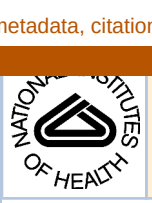

Published in final edited form as:

J Renin Angiotensin Aldosterone Syst. 2009 December ; 10(4): 230–236. doi:10.1177/1470320309352353.

Disordered aldosterone-volume relationship in end-stage kidney disease

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Abstract

Introduction—Sodium loading, and subsequent volume expansion, suppresses aldosterone levels in individuals with normal renal function. We hypothesised that loss of renal function impairs this volume-aldosterone relationship.

Materials and methods—With multifrequency bioimpedance spectroscopy, we measured total body water (TBW), extracellular volume (ECV), and intracellular volume in five haemodialysis patients at varied states of hydration and in five healthy volunteers during low-, normal-, and high-salt diets. Serum aldosterone, potassium, and C-reactive protein were measured simultaneously. Scatterplots and general estimating equations were used to examine the relationship among these variables.

Results—In healthy volunteers with salt loading, and in haemodialysis subjects with increased inter-dialytic weight gain, expansion of ECV led to reciprocal declines in serum aldosterone concentrations. The relationship was more profound in healthy volunteers ($p<0.001$) than in haemodialysis subjects ($p=0.1$). Notably, haemodialysis subjects posted consistently higher levels of ECV (median 49.6% TBW, IQR 43.9–51.8% compared to 41.1%, 39.9–42.8% in volunteers) and serum aldosterone (median 26.7 ng/dl, IQR 19.8–29.6 compared to 12.4 ng/dl, 8.8–16.0 in volunteers). Serum potassium did not appear to influence aldosterone concentration ($p=0.9$).

Conclusions—The shift of the volume-aldosterone curve in haemodialysis subjects suggests that end-stage kidney disease is a state of high volume and inappropriately high aldosterone. These data have important clinical implications, as dialysis patients may benefit from both volume reduction and mineralocorticoid receptor blockade.

Keywords

aldosterone; chronic kidney disease; extracellular volume; haemodialysis; mineralocorticoid receptor blockers

Introduction

Advances in non-invasive bioimpedance techniques allow accurate measurements of extracellular volume (ECV) among subjects with and without chronic kidney disease, including

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dialysis-dependent patients.[1-3] The ability to objectively assess ECV should provide opportunities to improve the health of end-stage kidney disease (ESKD) patients by attaining physiologic dry weight and optimising blood pressure targets.[4-6] Bioimpedance measurements can also serve as important research tools.[7]

In a seminal study performed more than 30 years ago, Brunner *et al.* demonstrated that 24-hour urine aldosterone levels were suppressed in subjects with high 24-hour urine sodium levels.[8] These measurements – and their resultant aldosterone-sodium curves (figure 1A) – proved crucial for diagnosing hyperaldosterone states in which sodium loading did not result in appropriately suppressed aldosterone levels. An inherent assumption in these curves, which has yet to be formally tested, is that sodium excretion, a valid marker of sodium intake during steady state, also serves as a marker of ECV.

Using whole body bioimpedance, we studied healthy volunteers on low-, normal-, and high-salt diets, and maintenance haemodialysis subjects pre-ultrafiltration at varying degrees of inter-dialytic weight gain, to replace the classic sodium-aldosterone curves with ECV-aldosterone curves. We hypothesised that ECV elevations would lead to reductions in serum aldosterone for both healthy volunteers and haemodialysis subjects, but that this relationship would occur at higher volumes *and* higher aldosterone concentrations for the haemodialysis subjects. In other words, we hypothesised that the volume-aldosterone curve would 'shift to the right' as renal function declined (figure 1B).[9]

Methods

Subjects

Five clinically-stable, long-term (i.e. vintage ≥ one year) haemodialysis patients from the outpatient dialysis units of the University of North Carolina Kidney Center, believed to be at variable levels of hydration, were enrolled in this study. Exclusion criteria were age < 10 or > 80 years, significant residual renal function (defined as urine output > 250 ml/day), hospitalisation within the last three months, myocardial infarction or stroke in the preceding six months, congestive heart failure (defined by ejection fraction < 40%), simultaneous participation in another clinical study, pregnancy, amputation of a limb, and presence of a pacemaker, implantable defibrillator, or artificial joint.

