showed relatively minor variations between the three groups: Weekend_1 ("humid-warm"): 2,973 ± 1386 mL; Weekend_2 ("dry-hot"): 2,684 ± 1368 mL and Weekend_3 ("dry-warm"): 2,926 ± 1311 mL". There was no difference

among these results when the Friedman one-way ANOVA test was applied among the three groups (r = −0.178; p = 0.098). However, it makes more sense and the statistical manipulations are more meaningful if we examine the association between these groups as pairs. "Paired-samples testing for difference showed higher expected fluid gains on the humid-warm (239 mL; 95 % CI 21–458 mL; p = 0.032) and on the dry-warm weekends (222 mL; 95 % CI −8 to 453 mL, p = 0.059), when compared to the dry-hot weekend. There was no difference in IDWG between the humid-warm and dry-warm weekends (p = 0.676)." Further statistical inquiries were performed using "multiple regression analysis with IDWG as dependent outcome in stepwise selections revealed that the overall models explained only 16–26 % of IDWG variations and least so under dry-hot climatic condition. Weight, as expected, had a persisting positive association, whereas age had a negative association with weight gain, as seen in other studies (47) (elderly subjects are likely to drink less). Most importantly, the amount of residual urine output lost its significance under dry-hot climatic conditions, likely implying increased insensible losses with a more effective sweating process."

Significant determinants of interdialytic weight gain – weight, age and residual urine volume – had a minor degree how many standard deviations a dependent variable will change. These values of standardized beta coefficients ranged from -0.182 for residual urine volume (but on dry "warm-day" only) to 0.38; age had a consistent value of -0.21 – -0.26.

Further analysis whether residual urine output had a discriminating effect on the IDWG data showed little difference. The IDWG is depicted in Table #5 according to the presence or absence of residual urine output (n = 100) as presented in reference (48).

Table 5. [Reference #(48)] **Interdialytic weight gains under specific climatic conditions**. RUO: residual urine output

	IDWG (kg), anuric subjects (RUO ≤ 100 mL, n = 51)	IDWG (kg), non-anuric subjects (RUO > 100 mL, n = 49)	*p* value
Humidity 93 %, T = 24 °C	3.27 ±1.27	2.65 ±1.43	0.024
Humidity 38 %, T = 33 °C	2.75 ±1.50	2.60 ±1.20	0.589
Humidity 30 %, T = 24 °C	3.00 ±1.17	2.84 ±1.44	0.567

When the cohort was separated according to the presence of residual urine then it was apparent that not being anuric only made a difference when the ambient humidity was excessively high.

5.2.1. Implications of BCM-Study population behavior results

As we have seen (48) this is essentially a negative study. Further statistical manipulation of the data would not do justice to the clinical importance of this retrospective data analysis. The value of this study is in, first to characterize this patient cohort who were the subjects of all subsequent studies using the bioimpedance apparatus, and second, it showed that climatic or environmental differences do not influence IDWG in dialysis patients to a great degree but rather it is intrinsically, behaviorally – or culturally – determined what patients perceive as appropriate for their fluid consumption. It also showed that the factors that can potentially alter the patients' fluid or water intake are the same as what the literature has already determined, namely age – elder patients are less indulgent on fluids – and body weight as heavier patients may have a higher IDWG.

5.3. BNP-Study results; BNP-directed ultrafiltration in the hospital:

"Eight patients (42%) were diagnosed on clinical grounds by the physician to have CHF at the time of admission. However, the mean predialysis BNP value was 2,412 pg⁄mL (range, 561 to >5,000 pg⁄mL; median, 2,288 pg⁄mL). This indicates that essentially all patients had volume overload, which was clinically appreciable in less than half the patients. Two-dimensional echocardiography was used to quantify the left ventricular ejection fraction and could be obtained in 16 of 19 patients; its mean value was 44% (median, 45). The mean pre-UF BP was 154⁄81 mmHg (median, 150⁄94 mmHg), which is in line with the above. Of note, chest pain was an infrequent presenting symptom, being found in only 3 cases (15%)." The protocol results of our BNP-directed ultrafiltration treatment schema is summarized by the next table, below.

Results of BNP-directed ultrafiltration

Table 6. Results of a BNP-directed ultrafiltration protocol of hospitalized patients needing hemodialysis for renal replacement therapy. (After reference #(45))

RESULTS	AT THE TIME OF PROTOCOL **INITIATION**	AT THE **END** OF PROTOCOL	*P* VALUE
B-type natriuretic peptide [pg/mL]	2412 ±1479 (range: 561–5000)	1245 ±1173 (range: 345–5000)	0.0013
Number of antihypertensive medications	3.8 ±2.0	2.3 ±1.7	0.00058
Body weight [kg]	88.9 ±27.9	78.1 ±25.6	0.0002
Systolic blood pressure [mmHg]	153.6 ±43.8	132.1 ±27.9	0.0222
Diastolic blood pressure [mmHg]	80.6 ±21.8	68.9 ±14.6	0.0133
Mean arterial pressure [mmHg]	102.4 ±27.3	89.9 ±16.6	0.0329

The ultrafiltration treatment protocol that continued fluid removal targeting a BNP value of 500 pg/mL made a very significant change in every measure we set out to improve. The fluid overload marker that has been traditionally only used to diagnosed congestive heart failure seems to have decreased significantly. The study was conducted for the duration of these patients' hospitalization. Their dialysis and dialysis status was incidental to their hospitalization. Patients were discharged from the hospital by their primary team; the decision to discharge was not related to the dialysis management. Every aspect of this kind of treatment achieved an improvement; if BNP is indeed only an indicator of CHF then CHF has improved but if we use BNP as a marker of fluid excess only then fluid excess improved by a significant

degree. Body weight came down by 10.8 kg on the average and blood pressure decreased very significantly. Importantly, these changes are not significant by numeric differences only or statistical comparison only, but also clinically. An excess of 10.8 liters of fluid has a great clinical impact. Decreasing polypharmacy by an average of 1.5 antihypertensive medications can also make a significant clinical impact beyond its economic value. As expected, blood pressure also decreased both in systolic (by 21.5 mmHg) and diastolic readings (by 11.7 mmHg) and their derivative mean arterial pressure by 12.5 mmHg.

Graphical display of some of these results are below, in figure 2.

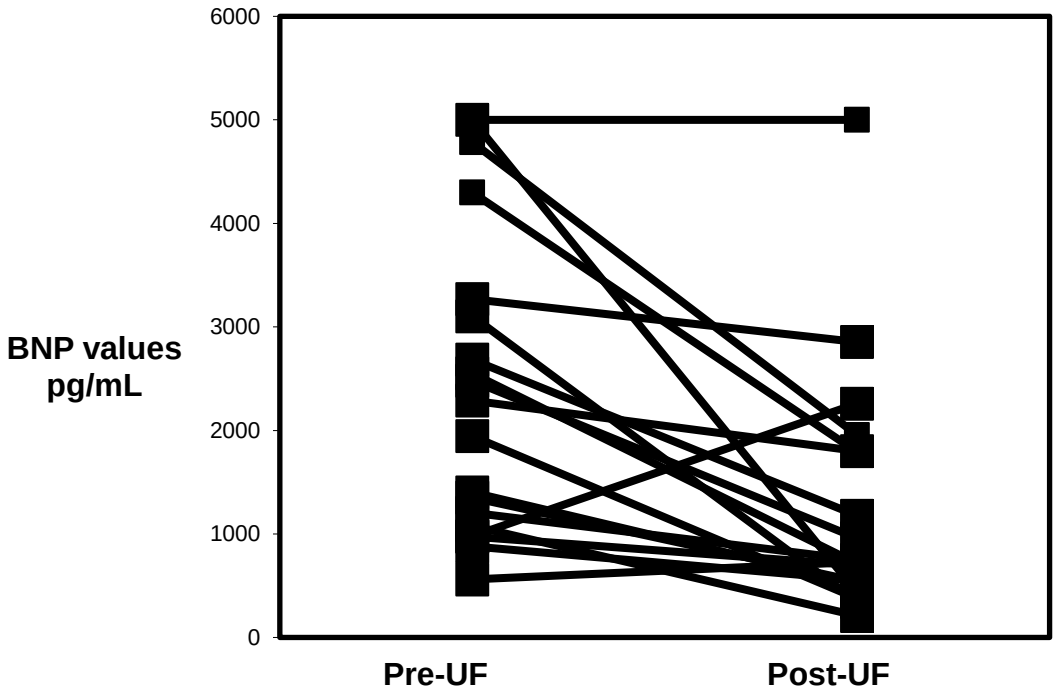

Figure 2. BNP values at the beginning of hospitalization (Pre-UF) and at the time of discharge (Post-UF) of a BNP-directed ultrafiltration protocol of hospitalized patients needing hemodialysis for renal replacement therapy. (After reference #(45))

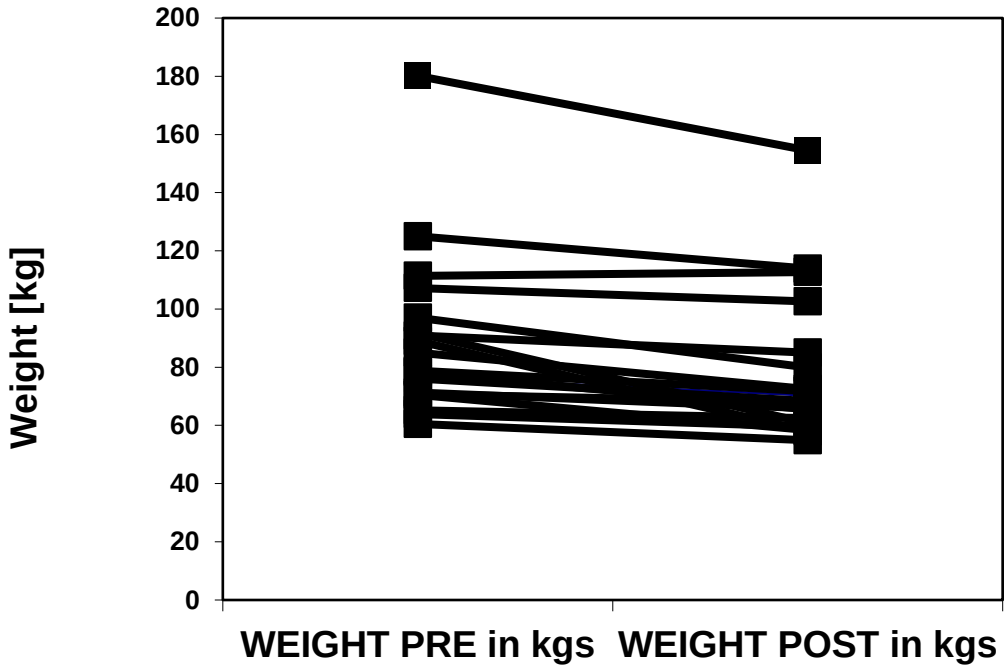

Figure 3. Body weights Pre- and Post- BNP-Directed UF. Body weights of a BNP-directed ultrafiltration protocol of hospitalized patients needing hemodialysis for renal replacement therapy, at the beginning of the protocol (weight pre) and at the time of hospital discharge (weight post). (After reference #(45))

5.4. Presentation of a representative case; BNP for the detection of volume overload:

This is a case (53) where a 58 years old African-American veteran was admitted to the Shreveport, Louisiana Veterans' Hospital when he was found to have an infected aneurysm of his dialysis arterio-venous fistula. He has been on hemodialysis for 2 years prior to admission and used his fistula for dialysis access. At the time he was admitted his blood pressure was 175/93 mmHg despite of 4 antihypertensive medications. His AV Fistula was surgically tied off and his infected aneurysm was resected and he was given antibiotics. Because of acute dialysis access need we placed a 19.5 cm long double lumen dialysis catheter Mahurkar type double lumen dialysis catheter. While the catheter placement was done by a nephrology trainee the procedure was "easy", his right femoral vein was promptly found by the search needle, a

guidewire was passed through the needle and after the usual 2 dilators the catheter was placed without any adverse event. At this time his dialysis was started but he started to bleed next to his dialysis catheter to a significant degree, using up several sets of sterile bandages even though we dialyzed him heparin-free. The patient did not consent to potentially life-saving fresh frozen plasma or blood transfusion because he was a Jehovah's Witness. Attempts were made to control bleeding using sand bags and local pressure to no avail. A thorough hematological work-up was done which was negative that included. Then the dialysis catheter was removed to the advice of vascular surgical consult, however, the site continued to bleed even though pressure and sandbags were applied. The patient was in need of dialysis as he had missed several days of dialysis prior to admission to the hospital. Then a left sided femoral venous catheter of the same type and length was placed, again without difficulty. At this time he started to lose blood near his left sided catheter too; he started to ooze blood significantly. Urgent hematological work-up was done but was entirely negative with normal PT-INR, PTT, von Willebrand factor essay, factor VIII, factor VIII activity and platelet count, although admittedly a bleeding time was not performed. Clinically he was not uremic, his usual Kt/V's were in the 1.9 range. His emergency CT scan of the abdomen and pelvis did not reveal any perforation, hematoma, vascular lesion or catheter-related vascular injury. Vascular surgery was re-consulted but their recommendation to remove this catheter too was not followed in fears of more blood loss as the contra-lateral site continued to bleed. The left sided catheter was sutures in place but the patient continued to lose blood until his hemoglobin decreased from 9.1 g/dL to 4.8 g/dL.

