Do pre-haemodialysis estimates of extracellular volume excess using bioimpedance and N terminal brain natriuretic peptide correlate with cardiac chamber size measured by magnetic resonance imaging?

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Abstract

Background

Bioimpedance can be used to measure extracellular water (ECW) and total body water (TBW) in haemodialysis (HD) patients and estimate ECW excess. However, ECW excess potentially includes both an increase in the plasma volume and also the extravascular volume. Overestimating the amount of fluid to be removed during HD risks intra-dialytic hypotension. We wished to determine the association between estimates of ECW excess comparing several different equations using bioimpedance, brain N-terminal pro-brain natriuretic peptide (NT-proBNP) with cardiac chamber volumes and function as determined by cardiac magnetic resonance imaging (MRI)

Methods

Pre-HD measurements of ECW and TBW were made using multi-frequency bioimpedance and cardiac chamber sizes and functionwere determined by MRI .

Results

30 patients, 20 males (66.7%), mean age 64.4±15.3 years were studied. ECW and ECW/height were positively associated with indexed right ventricular end-systolic (RVESVi) and end-diastolic volume (RVEDVi) (RVESi r=0.46, r=0.43; RVEDi r=0.50, r=0.44, all $p<0.05$), but not with left sided cardiac volumes. Whereas NT-proBNP was associated with indexed left atrial and ventricular size (r= 0.47, r=0.58, $p<0.05$), but not right sided cardiac volumes.

Conclusion

Pre-HD NT-proBNP was associated with left sided cardiac chamber sizes, but not with right sided chamber sizes, whereas ECW/height was associated with right sided cardiac chamber sizes. As right sided cardiac chamber size is more responsive to and reflective of changes in intravascular volume than the left atrium and ventricle, then bioimpedance measured ECW is potentially more reliable in estimating plasma volume expansion.

Introduction

Although haemodialysis is an established treatment for patients with chronic kidney disease stage 5 (CKD5d), mortality remains higher than that for many common solid organ malignancies [1]. Haemodialysis patients typically gain weight between dialysis sessions, and the excess fluid then removed during the subsequent dialysis session, ideally returning the patient to a normohydrated state. Observational studies have reported that greater overhydration (OH) both prior to starting dialysis and post-dialysis is associated with an increased risk of mortality [2,3].

As such, it is important to be able to determine the volume status of dialysis patients. As most of the fluid gained is not confined solely to the plasma volume, many patients who attend for dialysis above their post-dialysis target weight do not have the classic signs of peripheral oedema, raised jugular venous pulsation and pulmonary oedema. Additionally, methods to determine target post-dialysis weight vary markedly between centres [4].

More recently bioimpedance devices have been introduced into dialysis centres to aid clinical decision making [5]. Although bioimpedance can be used to measure total body water (TBW), and by determining the relationship between resistance and reactance, can divide TBW into extracellular water (ECW) and intracellular water (ICW). However bioimpedance devices cannot sub-divide ECW into plasma volume and extravascular volume [5]. During dialysis, fluid is removed from the plasma compartment, and replenishment of this compartment relies upon fluid shifts from the intracellular and extravascular compartments. On one hand, excessive removal of fluid can lead to hypotension during dialysis [6], whereas persistent ECW excess may result in left ventricular hypertrophy and increased emergency hospital admissions due to acute cardiac decompensation [7].

It is therefore important to determine plasma volume expansion rather than total ECW excess, as this more accurately reflects the amount of fluid which can be removed during the dialysis session without increasing the risk of intra-dialytic hypotension [8,9]. To aid clinical decision making, a number of approaches using cardiac natriuretic peptides [10] and bioimpedance have been proposed to estimate ECW excess in dialysis patients [,11,12,13,14], including comparing ECW with normally hydrated tissue water content [15], and ratios of ECW to TBW [16], and ECW to height [17,18].

Whereas hypertension leads to changes in left ventricular wall thickness and chamber size over time, the right ventricle is more responsive to changes in plasma volume. As such, a change in plasma volume following a haemodialysis session leads to greater demonstrable changes in right ventricular volumes than left sided cardiac chamber sizes [9].