Five healthy volunteers were simultaneously enrolled. Inclusion criteria for entering the volunteer study protocol were age ≥ 18 and ≤ 65 years, no known past medical history, no chronic prescription medications, and ability to collect three 24-hour urine samples over a 10-day period. We excluded volunteers with systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, estimated glomerular filtration rate (calculated from serum creatinine) < 60 ml/min/1.73 m^2, and body mass index > 30 kg/m^2. All haemodialysis subjects and healthy volunteers provided informed consent for study procedures approved by the Institutional Review Board of the University of North Carolina.

Study procedures

We measured total body water (TBW), ECV, and intracellular volume (ICV) on five haemodialysis patients, every other week for 12 weeks, using a whole body (wrist to ankle) multifrequency bioimpedance spectroscopy (BIS) system (Xitron 4200). The measurements were done within the first five minutes of a routine haemodialysis session, before initiating ultrafiltration, and followed established methods of whole body BIS measurement; extracellular and intracellular resistance were calculated based on the Cole-Cole model with the raw data of resistance and reactance from 5 kHz to 1000 kHz as described elsewhere.[1,10,11] Xitron software then converted resistance values to ECV and ICV; TBW was the sum of

ECV and ICV values. Measurements of ECV and ICV were then converted to a percentage of TBW; measurements in litres are not considered a valid outcome without an internal, directly measured referent (TBW), as body habitus between subjects is variable. Blood samples were drawn concomitantly with half of the BIS analyses (approximately every four weeks). Serum was frozen for aldosterone assays but immediately sent for potassium and C-reactive protein measurements. No dietary or inter-dialytic weight gain recommendations were made for the dialysis subjects. No changes were made to the subjects' dialysis prescriptions, including no change in ultrafiltration goals or rates (beyond holding ultrafiltration until after completion of the bioimpedance measurements). Dialysate sodium concentration was standard (rather than modelled) for all subjects during the study period.

We performed similar BIS measurements for TBW, ECV, and ICV alongside aldosterone collections on five healthy volunteers during a 10-day period. The first measurements were done after a 24-hour period of urine collection for sodium excretion to establish baseline dietary salt intake and presumed euvolaemic measurements. The second measurements were done after a four-day period of low-salt intake during which subjects were encouraged to consume < 50 mmol/d (1.2 g/d) sodium. The third measurements were done after a four-day period of high-salt intake during which subjects were encouraged to consume > 150 mmol/d (3.6 g/d) sodium. Twenty-four-hour urine collections for sodium excretion were performed during the fourth day of low- and high-salt diets. The degree of salt loading in our healthy volunteers was milder than that employed in the experiments by Titze and colleagues that suggested osmotically inactive sodium storage in the skin or bone.[12-14] Therefore, salt loading in the volunteers should be confined to the extracellular space and reflected in the BIS measurements of ECV.

All blood collections for aldosterone were done prior to 10 a.m. after subjects had been supine for a minimum of five minutes. Two serum samples for each study session were prepared and frozen at −20°C. Serum aldosterone concentrations (ng/dl) were determined by enzyme immunoassay according to the manufacturer's instructions (Alpco Diagnostics, available at http://www.alpco.com/pdfs/11/11-ALDHU-E01.pdf).

Data analyses

All analyses and plots were performed separately for healthy volunteers and haemodialysis subjects using STATA version 9.2 (StataCorp, Texas, USA). Scatterplots were created to visually compare changes in aldosterone concentrations versus changes in ECV measurements. To account for repeated measurements, we used generalised estimating equation (GEE) models with robust standard error and an exchangeable correlation matrix to evaluate the degree of influence ECV had on aldosterone values. Because the original sodium-aldosterone curves and our own scatterplots for ECV-volume did not perfectly follow linear relationships, we repeated our GEE models using power transformations of aldosterone ($\text{aldosterone}^{0.5}$ and aldosterone^{2}). Scatterplots and GEE modelling were similarly used to examine the effect of serum potassium on aldosterone levels, and the effect of ECV and aldosterone on C-reactive protein levels. Two-sided hypotheses tests with a 5% type I error were adopted for all statistical inferences.