5.4.1. Detection of volume-related bleed

In order to quantify (53) the need for acute continuation of his dialysis a BNP was checked and it was noted to be 3,060 pg/mL. Therefore, it was concluded that the patient was volume overloaded and aggressive ultrafiltration was commenced.

His venous bleeding improved on the first day as his femoral cannulation sites bled less but he did not stop bleeding completely until the second day's 5L ultrafiltration volume was completed. At this time he no longer bled from either site. We ultrafiltrated him daily for 4-5 liters until he lost a total of 15.5 kgs which corresponded to 15.6% of his body weight. During this hospitalization his blood pressure decreased to 119/58 mmHg with only one blood pressure medication. By the 21st hospital day he received a tunneled dialysis catheter and he was discharged with a rising hemoglobin at 6.8 g/dL, though while receiving intravenous iron and intravenous erythropoietin.

His discharge BNP was 1,583 pg/mL though the lowest BNP reached 1,192 pg/mL (terminal BNP values not published). There were 8 BNP measurement throughout his 21 days of hospitalization which are denoted on the graphs below together with his body weight. The BNP decline is clearly shows a remarkable straight line though occasionally it rose as the peripheral vasodilator antihypertensive medications were discontinued successively.

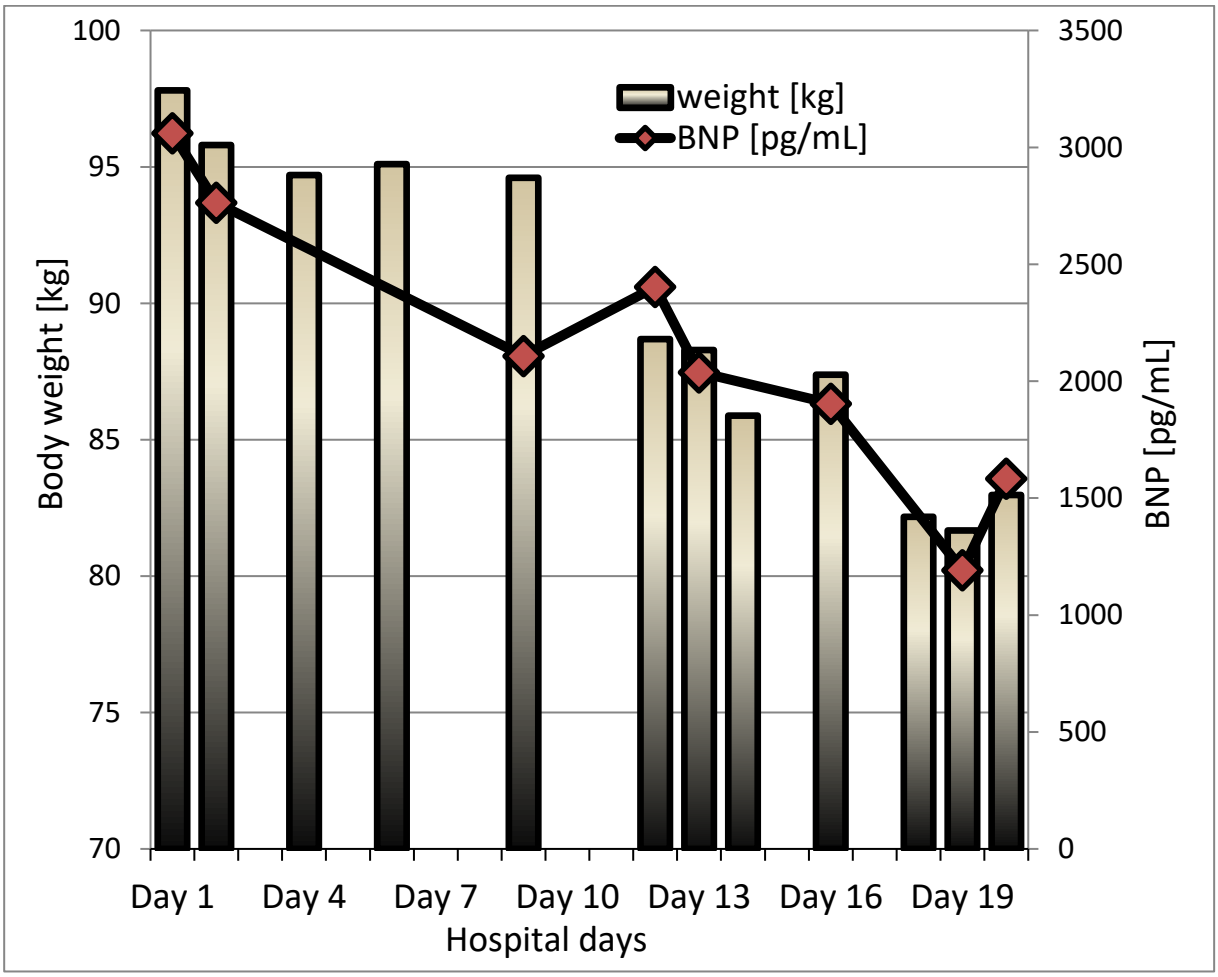

Figure 4. Hospital days vs. body weights and BNP Hospital days, body weights [kg] and BNP values of a representative patient case with hypervolemic bleeding. (After reference #(53))

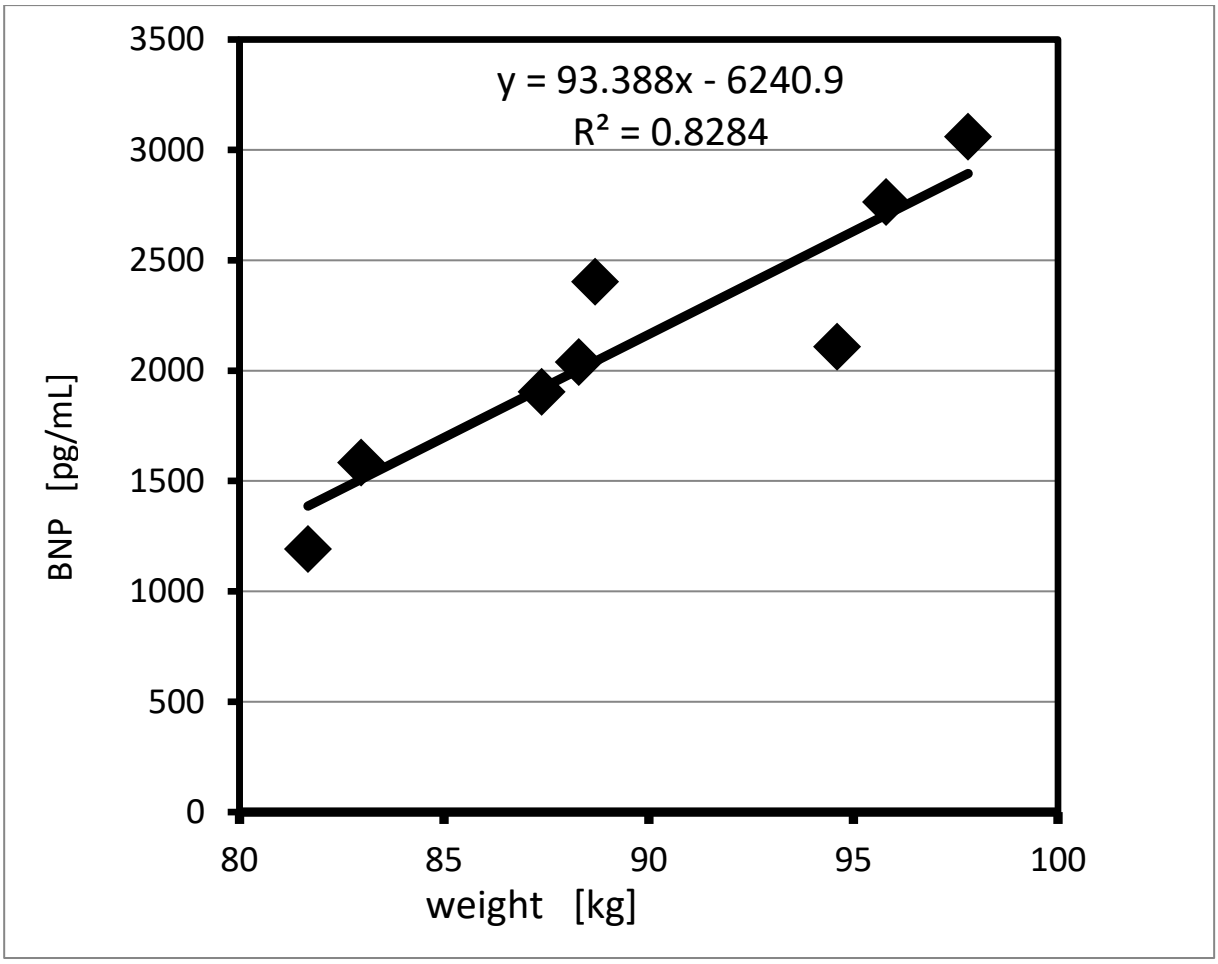

Figure 5. Correlation of body weight with BNP in a representative case of a dialysis patient with hypervolemia-related post-procedure bleed. (After reference #(53))

5.5. Results of Bioimpedance study; antihypertensive medications, obesity and blood pressure:

Table 7. (After Table 1. in reference #(49))

"There were only 22 (29.3%) patients who were managed with no or one antihypertensive medication and 11 (14.7%) patients had five or six medications; the mean medication count was 2.4 ±1.5 with a 50.7% prevalence of diuretic use. The patient population had a mean vintage of 66.5 ±57.1 months (range, 2–312 months) and a residual urine output of 442 ±521 mL/day. The difference in residual urine volume between those with 0 or 1 antihypertensive medication versus the rest of the cohort was nonsignificant (390 ±550 mL/day vs. 476 ±506 ml/day; p = 0.48). On the average, patients were overhydrated by 2.6 ±2.4 L."

Results (n: 79)	Mean ±SD
Body weight (kg)	78 ±16.6
Height (cm)	165 ±10.6
Systolic blood pressure (mm Hg)	133 ±22.3
Diastolic blood pressure (mm Hg)	75.7 ±10.4
Mean arterial pressure (mm Hg)	94.7 ±13.3
Mean number of blood pressure medications	2.4 ±1.5
Diuretics (%)	50.7
Beta blockers (%)	64
ACE-inhibitors/ARB (%)	53
Calcium channel blockers (%)	51
Other vasodilators (%)	23
Vintage (months)	66.5 ±57.1
Residual urine volume (mL/d)	443.7 ±521.2
Interdialytic weight gain (L)	2.2 ±0.9
% Interdialytic weight gain/body weight (L)	2.8 ±1.1
Body composition monitor measurements	
Overhydration (L)	2.64 ±2.4
Urea volume of distribution (L)	35.1 ±7.7
Extracellular water (L)	18.4 ±4.0
Intracellular water (L)	17.9 ±4.2
Lean tissue mass LTM (kg)	34.5 ±11.3
Body mass index (kg/m^2)	28.9 ±5.7
Fat (absolute amount) (kg)	29.8 ±11.7
%Fat/body weight	36.4 ±11.6

5.5.1. BCM Measurements and the number of antihypertensive medications

"We found a significant correlation between OH and systolic blood pressure (r = 0.39; p = 0.0006) with each liter of OH generating 3.6 mm Hg. This positive correlation between the number of antihypertensive medications and the degree of OH held true even when those

patients with no blood pressure medications and those with five or more medications were excluded (r = 0.33; p = 0.047)."