To determine whether natriuretic peptides or bioimpedance derived ECW excess could be useful in clinical practice as non-invasive estimates of plasma volume excess pre-dialysis, we compared these with measurements of cardiac MRI chamber size.

Methods

We reviewed the data on consecutive haemodialysis patients who had both pre-dialysis bioimpedance and cardiac MRI. Patients with pacemakers, other implantable cardiac devices, intra-cranial metallic clips, amputees, and those unable to tolerate cardiac MRI scanning due to claustrophobia or symptomatic pulmonary oedema were excluded. Patients were fasted over-night and first had a cardiac MRI scan with a 1.5T MRI scanner (Magnetom Aera, Siemens Healthcare, Erlangen, Germany). A standard protocol was implemented including localisers and cine images using steady-state free precession (SSFP) imaging (or real-time where the patient had arrhythmia or was unable to perform breath holds). All scans were analysed offline using Osirix MD 9.0 (Bernex, Switzerland) using customised plug-ins, and compared with healthy controls scanned at the Royal free Hospital. To measure left

and right ventricular chamber sizes, manual contours were traced at the endocardial borders in end-diastole and end-systole of each short axis slice. Papillary muscles were included as part of the ventricular mass and not the ventricular cavity. Atrial areas were measured in the 4-chamber slice at end-systole. All parameters were indexed according to body surface area [19].

Patients were then sent straight from the MRI scanner to dialysis. ECW and ICW were then measured immediately pre-dialysis using multifrequency bioelectrical impedance assessment (MFBIA), with an 8 electrode multi-frequency segmental bioimpedance device (InBody S10, Seoul, South Korea) using a standardised protocol, after the patient had emptied the bladder, then rested supine prior to dialysis [20,21]. The bioimpedance machine was regularly serviced and calibrated. We measured ECW, and to be able to compare ECW excess between patients we used previously reported methods describing underhydration, normal hydration and overhydration. We categorized patients both in terms of absolute ECW excess, using ECW volume cut offs of less than, and more than 2.0 litres of the normal ECW predicted from the ICW measured by , and also by the overhydration index (OH index) proposed by Chamney and colleagues using their OH index cut offs of less than and more than 15% [15,22]. In addition we calculated ECW excess using the equation developed by Abbas and colleagues [13], and also the ratio of ECW/height cut offs using 2 standard deviations based on normative data to categorise underhydration and overhydration [11-18].

Blood tests were taken concurrently pre-dialysis and analysed by standard methods for urea, creatinine, albumin, haemoglobin (Roche Cobas 400, Roche Diagnostics, Sysmex, Milton Keynes UK), and NT-proBNP (Roche Diagnostics, Burgess Hill, UK) [23,24].

Relevant medical history and medications were obtained from hospital computerised medical records, and patient co-morbidity was assessed using the Davies-Stoke co-morbidity scoring system [25].

Ethics

Our study was approved by the national research ethics committee, and all patients provided written informed consent in keeping with the Helsinki agreement.

Statistical analysis

Data is presented as mean ± standard deviation, median (interquartile range), or as percentage. We used the D'Agostino & Pearson normality test, and depending upon data normality, univariate correlation was performed using Pearson or Spearman analysis as appropriate. Statistical analysis used Prism 7.0 (Graph Pad, San Diego, USA) and Statistical Package for Social Science version 24.0 (IBM Corporation, Armonk, New York, USA). Statistical significance was taken as $p<0.05$.

Results

We recruited 30 consecutive established haemodialysis patients with contemporaneous pre-dialysis MRI and MFBIA measurements. Patient demographics are set out in table 1. Twenty-seven patients (90%) had a history of hypertension and 17 (56.7%) were prescribed antihypertensive medications, with a median number of antihypertensive medications of 1 (0-1), with 40% prescribed beta-blockers, 16.7% calcium channel antagonists, 13.3% alpha blockers and 6.7% angiotensin receptor blockers. Eight (26.7%) patients had a history of previous myocardial infarction. The median Stoke-Davies co-morbidity score was 1.0 (1.0-1.3).