Results

All subjects completed the study protocol without interruption or complications. The healthy volunteers were all male, with median age 38 years (range 32–62). The mean 24-hour urine sodium for the healthy volunteers was 28.6±25.2 mmol/d during the low-salt phase and 173.0 ±60.3 mmol/d during the high-salt phase. The dialysis subjects consisted of two males and three females, with median age 50 years (range 11–80). None were diabetic, and all had body

mass indices below 30 kg/m^2. Inter-dialytic weight gain during the study period for these subjects ranged from 0.7 to 4.1 kg (median 2.7, IQR 2.0–3.3).

ECV (expressed as % of TBW) increased in healthy volunteers with greater amounts of salt in the diet (range 32.6–46.8% TBW) and in haemodialysis subjects with greater amounts of inter-dialytic weight gain (range 41.7–54.5% TBW) (Table 1). In healthy volunteers, ECV expansion clearly led to reductions in serum aldosterone concentrations (figure 2A). We ran three GEE models of aldosterone, aldosterone$^{0.5}$, and aldosterone^2 versus ECV. These yielded beta-coefficients (95% CIs, p values) of −130.7 (−167.7731, −93.53762, p<0.001), −18.2 (−26.3, −10.0, p<0.001), and −4,040.8 (−4,653.5, −3,428.1, p<0.001), respectively. In haemodialysis subjects, a similar trend towards lower aldosterone levels at higher states of ECV was observed (figure 2B). GEE models of aldosterone, aldosterone$^{0.5}$, and aldosterone^2 versus ECV yielded beta-coefficients (95% CIs, p values) of −99.4 (−218.1, 19.4, p=0.1), −10.1 (−22.6, 2.3, p=0.1), and −4,952.6 (−10,670.6, 765.4, p=0.09), respectively. Overall, compared to the healthy volunteers, haemodialysis subjects clearly demonstrated both higher ECV (median 49.6% TBW, IQR 43.9–51.8% TBW versus median 41.1% TBW, IQR 39.9–42.8%) and serum aldosterone measurements (median 26.7 ng/dl, IQR 19.8–29.6 ng/dl versus median 12.4 ng/dl, IQR 8.8–16.0 ng/dl) (figures 2C and 2D).

Serum potassium was generally well controlled in the haemodialysis subjects (median 5.0 mmol/L, range 3.8–6.2 mmol/L) and did not, in GEE models, influence aldosterone concentrations (p=0.9) (figure 3). Approximately 75% of C-reactive protein levels in the haemodialysis subjects were above 1.0 mg/L, the upper limit of normal for this assay, and were more influenced by aldosterone concentrations (p<0.001) than ECV measurements (p=0.2) (figure 4).

Discussion

In this study, we used multifrequency BIS to measure ECV in five healthy volunteers on low-, normal-, and high-salt diets and in five haemodialysis subjects at various states of inter-dialytic weight gain. Serum aldosterone concentrations were drawn simultaneously, allowing us to construct volume-aldosterone curves that updated similar sodium-aldosterone curves created more than 30 years ago. The curves confirm that in individuals with normal renal function, 24-hour urinary sodium excretion is a reasonable surrogate marker for ECV status, and ECV expansion leads to suppression of aldosterone secretion. More importantly, the shift of the volume-aldosterone curve seen in the haemodialysis subjects suggests that ESKD is a state of high volume *and* inappropriately high aldosterone for this degree of volume expansion. These results have significant clinical implications.