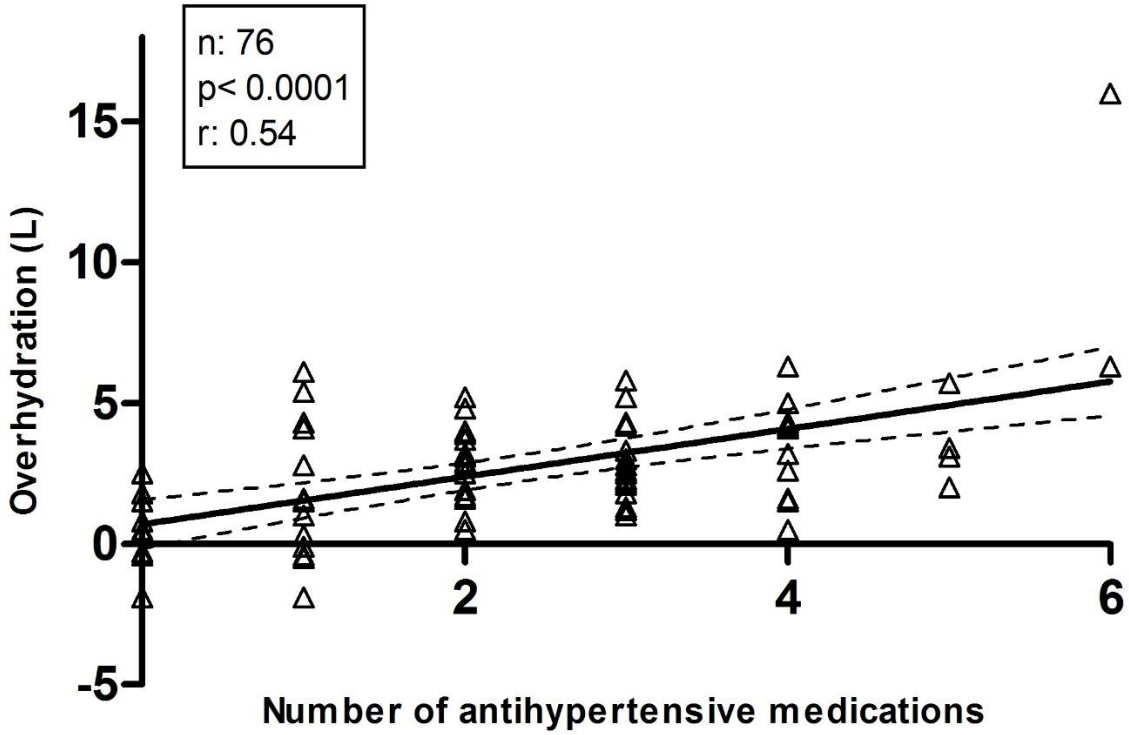

Figure 6. The number of antihypertensive medications and overhydration. (After Fig.2 in reference #(49)) The number of antihypertensive medications has a strong relation to the degree of overhydration as measured by bioimpedance. Linear regression analysis: n = 76, p <0.0001, r = 0.54 and multivariate regression analysis coefficient: 0.673, p <0.0001.

5.5.2. BCM Measurements and the use of diuretics

Additionally, the use of diuretics in dialysis patients does not seem to prevent fluid excess. "We also found a positive correlation between the use of diuretics and OH (p ±0.003, two-tailed Student's t test); diuretics provided no protection from OH." There are multiple claims and schools of thought to give diuretics to patients with ESRD on peritoneal (54) dialysis, or in the intensive care unit while the patient has acute kidney injury (55) or to patients on HD (56) mostly with the perceived potential to decrease symptoms of pulmonary edema secondary to volume overload. Our study, in fact seems to confirm the opposite as seen on Figure 6. The

scatter plot clearly shows a reverse association between diuretics use and overhydration measured by BCM and expressed in liters.

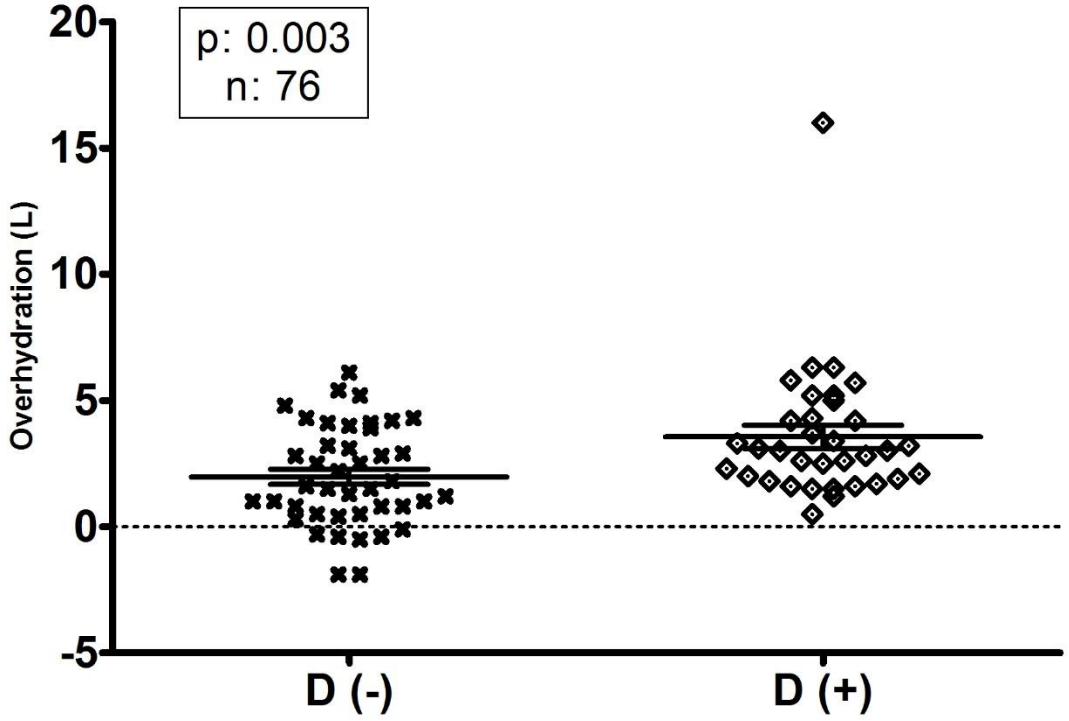

Figure 7. Overhydration in the presence of diuretics

(After Fig.2 in reference #(56)) In the presence of diuretics D (+), the degree of overhydration is significantly greater than in its absence D (-). p = 0.003, two-tailed Student's t test.

5.5.3. BCM Measurements and body mass index (BMI), fat and body weight

"We found no evidence for OH having a relation to body weight (r = 0.001; p = 0.99), body mass index (r = 0.17), age (r = 0.08), and vintage (r = 0.04). When obesity is expressed in percent body fat, it had a very significant negative correlation (r = -0.53; p = 0.0001). With every 10% increase in body fat, there is a decrease of OH by about 1.2 L. Such protection from OH could not be demonstrated by a correlation between the residual urine output and OH (r = 0.07); interestingly, residual urine output did not correspond with blood pressure readings (albeit, admittedly inaccurate blood pressure readings; r = 0.01). The multivariate regression analysis revealed similar results. Factors associated with OH were the total number of antihypertensive medications (standardized coefficient, 0.673; p <0.001), percent body fat (standardized coefficient, -0.492; p = 0.002), and serum albumin (standardized coefficient, -0.191; p = 0.051)."

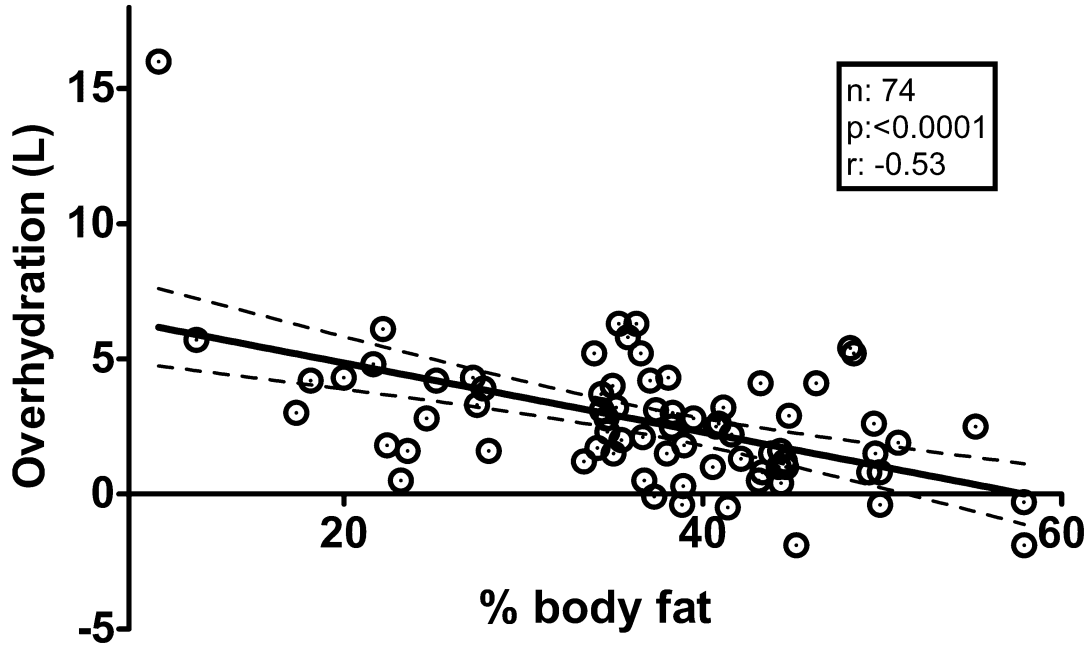

Figure 8. Overhydration and % body fat. (After Fig. 3. in reference #(56)) Scatter plot of percent body fat versus overhydration: "an inverse relationship indicating that a greater body fat is associated with significantly less fluid retention. $p < 0.0001$, $r = -0.53$; multivariate regression analysis coefficient: -0.492, $p = 0.002$". Linear regression line with 95% confidence interval is shown; note its relatively narrow spread.

"We also found that obesity is not associated with fluid retention when OH is correlated with body weight ($r = <0.01$) or BMI ($r = 0.1$). Percent body fat, however, does have a reversed relationship with OH; the equation of the linear regression line between percent body fat and OH is **$y = -0.128x + 7.041$** ($r = 0.53$; $p < 0.0001$."

Note that very obese patients are very unlikely to have excess fluid and very thin (and frail) patients are very likely to have fluid overload.

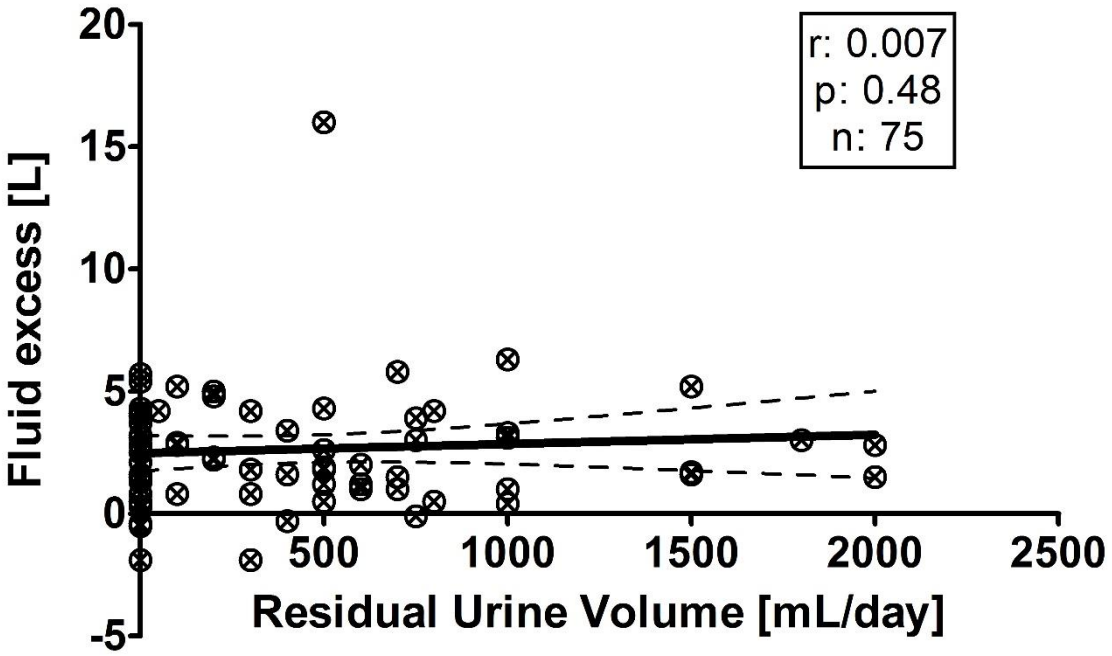

Figure 9. Residual urine volume and fluid excess. (After Figure 4. in reference #(56)) Residual urine volume and fluid excess: no relationship could be shown between residual urine volume and the degree of overhydration. n = 75, r = 0.007, p = 0.48; multivariate regression analysis coefficient: 0.009, p = 0.93.

5.5.4. BCM Measurements and residual urine

"Residual urine output has no relationship (r = 0.007) with OH, and we found no correlation (r = 0.04) between dialysis vintage or patient age (r = 0.08) and OH. Interdialytic weight gain or percent interdialytic weight gain offered little (r = 0.04) to associate OH (standardized coefficient, 0.189; p = 0.851). Therefore, it is not the amount of fluid patients gain that cause OH nor the amount of urine output that determines volume overload, but perhaps the amount of ultrafiltration that could not be achieved because of antihypertensive medications; perhaps antihypertensive medications exacerbate volume overload by preventing a safe, hypotension-free ultrafiltration." Hence the futility of diuretics in dialysis patients.

5.6. Results of fluid space determination; the source of ultrafiltrate

Results are summarized in Table 8.

Table 8. BCM measurement results after ultrafiltration (After Table 1. in reference #(50)) Established by with weight difference (weight before dialysis - weight after dialysis). BP = blood pressure.