We measured both pre-dialysis ECW and then calculated estimates of ECW excess (table 2) and also derived cardiac chamber dimensions and cardiac function from cardiac MRIs (table 3).

Pre-dialysis serum NT-proBNP levels were positively associated with MRI measurements of left ventricular size and negatively with left ventricular function, but not with right sided cardiac measurements (table 4). There were no significant correlations between NT-proBNP and either ECW or any of the estimates of ECW excess. ECW and ECW adjusted for height were associated with right ventricular volumes (Figures 1,2), but not left ventricular size. In addition, there was an association with systolic blood pressure. However, when we compared different indexing measures used to determine ECW excess, then only the pre-dialysis ratio of ECW/TBW was associated with right ventricular end systolic and diastolic volumes (table 5). There were no positive associations between ECW excess and cardiac dimensions when calculating overhydration [15,22], whereas ECW excess [14] was associated with right ventricular volumes. Depending on the method used, there were associations between estimates of ECW excess and indexed left ventricular ejection volumes.

There was no association between haemoglobin or haematocrit and NT-proBNP or ECW, but ECW/TBW and ECW excess [14] were negatively associated with haemoglobin, haematocrit and serum albumin.

Discussion

Bioimpedance is increasingly being used to aid clinical decision making tp determine volume status in dialysis patients [5, 26]. A number of equations have been developed to estimate ECW pre-dialysis. However, studies using these estimates of overhydration have reported accelerated loss of residual renal function [27]. This has raised concerns that ECW measured by bioimpedance predominantly measures extravascular fluid volumes and not plasma volume [28,29]. We therefore compared several equations currently used to estimate ECW excess with NT-proBNP [30,31] and cardiac chamber dimensions directly measured by MRI, in particular the the right ventricle which is more sensitive to changes in

plasma volume than the left ventricle [33], to determine whether any of these equations, or NT-proBNP reflected intracardiac volumes .

We found that NT-proBNP was increased in patients with left atrial and ventricular chamber enlargement, and also those with reduced left ventricular systolic function, and increased left ventricular diastolic dysfunction determined by the mitral annular plane systolic excursion (MAPSE). . However, there was no association with right sided cardiac chamber sizes or function. The close association with left sided cardiac dysfunction most likely accounts for the reported association between increased cardiac natriuretic peptides and mortality [22,34

We used a number of reported measures of ECW, including ECW/TBW and ECW/height ratios, over hydration (OH) and ECW excess. Whereas ECW, ECW/height and ECW excess were positively associated with right ventricular end diastolic volume index (RVEDVi), right ventricular end systolic volume index (RVESVi) and right ventricular mass index (RVMi), there were no statistical associations between ECW/TBW or overhydration and right ventricular chamber size. None of our measures of ECW or ECW excess had any association with right ventricular function assessed by right ventricular ejection fraction or tricuspid annular plane systolic excursion (TAPSE). Bioimpedance measures ECW, which includes both the vascular compartment and the extra-vascular compartment. The ratio of ECW/height and ECW excess using the equation proposed by Abbas and colleagues [14], were associated with right ventricular cavity size, suggesting that these measures more closely reflect changes in the intravascular compartment compared to other estimates of ECW excess. Although the ratio of ECW/TBW can be increased due to an increase in ECW, it can also be increased by a fall in intracellular water (ICW). In our cohort of patients as the ECW/TBW was negatively associated with haemoglobin and serum albumin, this potentially suggests that patients with lower haemoglobin and serum albumin could have had higher ECW/TBW ratios associated with inflammation and loss of cell mass with a corresponding fall

in ICW [34]. Whereas, Abbas and colleagues estimated ECW excess based on measured ICW [14], overhydration is determined as the difference between measured ECW and lean tissue mass, and this may have favoured extravascular ECW rather than intravascular ECW [15,22], as we found no association between overhydration and right ventricular volumes.