	Pretreatment	**Post-treatment**	***p* values**
Measured weight (kg)	71.0 ±15.5	68.6 ±15.5	<0.0001
Removed ultrafiltration volume (L)		2.38 ±0.98	
Systolic BP (mmHg)	142.7 ±22.9	124.6 ±17.9	<0.0001
Diastolic BP (mmHg)	83.3 ±13.3	76.2 ±9.8	0.0002
Mean arterial BP (mmHg)	122.9 ±19.0	108.5 ±13.9	<0.0001
Urea volume of distribution (L)	31.38 ±7.28	30.7 ±7.32	0.33
Extracellular water (L)	16.84 ±3.52	14.89 ±3.06	<0.0001
Intracellular water (L)	16.88 ±4.40	16.55 ±4.85	0.14
Overhydration (L)	2.35 ±1.44	0.58 ±1.24	<0.0001
Overhydration (%)	13.60 ±7.30	3.83 ±8.32	<0.0001

Measurement results and the results of the trial are tabulated above. “The mean degree of OH or excess fluid volume 2.35 ± 1.44 L, as measured by the bioimpedance apparatus, was similar to the removed UF during dialysis and corresponded to 13.60% ± 7.30% OH of the EC fluid space”. In this cohort, there was one patient with volume depletion, -1.1% below ECV and 9 patients were severely overhydrated (>15% of ECV). “After treatment, EC compartment volume overload improved significantly with decreased OH volumes 0.58 ± 1.24 L ($p < 0.0001$) and percentage OH 3.83% ± 8.32% ($p < 0.0001$). Although the IC fluid space also decreased from 16.88 ± 4.40 to 16.55 ± 4.48 L, the change was not statistically significant ($P = 0.14$). The EC fluid volume, on the other hand, decreased from 16.84 ± 8.42 to 14.89 ± 3.06 L ($p < 0.0001$). The percentage changes between the fluid spaces were 11.4% ± 4.8% decrease of the EC and 1.9% ± 7.4% decrease of the IC fluid spaces ($p < 0.0001$).”

Data of the fluid spaces are depicted on figures 10 and 11.

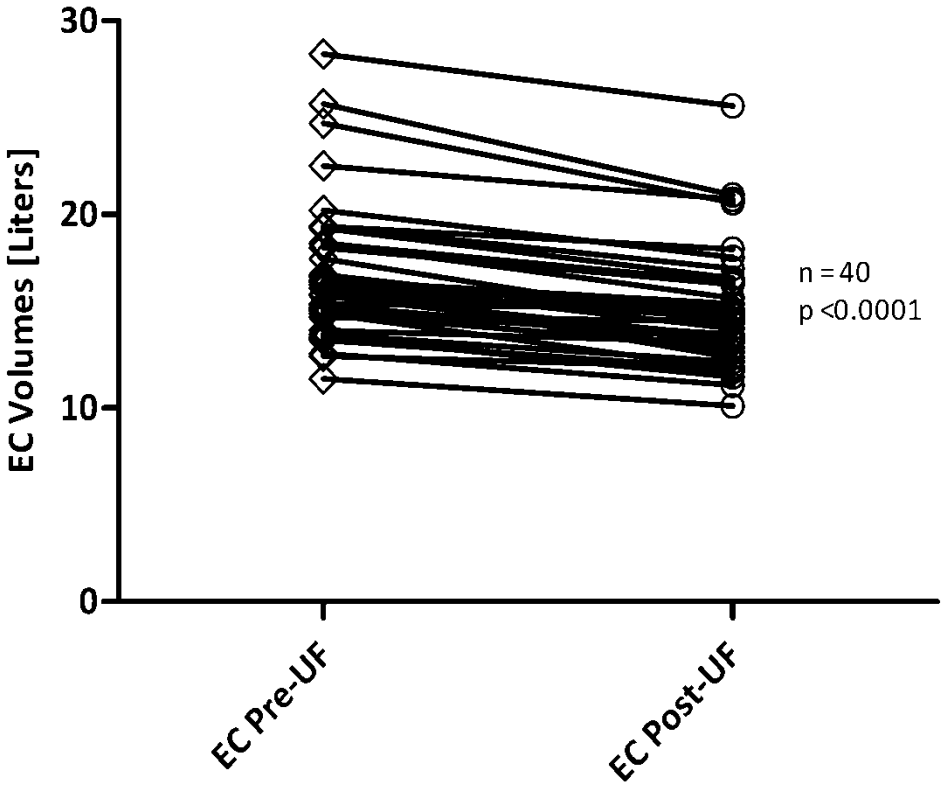

Figure 10. EC Volumes before and after treatments. (After Figure 1. in reference #(50)) Extracellular fluid volumes before and after ultrafiltration in 40 prevalent hemodiafiltration patients. EC pre-UF = extracellular fluid space before ultrafiltration; EC Post-UF = extracellular fluid space after ultrafiltration.

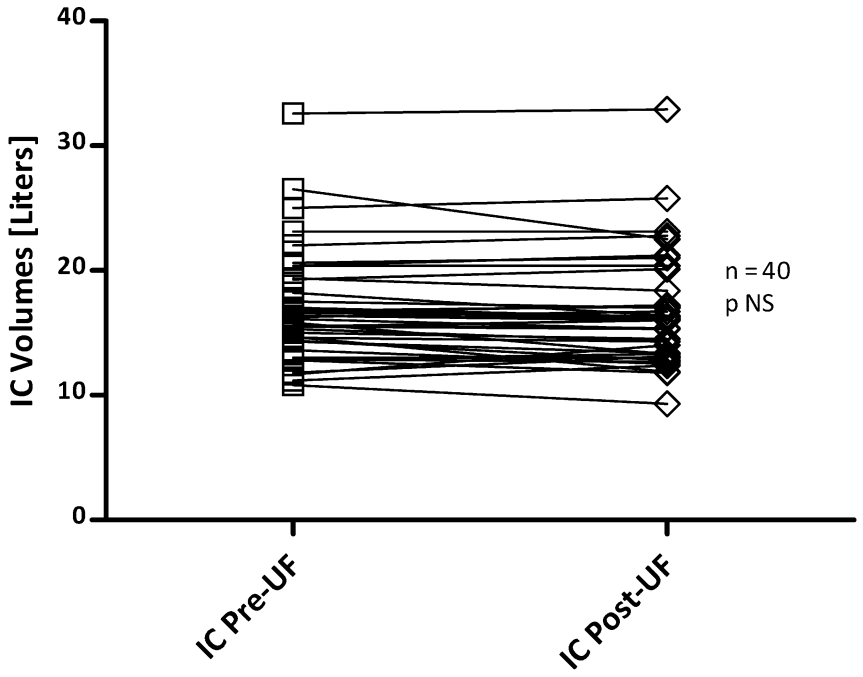

Figure 11. IC Volumes before and after treatment. (After Figure 1. in reference #(50)) Intracellular volume changes during hemodiafiltration. IC pre-UF = intracellular fluid space before ultrafiltration; IC Post-UF = intracellular fluid space after ultrafiltration.

5.7. Confirmatory study for fluid spaces after ultrafiltration

This study has shown that ultrafiltration has effectively decreased the extracellular fluid space and left the intracellular fluid volume intact. The question still remains whether the fluid is removed from the intravascular space. A confirmatory study (57) was performed on these very patients using echocardiography. "Forty-four ESRD patients on maintenance HD were examined just before and immediately after HD, and were compared to 44 normal controls (NC). Transthoracic 3D recordings were obtained using multi-beat reconstruction from 6 consecutive cardiac cycles. LV mass index (LVMi) was evaluated and 3D speckle tracking analysis was performed to calculate global longitudinal (GLS), circumferential (GCS), area (GAS) and radial (GRS) peak systolic strain."

Table 9. Echocardiographic results before and after dialysis (After Table 2. in reference #(57)) Data are presented as median (Inter-Quartile Range) NC normal controls, pre-HD patients before hemodialysis, post-HD patients after hemodialysis. ***** $p < 0.05$ versus NC, **#** $p < 0.05$ versus pre-HD values

	NC	**Pre-HD**	**Post-HD**
Left ventricular end diastolic volume index (mL/m^2)	55.9 (13.7)	56.3 (17.2)	55.6 (13.9)#
Left ventricular end systolic volume index (mL/m^2)	19.2 (4.3)	19.6 (8.6)	19.3 (5.7)#
Ejection fraction (%)	64 (4)	63 (9.5)	66 (10)#
Global longitudinal strain (%)	-20.5 (3)	-20 (3)	-21 (6)#
Global circumferential strain (%)	-21 (3)	-20 (4)*	-22 (7)#
Global area strain (%)	-36 (3)	-33 (5)*	-35 (10)*,#
Global radial strain (%)	61 (8)	50 (12)*	53.5 (20)*,#

This study confirmed that the ultrafiltration improved fluid distribution by reducing left ventricular end diastolic and systolic volume indices, improving and ejection fraction. Although the ultrafiltration increased ventricular strain it actually approached that of normal controls.

5.8. Results of the confirmatory study for fluid spaces due to diuretics' effect

"When the population was dichotomized according to sex (female vs male: 22 vs 38), it was clear that systolic BP was higher in men (140.7 mm Hg vs 129.7 mm Hg; p=.029) and that men were much more overhydrated than women (1.56 L, 6.4% vs 0.17 L, 1.11%; p=.02 vs .03, respectively). There was also a greater proportion of fat content in women when expressed as fat percentage (43.2% vs 31.7%, p<.0001), likely contributing to the greater degree of OH in men, with muscle retaining more water than adipose tissue. There were no other differences among the other indicators in this grouping. Ranking patients by age revealed that those younger than 65 years (n=36) were taking fewer antihypertensive medications (1.9 vs 2.8; p=.01), and

the use of diuretics was much more common among older patients than younger patients (75% vs 36.1%; p=.002). Of the patients taking diuretics, 100% were taking a thiazide-type diuretic (hydrochlorothiazide or indapamide) while one patient took both hydrochlorothiazide and spironolactone. There was no statistically significant association between diuretic use and reduced (<60 mL/min) creatinine clearance (p=0.35), overall creatinine clearance (P=.096), or serum potassium (p=.347). Younger patients' diastolic BP was also significantly higher (82.5 mm Hg vs 73.8 mm Hg; p=.02) but no other difference could rise to the level of statistical significance in bioimpedance-measured indicators of BMI or the presence of diabetes. As expected, patients with diabetes were more likely to have a greater BMI (34.0 kg/m2 vs 28.6 kg/m2; p=.001) and a larger fat content (fat percentage, 40.0% vs 34.1% P=.03); however, the BPs were not statistically different. No other parameter was significantly different in this grouping."

"While BMI >30 kg/m^2 is associated with a greater fat content (39.4% vs 33.3%; p=.01), it is also associated with a greater number of liters of ECV fluid (22.3 L vs 16.8 L; p<.0001) and intracellular (ICV) fluid (23.5 L vs 19.2 L; p=.004). While the number of liters of OH is greater in obese patients (1.7 L vs 0.58 L; p=.05), this degree of OH relative to the extracellular fluid (6.7% vs 21.9%; p=.11) is not significant. Obese patients take diuretics significantly more often (68% vs 40%; p=.03) than non-obese patients and are more likely to be diabetic (44% vs 20%; P=.04). BMI does not seem to relate to BP, as this dichotomy revealed a minor difference in systolic and diastolic BPs (138/80 mm Hg vs 135/78 mm Hg; p=.51). The use of diuretics (n=31) had no correlation with achieved BP (diuretics in treated vs untreated patients: 137/76 [±21.7/14.7] mm Hg vs 135/81 [±15.7/12.8] mm Hg, respectively; p=.66). Diuretic therapy was strongly associated with a more complex medical regimen (total number of antihypertensive medications: 3.2 ±0.9 with diuretics vs 1.3 ±1 without; P<.0001) and advancing age (66.7 ±12.1 years vs 57.2 ±12.6 years; p=.004). OH was increased to a nonsignificant degree in the group that used diuretics (5.9 ±11.3% vs 2.9 ±6.4%; p=.21)." "Total body water did not statistically differ in the two groups (41.8 L vs 40.5 L; p=.64) in the values of either ICV or ECV (Figure 11). The ratio of ICV:ECV, however, seems to have been significantly affected, with a ratio of 1.15 ±0.13 among those not taking diuretics but 1.05 ±0.16 among those taking diuretics (p=.017) (Figure 12). Q-Q plots of ICV: ECV distribution were in keeping with normal distribution for the entire cohort as well as for the subcohorts (treated vs untreated with diuretics). Linear regression was performed with stepwise selection, with multiple dependent variables included (Table 10). The final model (step 5) selected OH percentage, fat content

(percentage of body weight), presence of thiazide diuretics, BMI, and age as independent variables statistically associated, with ICV: ECV ratio as an independent outcome. The model's overall R2 improved significantly from step 1 (0.557) to step 5 (0.921); thus, the final model showed approximately 92% variation of ICV: ECV ratio."

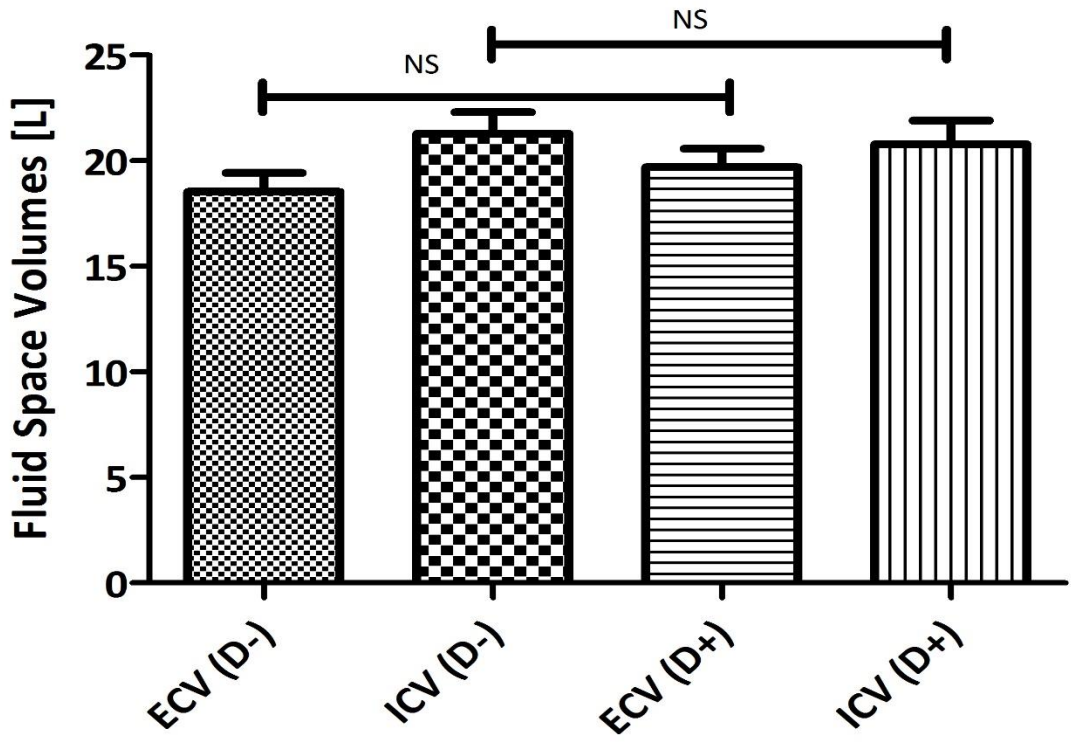

Figure 12. Fluid spaces in diuretic untreated and diuretic treated patients. (After figure 1. In reference #(51)) Fluid spaces in diuretic-untreated (n=29; D-) and diuretic-treated (n=31; D+) groups. ECV indicates extracellular volume; ICV, intracellular volume; NS, not statistically significant (by Student t test). Column heights indicate means and bars indicate standard deviations.

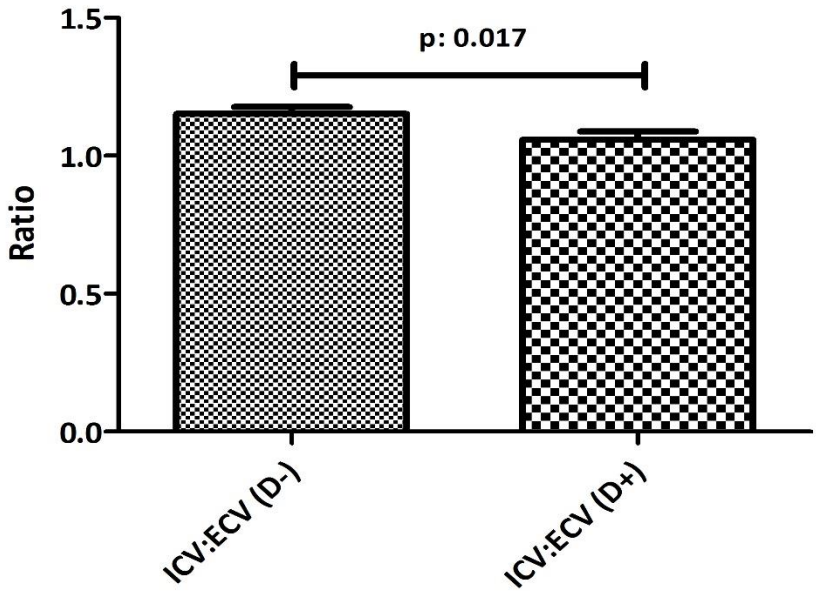

Figure 13. **ICV:ECV Ratios in diuretic untreated and treated hypertensive patients.** (After figure 1. In reference #(51)) "Intracellular volume/extracellular volume (ICV/ECV) ratios in diuretic-untreated (n=29; D-) and diuretic-treated (n=31; D+) groups. P indicates significance (by Student t test). Column heights indicate means and bars indicate standard deviations."

Table 10. Linear Regression Modeling of Predictors, ICV:ECV Ratio (R^2: 0.921): (After Table II. in reference #(51)) "Abbreviations: ECV, extracellular fluid volume; ICV, intracellular fluid volume; OH%, overhydration relative to the extracellular fluid volume; OH, overhydration as measured by bioimpedance. Result of linear regression modeling, with ICV: ECV as an independent variable in linear regression modeling with stepwise selection. Overall adjusted R^2 for the final model: 0.914. Excluded variables from the model (step 5) are sex, presence of diabetes mellitus, number of antihypertensive medications, and creatinine clearance (Cockcroft-Gault formula)."

Variables	Standardized Beta Coefficient	t	Significance
Constant		33.623	<0.0001
OH% of ECV	-0.799	-19.198	<0.0001
Fat mass % of body weight	-0.623	-13.863	<0.0001
Thiazides (yes/no)	-0.143	-3.356	0.001
Body Mass Index (kg/m^2)	0.135	2.953	0.005
Age	-0.09	2.052	0.045

5.9. Results of the synthesis study

"Data is reported with means and standard deviation for continuous variables and percentage (%) for categorical variables. Data analysis was performed at the Department of Mathematics of Louisiana State University by the mathematician-authors of this article. We calculated the area under the curve (AUC) using the receiver-operating characteristic (ROC) calculations. For the BNP true positives, we used a discrimination threshold by the BCM measurement of OH% > 15% (Figure 14). For the BCM true positive validation, we used a BNP value of >500 pg/mL as true positive (52).

"The patients' average albumin was 3.9 ±0.4 g/dL and the hematocrit was 33.8 ±5.1 mg%. The average residual urine volume was 243 ±376 mL/d. A total of 23 of the 41 hemodialysis patients took no antihypertensive drug class medications and the average number of medications was 0.75 ±1; 14 (34.1%) patients took beta-blockers, six (14.6%) took calcium channel-blockers, and the other medications were taken by less than 10% (52).

5.9.1. BNP results

"The average BNP value was 2694 ±3278 pg/mL for the entire cohort; 10 (24.4%) of the 41 patients had a BNP value of less than 500 pg/mL, with an average value of 260.7 ±108.5 pg/mL for these. We measured an 8.5 ±7.0% OH among those with a BNP of less than 500 pg/mL, while the rest of the population had an OH% of 21.4 ±8.0%, corresponding to excess volumes of 1.6 ±1.3 L and 4.4 ±3.8 L, respectively. Those with a lower BNP took on the average 0.4 ±0.8 antihypertensive class medications and achieved a mean arterial pressure (MAP) of 95.7 ±14.4 mmHg, while the rest of the cohort (BNP ≥500 pg/mL) took 0.7 ±1.0 antihypertensive agents and had a MAP of 100.4 ±23.2 mmHg" (Table 10) (52).

5.9.2. BCM Results

"The BCM-measured OH% for our patients was 18.2 ±9.5%, corresponding to 3.7 ±2.6 L expansion of the extracellular volume. A total of 15 (36.6%) of the 41 patients were overhydrated by less than 15% (on average 9.6 ±5.8 %). These patients had a 1.9 ±1.3 L predicted expansion of the extracellular volume and a mean BNP of 674 ±853 pg/mL ($P < 0.0002$ and $P < 0.002$, respectively; both comparison with OH%≥15%). The group with a greater degree of OH (OH% ≥15%) had an excess volume of 4.8 ±2.5 L, that is 23.2 ±7.5% OH. The lower OH% overhydrated patients took an average of 0.6 ±0.8 antihypertensive drug class medications, while the more overhydrated patients took 0.8 ±1.1 antihypertensive agent, with a corresponding MAP of 101.5 ±16.3 mmHg vs. 103.3 ±21.3 mmHg (P = not significant [NS] for both comparisons). With this dichotomy of the population, the residual urine output was similar between the subcohorts: 283 ±425 mL/d vs. 217 ±365 mL/d (P = NS)." Further characterization of the two groups is delineated in Table 10. (52).

5.9.3. Correlation of BNP and BCM

"Our data analysis included an evaluation of correspondence between the two methods, BNP values or OH%. We found that the linear regression analysis describing this relationship could be expressed with the equation of $\mathbf{y = 209.83x - 1133.4}$ ($r = 0.6996$). This relationship was, nonetheless, much better described by an exponential regression analysis, which has more biological relevance. This time the correlation coefficient (r) was 0.6105 and the regression line was described by the equation of $\mathbf{y = 216.4e^{0.097x}}$. Herewith, the regression line intersected the Y axis (BNP value) at 216.4 pg/mL, when the OH% was predicted to be at zero (Figure 15). The ROC revealed a significant correspondence, with the AUC 0.885 for the BNP when the

OH% was set to 15% of OH or greater. Conversely, the AUC on the ROC for OH% was 0.918 when the BNP was set to be 500 pg/mL or greater for the abnormal values (52).

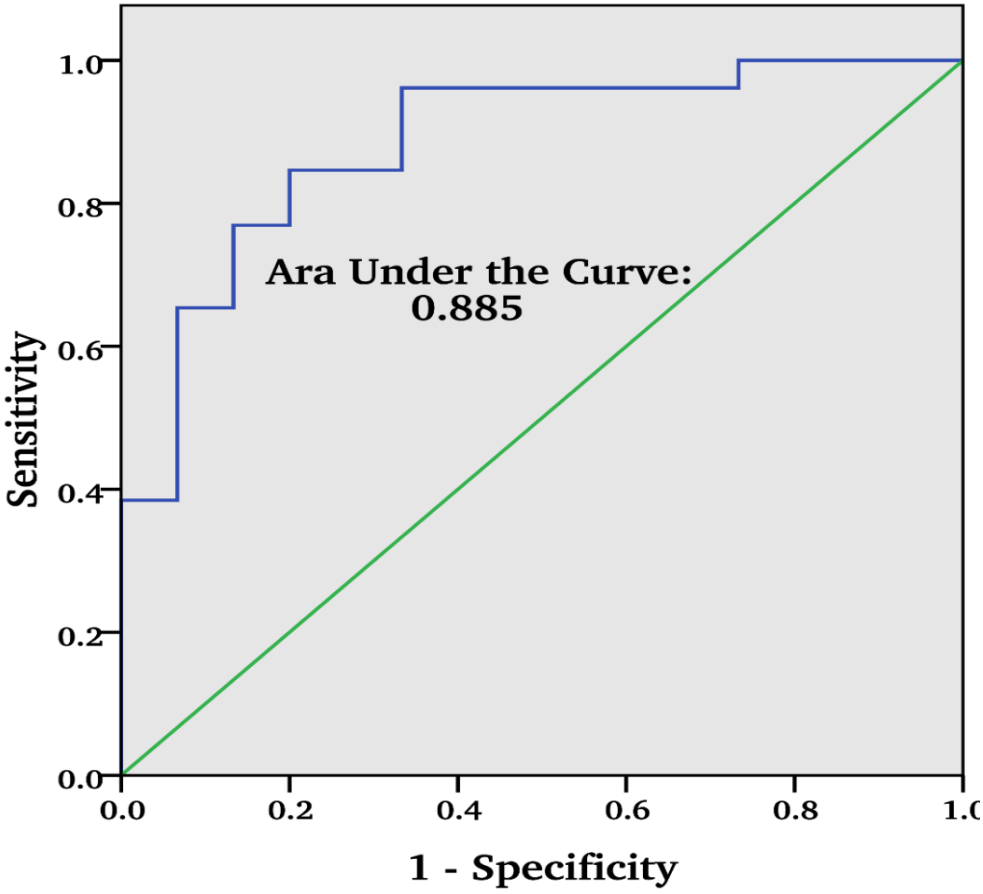

Figure 14. ROC Curve for BNP based on OH% >15. (After Figure reference #(52)) "Area under the curve (AUC) for the receiver operating characteristic (ROC) curve for the BNP (B-type natriuretic peptide) when the discriminating threshold between overhydration and normohydration is used as 15% of the extracellular water."