A number of biomarkers have been proposed to aid clinical decision making in determining haemodialysis patient volume status. We measured NT-proBNP whereas others have measured different cardiac natriuretic peptides or NT-proBNP but using different assays [10,22,32]. Previous reports have differed in their findings, and we found no association between NT-proBNP and right ventricular dimensions. Although, NT-proBNP has a longer half-life than adrenomedullin and atrial natriuretic peptide [22], we suspect that measuring other cardiac natriuretic peptides would not have altered our results. Similarly, we used one bioimpedance device, and there are now an ever-increasing number of bioimpedance devices commercially available. Our device measures ECW based on measurements from all four limbs and the trunk, whereas other multifrequency devices only make whole body measurements [5]. Proprietary equations derived from one bioimpedance device may not equally apply to all such devices, although we have previously compared devices [35-37]. Our device has been validated against water displacement and dual-energy x-ray absorptiometry [20], and some devices share common algorithms [37].

In summary, we compared several biomarkers which have previously been suggested to aid clinical determination of ECW, due to concerns that attempts to reduce predominantly extravascular ECW expansion may increase the risk of intra-dialytic hypotension and premature loss of residual renal function [6,27]. We found that NT pro-BNP was associated with left sided cardiac chamber sizes and negatively with left ventricular function, but not right ventricular dimensions, which would suggest that NT-proBNP does not reflect plasma volume. Using a number of methods reported to estimate ECW excess with bioimpedance, we found that ECW excess, as determined by the ratio of ECW/height

and that calculated using the equation generated by Abbas and colleagues [14], were most associated with right ventricular dimensions, and therefore more reflective of changes in plasma volume than other approaches, including ECW/TBW ratio. Future prospective studies are required to determine whether using these assessments of ECW excess can reduce episodes of intra-dialytic hypotension, preserve residual renal function and lead to better fluid management and reduction in left ventricular hypertrophy over time.

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Figure 1. Spearman univariate correlation between right ventricular end diastolic volume indexed for size (EDVi (R)) and extracellular water adjusted for height squared (ECW/ht^2)

Figure 2. Spearman univariate correlation between right ventricular end diastolic volume indexed for size (EDVi (R)) and extracellular water excess or reduction according to Abbas and colleagues [14].

Table 1. Patient demographics and pre-dialysis blood test results. Values expressed as integer, mean ± standard deviation, median (interquartile range), or percentage.

Variable	Value
Male gender (%)	20 (66.7)
Age years	64.4 ±15.3
Diabetes (%)	14 (46.7)
Weight kg	72.1 (62.4-83.6)
Dialysis vintage months	35 ±42.9
Mean arterial blood pressure pre-dialysis mmHg	92.3 ±25.5
Body surface area m^2	1.88 ±0.29
Haemoglobin g/L	94.8 ±13.0
Serum albumin g/L	37.0 ±6.6
Serum sodium mmol/L	137.0 ±5.4
Serum urea mmol/L	16.7 ±5 .8
Serum creatinine umol/L	566 (422-719)
Serum N-terminal pro-brain natriuretic peptide pg/mL	12415 (3562-33152)

Table 2. Pre-dialysis bioimpedance measured extracellular water (ECW), and ratio of ECW to total body water, ECW adjusted for height (ECW/ht) [17], ECW overhydration Chamney et al [12,24] and ECW excess according to Abbas and colleagues [14]. Values expressed as integer, mean ± standard deviation, median (interquartile range), or percentage

Variable	Value
Intracellular water L	25.5 ±6.7
Extracellular water L	17.7 ±5.4
Extracellular water/total body water	0.408 ±0.021
Extracellular water/height L/m	10.2 (8.1 -11.7)
Extracellular water/$height^2$ L/m^2	6.15 (5.07-6.07)
Over hydration (ECW excess) L	0.6 (-2.0 to 2.7)
% over hydration (ECW excess)	3.2 (-10.8 to 13.1)
Extracellular water excess L	1.6 (0.5 to 5.1)
Extracellular water excess %	9.5 (2.8-20.3)

Table 3. Pre-dialysis cardiac magnetic resonance findings. Values expressed as integer, mean ± standard deviation, median (interquartile range), or percentage