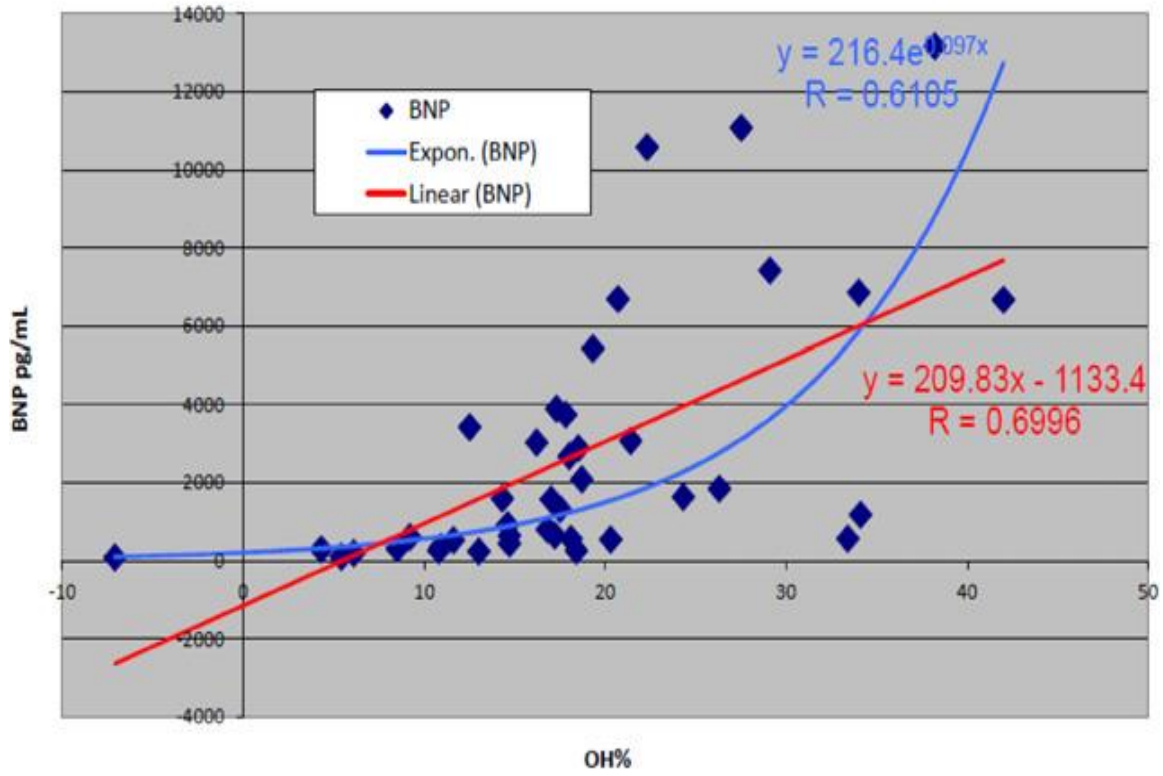

Figure 15. Percent Overhydration (OH%) vs. BNP Values. (after Figure 2. in reference #(52)) "Relationship between OH% (percent overhydration to the extracellular water) and brain-type natriuretic peptide (BNP) values. Linear and exponential regression lines indicate the degree of correspondence between the variables; the exponential regression analysis appears to have a similar degree of correlation "r" and intersects the BNP axis at a clinically meaningful value of 216 pg/mL."

"Our study has attempted to validate measurement of BNP against an instrumentation-based method, bioimpedance measurement, an approach that has received only limited attention so far. We chose a dichotomizing BNP value of 500 pg/mL in keeping with the works of Lee et al.(32) who validated this cutoff value between intravascular volume overload vs. normal intravascular volume. These authors utilized two-dimensional echocardiogram to calculate inferior vena cava diameter to body surface area ratio and obtained an area under the ROC curve 0.819. We, therefore, considered those patients with a BNP ≥ 500 pg/mL as overhydrated or volume-overloaded. According to this criterion, we calculated an excellent AUC 0.918 for the bioimpedance assessment, a similarly strong indicator of the validity of the bioimpedance technique."

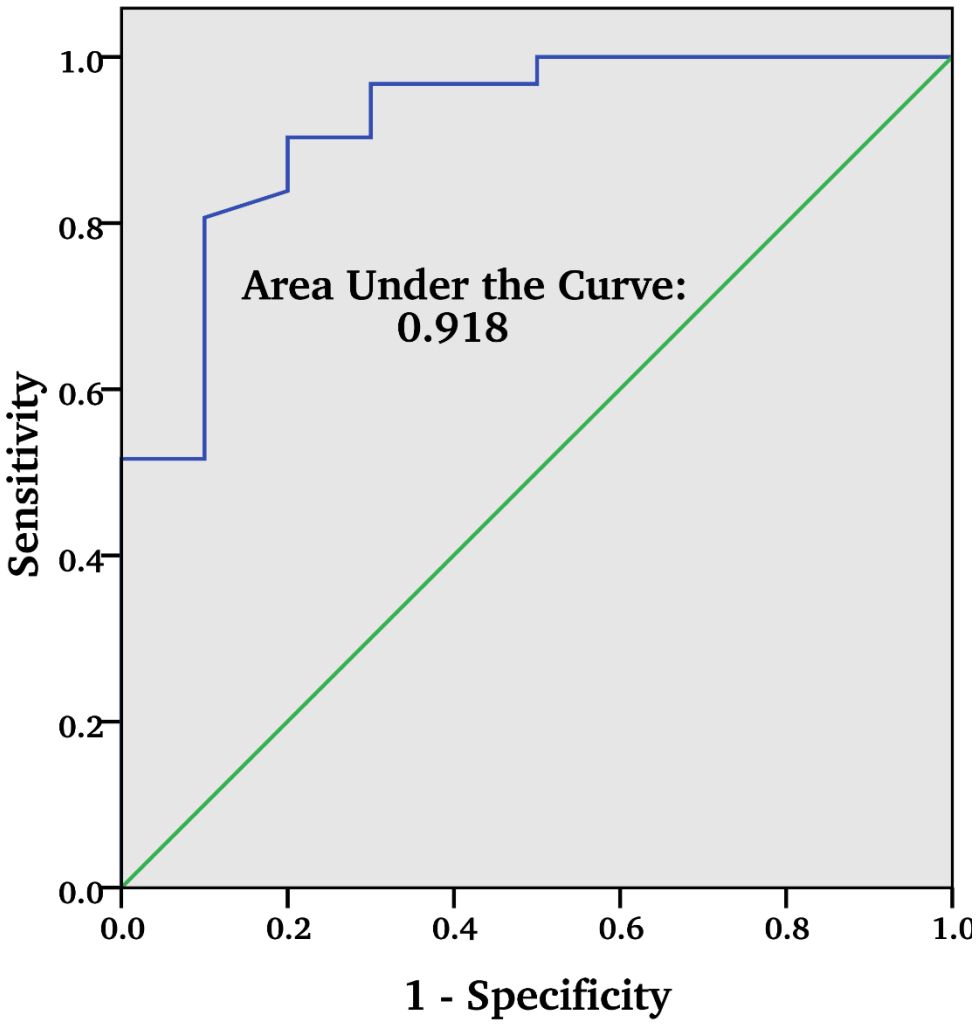

Figure 16. **ROC Curve for OH% based on BNP >500 pg/mL.** (Figure not published formerly) Receiver-operating characteristic curve of the BCM measurement based on the cut-off BNP value of 500 pg/mL, note the very high degree of true positives versus false positives.

6. DISCUSSION

Now that some of the studies aimed at establishing these two new methods have been presented in the preceding pages, it is time to answer the questions posed in the beginning of this dissertation. First, to answer the questions whether what the utility of the measurement of excess fluid may be in the dialysis patient population. While the answer seems obvious and it seems that we can answer that question simply by reminding ourselves to the fact that renal failure involves an inability to excrete fluid there are some less obvious answers answered by recent studies. An adequate fluid removal is dependent on a successful assessment if there is a retention of extracellular – most of the time intravascular – fluid. What this paper is about is to give a feeble attempt to find some diagnostic studies for the correct diagnosis of fluid retention. The main direction of this work is diagnostics rather than therapeutics even though a successful therapy is dependent on a successful and correct diagnosis and even though some of the works presented above appear as describing therapeutic approaches.

If that is true than we should investigate outcomes in relation to diagnostic approaches too not only to the therapeutic interventions. Incorrect diagnostic results can mislead the clinician to take incorrect therapeutic steps. Therefore, discussing outcomes in relation to diagnostics is a valid undertaking.

6.1 Discussion of outcomes researches

With respect to outcomes research the most important hard end point is survival of the dialysis patient who already have a miserable mortality rate only comparable to certain cancers (58). The mortality rate of dialysis patients has been decreasing both in the US (58) and in Europe (59). At the same time, there are still many modifiable risk factors for the mortality of dialysis patients. These include comorbid conditions like diabetes, or peripheral vascular disease (60) or age, cardiomegaly, psychiatric illness, smoking and others as identified by the DOPPS study (61). The number of risk factors for dialysis patients' mortality is in fact quite large but the focus of this investigation is to identify dialysis-related risk factors. The reason for this is twofold, of course; we do want to satisfy the ethical mandate of causing no harm to our patients when we prescribe or deliver renal replacement therapy and second we do want to do our job of treating dialysis patients better. Until 2003 the "crude 1-yr mortality rates among hemodialysis patients were 6.6% in Japan, 15.6% in Europe, and 21.7% in the US" (61) – which then took a turn to the worse until 2011 but then improved again – indicating that there is still

a way to go before patients on renal replacement therapy can be considered a to simply have "another chronic condition".

There are multiple dialysis related risks factors such as inadequate clearance of waste products expressed as Kt/V (62) as identified in the early dialysis studies such as the National Cooperative Dialysis Study (NCDS) or the type of dialyzer membrane used. A more intensive solute clearance with longer dialysis session times and more clearance have been shown in observational studies, most notably in the Tassin-sur-la-Lune dialysis experience (63) or in the USA (64). An augmented clearance has even been shown to be associated with survival in the intensive care units in acute renal failure by our group (65) at the Cleveland Clinic Foundation where we could showed in an observational study that increasing the Kt/V from 0.89 to 1.09 improved survival. Our enthusiasm was quickly tempered by our own study of acute renal failure patients when we analyzed their data and saw that some patients could improve "no matter what we did" and recover but some patients died "no matter what we did" (66). Just as in the acute renal failure arena, increasing clearance has its limits, however, as a large, prospective, clinical trial, called the Hemodialysis (HEMO) (67) revealed that there are limits to what we can do to improve outcome and neither dialysis adequacy nor from high-flux membranes.

Dialysis access has also been an important topic of dialysis related mortality risk mitigation, namely to move away from dialysis catheters and grafts towards arterio-venous fistulas for the purpose of dialysis access. Dialysis catheters have been shown to have worse survival, increased risk of infection and other morbidities (68).

Dialysis session length, longer treatment times also improve survival (69) and longer times between dialysis sessions such as a week-end (70). A study (71) done over 25 years ago has provided evidence that receiving hemodialysis for less than 3.5 hours (three times a week) could double (RR: 1.17-2.18) the mortality compared to those who received more than 3.5 hours in a large European cohort involving 36 dialysis units with 600 patients. Although this too was a retrospective data analysis the results have been confirmed by other data analyses (69). This latter study for the DOPPS group has also shown that the rate of ultrafiltration may be one reason why a longer dialysis session is more beneficial, perhaps fluid removal needs to be limited – on the long-term – in order to improve outcome. These authors found that an ultrafiltration rate (UFR) >10 ml/h/kg bodyweight was associated with a worse outcome. Others(72, 73) found this number to be around 13 mL/h/kg but they all concluded that "UFR's

are independently associated with increased mortality risk in HD patients"(72) with a hazard ratio for death, for example between 1.59 - 1.71 (n = 1846).

As mentioned above (74), a longer interdialytic interval may confer a higher incidence of death and also a higher incidence of other morbidities. These include the incidence of congestive heart failure (presence vs. absence: 29.9 versus 16.9/100 patient-years), any cardiovascular event (44.2 versus 19.7/100 patient-years) or stroke (4.7 versus 3.1/100 patient-years) among other morbidities and mortality.

It is thus highly likely that the adverse results of an extra dialysis-free day on the week-ends is not due to the absence of clearance or the absence of waste product removal but likely the absence of adequate fluid removal. It is notable that cardiovascular events such as myocardial infarcts or congestive heart failure are all directly related to fluid volume excess. Therefore a potential cause for these adverse events is highly likely to fluid accumulation in addition to the possibility of electrolyte abnormalities or more rapid hemodynamic changes on the first day of hemodialysis.

Fluid excess, has in fact been demonstrated to increase mortality in the dialysis population. In a landmark study of 269 prevalent HD patients using BCM measurements Wizeman and co-workers (75) showed that a volume overloaded state by more than 15% of the extracellular volume increased mortality significantly. Their cohort of hyperhydrated patients (n = 58) compared to their normohydrated (n = 211) patients had a statistically significantly less body mass index, more antihypertensive medications, much higher OH% (19.9 vs. 5.7). Their findings were very similar to the studies presented by us. Their pre-dialysis overhydration ΔHS_{pre} (>15%) conferred them a hazard ratio of death of 2.102 (p = 0.003; 90% CI: 1.389-3.179) compared to the normohydrated patients. At the same time hypertension, just as in many other studies, was not directly related to mortality, HR: 0.986 (90% CI: 0.979-0.995 p = 0.014); hypertension in fact seems to provide a certain degree of protection…

In addition to the conclusion of this paper it has been known that volume control can improve survival when volume control is achieved through ultrafiltration and volume monitoring. A Turkish group (76) had monitored and regularly checked their patients' volume status using the cardio-thoracic index (CTI) on chest X-rays and found that a strict fluid or volume control guided by means of a device – here by the CTI on chest X-rays – their patients will benefit. Thus the mandate of driving the ultrafiltration by some objective measurement rather than physical exam alone is strong and ought to be followed. Just as the previous paper by Wizeman

(75) this paper by Ozkahya (76) also showed that blood pressure can significantly be improved all the while the number of antihypertensive medications are decreased provided the intravascular fluid status is improved by decreasing it according to some kind of objective guide.

6.2. Discussion of physical exam-guided fluid management

As a response to this situation, namely that clinicians need to guide their management of hypertension and fluid status based on objective measurements were the studies presented before. The underlying problem is that physical exam is just simply not objective enough and simply unable to assess a patient's fluid status enough to safely guide therapy. In a well-known study, or rather, registry, conducted among community physicians – The Acute Decompensated Heart Failure National Registry (ADHERE) (77) – revealed that those who practice clinical cardiology (cardiologist), were simply unable to guide their diuretic therapy based on physical exam. That study tabulated patients' indicators and body weight of all enrolled discharges from October 2001 to January 2004; the change in weight was assessed in 51,013 patient episodes. All patients were admitted with acute, decompensated heart failure (ADHF), that is, volume overload. The findings revealed that 33% of patients treated and released by cardiologist lost 0 to 5 lbs (about 2L) of weight only. Essentially, an unbelievably small amount of fluid, or nil. Sixteen percent of these ADHF patients released home, had actually gained weight, not lost any; 3% gained 5-10 lbs and 2% more than 10 lbs! Just as the study by Dao (20) and Torino (21) point out the findings of physical exam when compared with an objective measurement do not measure up. "Lung congestion by crackles, edema, or a combination thereof poorly reflected the severity of congestion as detected by ultrasound B lines" as did physical findings when compared to BNP measurements.

6.3. Discussion of objective measurement-directed ultrafiltration

What the presented papers and clinical studies using BNP or BCM have shown is an alternative to "driving blindly". There is no reason why biomarkers such as BNP should not be used in the regular clinical practice. In our study (45) where we directed our UF procedure according to the BNP values of acute hospitalized, chronic dialysis patients we have demonstrated that this method was clinically usable and applicable but even more importantly, as the title claims, it improved care. Even though we were not able to achieve a new dry weight during this

hospitalization of these patients we were able to ameliorate their clinical status. First, we were able to reduce their dry weight by an average of 10.7 ±9.7 kg, the greatest reduction being 30.9 kg. Considering that these "dry weights" were established by our colleagues in the community this indicates that these patients' dry weight was seriously amiss! These patients carried an extra 10.7 kg they did not need. These patients were mostly admitted to the hospital not for heart failure but for other reasons. On the other hand we were able to identify patients with severe volume overload without overt signs of CHF by using BNP measurements; thus the second benefit of using BNP in this patient population was to diagnose heart failure without over signs of such. It then "It appears that the use of BNP is superior to physical examination to identify volume overload, as 11 of the 19 patients were not clinically diagnosed as having CHF." Relying solely on physical exam would have missed 50% of the volume overload. Thus physical assessment is as good as a coin toss! The same could be demonstrated by the case presented (53) after this study; the patient was not obviously fluid overloaded. That patient, however, had an excess of 15.5 kg fluid that was not apparent and we related to the cause of his venous overfill, to his volume overload. Removing the venous congestion improved his care because the source and mechanism of bleeding disorder was discovered: venous overfill. This patient singularly was helped by the BNP method as he was someone who could not be transfused because of religious reasons.

The third benefit of BNP directed ultrafiltration is the improvement of blood pressure control. The above article has demonstrated that removal of fluid will decrease blood pressure and discontinuation of antihypertensive medications become a possibility. This UF method permitted us to reduce the number of antihypertensive medications from 3.8 ±2.0 to 2.3 ±1.7 ($p = 0.00058$) all the while the blood pressure decreased as well; the mean arterial pressure decreased from 102.4 ±27.3 mmHg to 89.9 ±16.5 mmHg; the same was demonstrated in the case report. The additional, forth benefit was that we could decrease the number of medications. While veterans receive medications free of charge it still had a financial impact because these veterans did not need to make clinic visits to adjust their blood pressure medications. Polypharmacy, however, is dangerous not only because of the financial burden it involves but firstly because of the drug-drug interactions and the side-effect profiles that patients accumulate when taking more and more medications. Pill burden is another concern as that is a known risk for patient non-adherence. Another DOPPS study (78) by Fissell and others has demonstrated that taking too many pills will decrease compliance with phosphate binders. Why this is so important is because taking phosphate binders is critically important (79). Those dialysis

patients who use phosphate binders have a survival advantage over those who do not. Additionally, it does not matter what kind of phosphate bonders these patients take, as long as they do take something, according to this prospective study. Polypharmacy instigated by a myriad of antihypertensive medications, and it being a precipitator of non-adherence to phosphate binders is a sad commentary on patient care. A potentially outcome and disease modifying group of medications – phosphate binders – not taken by dialysis patients for the sake of taking medications for dubious reasons – hypertension – is a diminution of patient care!

6.4. Discussion of blood pressure and fluid status

The clinical benefits of blood pressure control in dialysis patients with antihypertensive medications is not at all straight forward and it is a matter of controversy. The idea of decreasing blood pressure is in the hopes to decrease mortality, cardiac events or stroke. This, however, is not demonstrated so clearly by the literature. The above article by Wizeman (75) demonstrated that volume overload was associated with hypertension and volume overload strongly associated with mortality when the ECV was greater than 15%; however, they also mention in their data that a history of hypertension was protective and gave a survival advantage! The Cox adjusted hazard ratios for mortality was 0.986 (90% CI: 0.979-0.995 p = 0.014) in that study. Zager (80) had found no harm for having a pre-dialysis systolic blood pressure up to 180 mmHg – but did find it harmful to have a pre-dialysis systolic BP less than 120 mmHg – in his dialysis cohort of 5,433 HD patients in DCI (Dialysis Clinics, Inc.). On the other hand a post dialysis HTN was systolic BP > or = 180 mm Hg (RR = 1.96, P < 0.015) was harmful. Importantly, post-dialysis blood pressure is more reflective of volume overload. Salem's findings(81), however, are even more troubling. When evaluating blood pressures (n = 649) he compared severe hypertension having a relative risk (RR) of death equal to 1.0; those patients with a moderate hypertension had a RR of 1.52 (p = 0.13), mild hypertension 1.71 (p = 0.04), high normal 2.46 (p = 0.002) and those with a normal pre-dialysis blood pressure 2.59 (p = 0.02). These patients' blood pressure was "normalized" with antihypertensive medications, thus he concluded that "that hypertension has no adverse effect on survival at 2 years in the haemodialysis population". It is, however, well known that good dialysis, done over long hours and aiming to achieve dry weight (82) can achieve both a good blood pressure control and good survival, in addition to achieving this with no or a very small amount of antihypertensive medications. This above cited group led by Charra and Chazot demonstrated(83) that only 1.1%

of their patients needed any medications for BP control and their patients 24-hour ambulatory blood pressure monitoring systolic BP was 119.4 ±19.9 mmHg; diastolic BP: 70.6 12.9 mmHg and mean (MAP) was 87.6 ±13.9 mmHg.

6.4.1 Antihypertensive medications for blood pressure management in dialysis

Our initial hypothesis to resolve this apparent contradiction was that antihypertensive medications actually interfere with adequate fluid removal on dialysis exacerbating intradialytic hypotension. In order to assess what antihypertensive mediations do to blood pressure in dialysis patients we performed a cross sectional study(84) in the previously described cohort in North-West Louisiana. We simply counted how many antihypertensive medications our patients took without change in dose or new prescription for at least 2 months and compared that to their actual pre-dialysis blood pressures. While this study could potentially fall in the error of assignment, that is those patients get more medications who are more hypertensive, we concluded the reverse. We found that the more medications patients received the higher their blood pressure ended up being, as seen on Figure 17. (85)

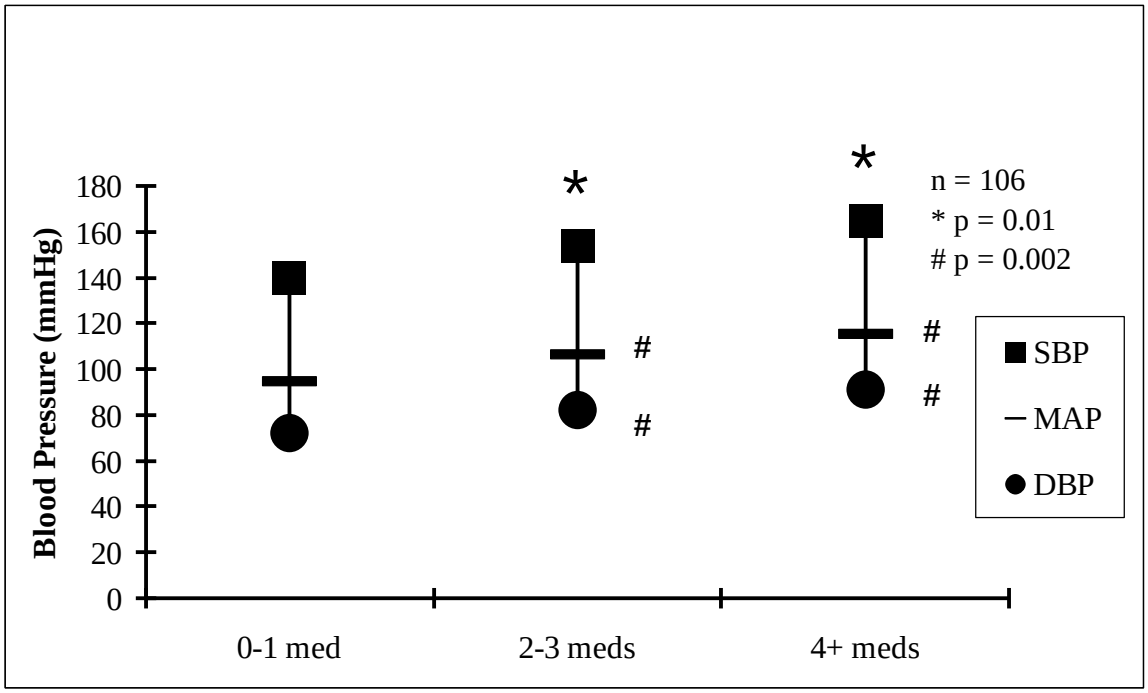

Figure 17. Mean blood pressures grouped according to the number of medications.
(After figure 1 in reference #(84)) "Mean blood pressures (BPs) grouped according to the

number of antihypertensive medications. SBP, systolic BP; MAP, mean arterial pressure; DBP, diastolic BP" Systolic BP is the top of the line, diastolic is the bottom and MAP is the horizontal notch.

Our (84) historical question what the relationship of hypertension, antihypertensive medications and outcome in dialysis patients may be explained by all the above investigations presented and therein lies the clinical utility of objective fluid assessment, by any method. We have shown (84) that escalating antihypertensive medications, giving more and more medications to dialysis patients in fact does not improve their blood pressure control, or is not associated with a better blood pressure control. We have, however, demonstrated in the preceding studies (45) and report (53) that fluid removal will decrease blood pressure.

6.4.2 Fluid management and blood pressure

Fluid removal, will hopefully move patients to the better survival curve Wizeman (75) described, that is fluid removal may eliminate the excess mortality risk described by Wizeman. Onofriescu (85) has shown just that; in a single dialysis unit of 131 patients those patients (n = 62) whose dry weight was managed with bioimpedance versus those whose dry weight was managed based on clinical judgement only without the use of bioimpedance – or any other objective measure of fluid status – had a better survival with an unadjusted hazard ratio for all-cause mortality 0.100 (95% CI, 0.013-0.805; p = 0.03). Additionally, "after 2.5 years, we found a greater decline in arterial stiffness, relative fluid overload, and systolic BP in the bioimpedance group than the clinical-methods group. Between-group differences in change from baseline to the end of intervention were -2.78 (95% CI, -3.75 to 1.80) m/s for pulse wave velocity (p <0.001), -2.99% (95% CI, -5.00% to -0.89%) for relative fluid overload (p = 0.05), and -2.43 (95% CI, -7.70 to 2.84) mmHg for systolic BP (p = 0.4)" (85)

Clinical studies about the utility of achieving dry weight in dialysis show a controversial array of answers. The explanation may be rather simple. One paper for example summarized the message they feel so strong about in the title of the paper: "B-type natriuretic peptide is not a volume marker among patients on hemodialysis"(86). The author "probed" dry weight in dialysis patients and found that "no relationship existed between decline in post-dialysis weight upon probing dry weight and baseline BNP. Furthermore, reduction in the BNP was not required for decline in post dialysis weight. Predialysis log BNP modestly predicted ambulatory systolic

and pulse pressure independently of other risk factors. No relationship was found between decline in BP upon probing dry weight and baseline BNP". "Probing" for dry weight is another expression used when the quotidian word "challenge" is replaced by a more benign sounding word, however, this is still quite horrific. Dialysis challenge means the progressive ultrafiltration to the point where the patient loses consciousness because of hypotension and he has to be fluid-resuscitated. In fact these patients in this author's study had a median BNP concentration that was 93 pg/mL (interquartile range 31-257 pg/mL). These patients were way too "dry". The normal BNP in dialysis patients with absent renal function should be around 500 pg/mL. Because Neutral Endopeptidase function is seriously compromised in end stage renal disease the degradation of BNP should be much higher than in "simple" heart failure patients.