Variable	Value
Left ventricular end diastolic volume index mL/m^2	95 (98-117)
Left ventricular end systolic volume index mL/m^2	41 (26-61)
Left ventricular stroke volume index mL/m^2	52 ±14
Left ventricular ejection fraction %	55 ±16
Left ventricular mass index g/m^2	95 ±35
Right ventricular end diastolic volume index mL/m^2	80 (67-96)
Right ventricular end systolic volume index mL/m^2	32 (24-52)
Right ventricular stroke volume index mL/m^2	48 ±15
Right ventricular ejection fraction %	62 (55-65)
Right ventricular mass index g/m^2	26 (5-33)
Mitral annular plane systolic excursion mm	10.9 ±3.1
Tricuspid annular plane systolic excursion	19.2 ±5.5
Left atrial area index cm^2/m^2	10.1 ±3.0
Right atrial area index cm^2/m^2	8.5 ±1.9

Table 4. Univariate analysis of estimates of volume status: serum N-terminal brain natriuretic peptide (BNP), extracellular water (ECW), ECW adjusted for height (ECW/ht), ECW to total body water (TBW) ratio, ECW excess compared to ECW expected from ICW, and as a percentage of ECW estimated by equations of overhydration from Chamney et al [15,22] and ECW excess from Abbas and colleagues [14] and cardiac ventricular dimensions : left ventricular end diastolic volume index (LVEDVi), left ventricular end systolic volume index (LVESDi), left ventricular ejection fraction (LVef), Left ventricular mass index (LVMi), right ventricular end diastolic volume index (RVEDVi), right ventricular end systolic volume index (RVESVi), right ventricular ejection fraction (RVef), right ventricular mass index (RVMi), Mitral annular plane systolic excursion (MAPSE), tricuspid annular plane systolic excursion (TAPSE), systolic blood pressure (SBP), haemoglobin (Hb), haematocrit (hct). Non-significant (NS)

	BNP	ECW	ECW/ht	ECW/TBW	Overhydration	% overhydration	ECW excess	% ECW excess
LVEDVi	R=0.50 P=0.005	NS	NS	NS	NS	NS	NS	NS
LVESVi	R=0.58 P<0.001	NS	NS	NS	NS	NS	NS	NS
LVSVi	NS	R=0.48 P=0.008	R=0.47 P=0.008	NS	R=-0.58 P=0.030	R=-0.51 P=0.004	R=0.56 P<0.001	R=0.51 P=0.004
LVej	R=-0.59 P<0.001	NS	NS	NS	NS	NS	NS	NS
LVMi	R=0.55 P=0.002	R=0.52 P=0.004	R=0.49 P=0.001	NS	NS	NS	NS	NS
RVEDVi	NS	R=0.50 P=0.006	R=0.44 P=0.014	NS	NS	NS	R=0.41 P=0.025	R=0.39 P=0.036
RVESVi	NS	R=0.46 P=0.001	R=0.43 P=0.013	NS	NS	NS	r=0.37 p=0.048	R=0.39 P=0.037
RVMi	NS	R=0.42 P=0.024	R=0.41 P=0.024	NS	NS	R=-0.51 P=0.050	R=0.53 P=0.003	R=0.48 P=0.009
RVef	NS	NS	NS	NS	NS	NS	NS	NS
MAPSE	R=-0.52 P=0.004	NS	R=0.37 P=0.050	NS	NS	NS	R=0.44 P=0.021	NS
TAPSE	NS	NS	NS	NS	NS	NS	NS	NS
SBP	NS	R=0.45 P=0.013	R=0.44 P=0.013	NS	NS	NS	NS	NS
Hb	NS	NS	NS	R=-0.38 P=0.036	R=0.42 P=0.021	NS	R=-0.44 P=0.016	R=-0.44 P=0.016
Hct	NS	NS	NS	R=-0.36 P=0.050	R=0.39 P=0.034	R=0.40 P=0.029	R=-0.39 P=0.034	R=-0.39 P=0.033
albumin	NS	NS	NS	R=-0.65 P=0.011	NS	NS	NS	NS