Our study (52) showed that the exponential regression line crossed the Y axis at the BNP value of 216 pg/mL while Lee (32) found this BNP value to be around 500 pg/mL. His patients were categorized whether fluid overloaded or not based on inferior vena cava diameter-body surface are ratios but he also used bioimpedance measurement to confirm his results. Thus Agarwal's (86) patients were volume depleted and the BNP could not help him with more aggressive ultrafiltration. Furthermore, the Breathing Not Properly (BNP) (87) study established patients with an eGFR <30 mL/min should have a BNP to diagnose CHF >90% of the time. Typically studies finding poor correlation between dialysis patients' volume status and BNP are those whose cut-off point is the same as that of patient without renal dysfunction.

6.5. Critical studies on BNP-directed therapy

Others, for example in an Australian emergency room patient cohort claimed that there is no clinical utility of using BNP (88) at all, renal failure or not. This was a study where emergency room physicians were blinded to the results of BNP and when they found out the results they were not supposed to act upon its value. This was a faulty design, with a poor results. The poor results, however, are not due to the problems with BNP because there was no action plan in the study. Therefore testing and knowing BNP results did not affect management and outcome of patients with dyspnea (89). BNP and NT-pro-BNP can accumulate in patients with left ventricular dysfunction (90), with or without symptoms the likelihood that this is related to volume overload is quite high.

Another aspect of using BNP is whether BNP or NT-pro-BNP is used. As we have seen pre-pro-BNP is split to NT-pro-BNP and BNP and thus they are generated in equimolar quantities. However, their degradation is different, the biological half-life is about 2 hours for BNP but for

NT-pro-BNP it is much longer. Thus NT-pro-BNP can and does accumulate while BNP does not. In the heart failure population DiSomma (91) has demonstrated that serial BNP's do track fluid status; diuresing patients with CHF will decrease their BNP, however, NT-pro-BNP will continue to rise, despite of fluid loss – for 24 hours more.

Mitral regurgitation, however, often increases BNP levels (92) – as well as NT-pro-BNP – and give the impression of greater volume-overload that actually present. Additionally, the BNP will improve with repair of the mitral regurgitation(93) indicating that perhaps it is the jet on the left ventricular wall caused by regurgitating blood that elevates BNP. It is not the pressure that raises BNP but the extracellular fluid volume that distends the heart (93). It thus appears that BNP is a reliable marker of volume overload and its clinical use in dialysis patients has a strong potential to improve their care.

6.6. Synthesis of fluid management by objective guides

We have also seen that using a device for assessing volume status will improve care. First it will identify volume overload when present. It can guide in further reducing the estimated dry weight until the BCM-indicated fluid status normalizes. As we have seen in the Wizeman (75) study fluid overload can translate to increased mortality. Hypertension in the dialysis population may simply be a marker of volume overload, a symptom or finding rather than a disease in itself. We have shown in the preceding studies that an ultrafiltration regimen can progressively reduce blood pressure as well. Although hypertension in the dialysis population is a subject of debate and the ideal blood pressure has not been identified in the European guidelines, in the American guidelines or any other guidelines because of this problem. We do not know what blood pressure dialysis patients do best with. However, an elevated blood pressure can certainly indicate volume overload and reducing volume will reduce blood pressure as well as this method will reduce the number of antihypertensive medications necessary to mask the hypertensive presentation of an expanded ECW space. This may be the second benefit of using a device, such as BCM to guide ultrafiltration.

The third benefit or clinical utility of this device is to identify vulnerable populations. We have shown – as others have also – that obese patients do not have as much fluid overload as thin and frail patients. We have shown in three studies (49, 51, 52) that leaner patients have much more fluid overload. They are for this reason more vulnerable because it is easier to overlook their fluid excess that that of an obese patient. Identifying those at risk is an added benefit and advantage we should exploit.

The forth utility of using BCM to guide ultrafiltration is that it will help reduce polypharmacy. Polypharmacy is a major risk factor not only for non-adherence as discussed previously but also for fall and cognitive function. A study (94) found that "Community-dwelling adults aged 55 years and older who take five or more daily medicinal molecules are at high risk for both mobility and cognitive impairments". Another found (95) that patients with more than 7 medications are at a heightened risk for developing any kind of adverse drug events (ADE's). It is then quite important to reduce medication count in a safe manner. Both populations presented have been able to achieve to reduce polypharmacy. Both those whose volume management was guided by BNP levels and those who were treated using the BCM to monitor success with fluid status. Furthermore, "avoiding medication-directed control of BP may enhance the opportunity to probe dry-weight, facilitate removal of volume, and limit the risk for pressure-volume overload, which may be a significant concern leading to myocardial remodeling in the hemodialysis patient. Probing dry-weight among patients with ESRD has the potential to improve dismal cardiovascular outcomes"(96).

Over ten years ago Ishibe and Peixoto (97) were much more skeptical about the use of any biomarker or device to evaluate fluid overload. They found that "inferior vena cava ultrasound is effective, but cumbersome and costly", BNP measurements were fraught with problems and had "poor correlation with volume status" and bioimpedance had "significant shortcomings when used as isolated measurements". They concluded that "at this time, the assessment of a patient's dry weight is based on the clinician's judgment…", however, this papers proposition is that we are now in a different era, we can now positively assess fluid status with objective measurements and thus make a difference in patients' lives.

These studies using BNP and BCM have demonstrated the clinical utility of using an objective method for volume monitoring while ultrafiltrating patients. The advantage of BNP is that it is widely available in many clinical settings. It can detect volume overload and it can be monitored as demonstrated by the case presentation cited earlier. The advantage of BCM over BNP is that it is highly accurate in telling how many liters of fluid the patient has in excess. It can actually guide the clinician to remove as many liters of fluid as indicated by the device. Furthermore, it will also indicate if a patient is volume depleted and it can ascertain a good value for the quantity of fluid missing. While these studies presented were not clinical trials in the sense of having controls and patients being randomized these observational and cross sectional studies will hopefully provide evidence to change clinical practice.

7. CONCLUSIONS

What this dissertation has done is the integration of the previously proposed (96) method of blood pressure control in dialysis patients and demonstrating in clinical practice how it can be done successfully. These studies have demonstrated that the safe way to go from polypharmacy and volume overload is to slowly decrease patients' weight while decreasing the antihypertensive medication burden. This can be done in a safe way by continuously monitoring their volume status by the use of BNP or BCM — "turn the lights on when driving at night". These clinical studies have all lined up in a string of idea that blood pressure control ought to be done not by medications but by eliminating the cause of hypertension.

Others have shown that hypertension control in dialysis patients may not be so important (80, 81) as the control of extracellular volume. Wizeman (75) clearly demonstrated that volume overload is a major cause of mortality in dialysis patients and Günal's (98) study determined that antihypertensive treatment with medications alone does not lead to amelioration of indicators of cardiovascular mortality. Agarwal (96) proposed that medication-free blood pressure control may improve cardiovascular outcome. These studies described in this dissertation confirm that we should treat hypertension without antihypertensive drugs in the dialysis population so that we can eliminate the greater mortality risk factor: volume overload. We ought to use one of these instruments to control fluid status safely. For the first time we demonstrated that BNP or BCM-directed fluid control actually improves care!

The conclusions therefore include that fluid overload can be safely decreased when objective measurements guide therapy. Polypharmacy can be improved with BNP- or BCM- directed ultrafiltration and an excessive number of antihypertensive medications impede volume control.

8. SUMMARY

Sustaining mammalian life involves a cautious fluid management by the organism itself. There are multiple physiological methods for this. In the pathological state of renal failure where fluid management is seriously amiss fluid management takes on a life-sustaining importance, however, this needs to be done by the medical community. The correct fluid assessments upon which therapy is based must be on a sure footing. This need cannot be filled by the "good old" physical exam because clinical studies have shown that it is as accurate as a coin toss. Two methods are thus introduced, the B-type natriuretic peptide and bioimpedance apparatus as a biomarker and a device of fluid measurement.

Clinical studies are presented to show the clinical utilities of these aides including the biomarker's utility in acute management of hospitalized patients, the utility of BCM is also discussed in several studies. BCM points to the direction of fluid management's importance in avoiding unnecessary polypharmacy and pharmaceutical overtreatment that can actually prevent and frustrate adequate fluid management.

The feasibility of using either BNP in the day-to-day practice is demonstrated in papers presented describing clinical situations in which BNP provided guidance for achieving the proper target weight of dialysis patients. It is also demonstrated that the use of BNP can uncover occult fluid overload and improve clinical patient care. Similar studies show that patients' blood pressure or fluid overload can be improved when the BCM technology is used.

Outcomes research is presented in blood pressure management and its relation to fluid management. Excess antihypertensive medications will prevent adequate fluid removal and prevent ultrafiltration. The relationship of BNP and BCM is also discussed.

Finally, as R. Agarwal remarks "avoiding medication-directed control of BP may enhance the opportunity to probe dry-weight, facilitate removal of volume, and limit the risk for pressure-volume overload, which may be a significant concern leading to myocardial remodeling in the hemodialysis patient"(96).

8.1. SUMMARY IN HUNGARIAN / ÖSSZEGZÉS MAGYARUL

Az emlősök életben maradásának fenntartása óvatos folyadékháztartást igényel. Többféle élettani folyamattal oldja ezt meg a szervezet. A veseelégtelenség kóros állapotában a folyadékháztartás súlyosan hibádzik, a folyadékegyensúly rendezésének azonban életbevágó fontossága van; ezt azonban az egészségügyi gondozás tudja csak ellátni. A helyes folyadékállapot megítélése ezért biztos lábakon kell álljon. Ezt a feladatot a "jól bevált" módszerek, mint például a fizikális vizsgálat nem tudják ellátni, mert a klinikai tanulmányok bizonyították, hogy ez annyira pontos, mint egy "fej vagy írás". Ezért két módszert mutattunk be, a B-típusú Natriuretikus Peptidet és a bioimpedancia készüléket, mint egy biológiai jelzőmolekulát és egy folyadéktér mérő készüléket. Klinikai tanulmányokat mutattunk be, amelyek ezen segédeszközök klinikai gyakorlati hasznát bizonyítják beleértve a jelző molekula hasznosíthatóságát az akutan kórházba felvett betegek heveny kezelésében és a BCM hasznát szintén számos tanulmányban mutattuk be. A BCM használata a folyadéktér rendezésének fontossága irányába mutat abban, hogy hogyan kerüljük el a szükségtelen polyphramatizálást és a gyógyszeres túlkezelést, amely egyébként megakadályozza és gátolja a helyes folyadéktér rendezést.

A felsorolt cikkekben a BNP használatának kivitelezhetőségét mutattam be és annak alkalmazhatóságát a mindennapi klinikai gyakorlatban, amely azokat a klinikai helyzeteket írják le, ahol a BNP alkalmazásával a dializált betegek helyes célsúlyát el tudtuk érni. Azt is bemutattam, hogy a BNP használata a rejtett folyadéktúlsúlyra fényt deríthet és így a klinikai betegellátást javíthatja. Hasonlatos tanulmányok mutatják, hogy a betegek folyadéktöbbletét vagy vérnyomását javíthatjuk amikor a BCM technológiát alkalmazzuk. A vérnyomásrendezéssel kapcsolatos kimenetel-tanulmányt is bemutattunk a folyadékterekkel kapcsolatban. A vérnyomásgyógyszerek száma és a folyadéktúlterheltség kapcsolatát is bemutattuk. A túlzott vérnyomás gyógyszerelés megakadályozza a szükséges folyadékeltávolítást és megakadályozza az ultrafiltraciót. A BNP és a BCM kapcsolatát is tárgyaltuk. Végül, amint azt R Agarwal megjegyzi: "A vérnyomás antihypertensivekkel való kezelésének elkerülése elősegítheti a szárazsúly óvatos meghatározását, a vértérfogat csökkentését és a nyomás-vértérfogat túlterheltség kockázatát korlátozhatja, amely egy jelentős aggodalmunk a dialízis betegek szívizmának átalakításában."

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