Despite advances in the diagnosis and management of kidney disease, mortality rates for patients on haemodialysis remains as high as 20–25% at one year and 50–60% at five years.[15] Cardiovascular disease accounts for the majority of these deaths, with sudden cardiac death being the leading cause.[16,17] In the last decade, two landmark clinical trials have demonstrated that mineralocorticoid receptor blockade with spironolactone or eplerenone significantly reduces mortality in patients with advanced congestive heart failure.[18,19] Notably, the mineralocorticoid receptor blockade doses used in these trials were relatively low, suggesting that the benefits of therapy were due not to blood pressure reduction or diuresis, but rather due to blockade of aldosterone's non-epithelial, pro-inflammatory, pro-fibrotic effects on the heart.[20,21] These non-epithelial effects of aldosterone are exaggerated in conditions, such as congestive heart failure, of elevated aldosterone levels and expanded ECV.[22]

We hypothesised that patients with chronic and ESKD similarly manifest relative hyperaldosteronaemic and hypervolaemic states, which become more pronounced as renal

function deteriorates.[9] The volume-aldosterone curves constructed in this study support this hypothesis. While volume (and apparently not potassium) influences aldosterone concentrations to a similar, albeit less rigorous, degree in ESKD as it does in normal renal function, the suppression is nonetheless inadequate and incomplete. Despite clear and objective evidence of volume expansion, the haemodialysis subjects posted only five of 30 (16.7%) serum aldosterone concentrations under 15 ng/dl, generally considered the upper limit of normal serum aldosterone measurements.[23] In other words, haemodialysis subjects may be seen as chronically failing volume suppression tests (as would be used to diagnose primary aldosteronism). In ESKD, hyperaldosteronism in the high volume state leads to activation of non-epithelial mineralocorticoid receptors, promoting vascular inflammation and fibrosis.[24,25]

A recent study using bioimpedance to measure ECV found that overhydration was an important and independent predictor of mortality in maintenance dialysis patients.[26] This study comes almost two decades after hypertension control without medication was shown to be the best single marker of survival in haemodialysis patients.[27] Therefore, nephrologists are keenly aware that expanded ECV is a major contributor to the high rates of cardiovascular morbidity and mortality in ESKD. Yet the discussion has heretofore centred primarily on blood pressure.[28,29] In our opinion, this has led to an unfortunate neglect of the inflammatory role of aldosterone in these high volume states.

This is not the first study to demonstrate that ESKD patients have abnormally high aldosterone levels.[30-35] Our study, however, is the first to objectively measure ECV alongside these aldosterone levels, and thus the first to demonstrate that expansion of ECV does suppress aldosterone concentration in ESKD, albeit suboptimally and to still inappropriately high levels. The resultant high volume-high aldosterone state may be a pro-inflammatory condition that explains, in part, the large burden of cardiovascular disease in this population.[33] In this study, we used C-reactive protein levels as a crude marker of inflammation. While C-reactive protein levels tended to increase with ECV expansion, they clearly decreased with higher aldosterone concentration; we thus propose that volume status plays a larger role than aldosterone concentration in determining the pro-inflammatory activation of non-epithelial mineralocorticoid receptors.

Obviously, these results are meant to fuel discussion about potential therapeutic decisions. The expanded ECV measurements demonstrated here and in other studies of haemodialysis patients clearly argue for a re-evaluation of current practice patterns regarding dietary sodium counselling, ultrafiltration goals, and overall estimation of dry weight.[6,26,36] Moreover, the markedly elevated aldosterone levels seen in ESKD suggest that mineralocorticoid receptor blockade could emerge as a crucial therapeutic intervention.[37] Indeed, already a number of small studies (and at least three more ongoing or recently completed studies) have looked at whether low doses of mineralocorticoid receptor blockade are safe in ESKD patients, for whom the intratubular potassium-sparing effects should be scant (in oliguria) to none (in anuria).[34,38-41]

Our study, which is limited by its small size and exploratory design, should be interpreted as a hypothesis-forwarding rather than hypothesis-confirming experiment. Of note, had we enrolled diabetic and/or obese subjects, we may have seen more extreme levels of aldosterone (both low and high) given the potential for hyporeninaemia in diabetes and hyperaldosteronism in obesity and the metabolic syndrome.[42-44] Further investigations are needed that incorporate a larger number of dialysis subjects, with and without known congestive heart failure, and a more sensitive marker of inflammation and cardiovascular disease risk than C-reactive protein levels. Nonetheless, we feel that the ECV-aldosterone curves constructed in this study should have major clinical implications, providing a new route by which nephrologists can approach

the tremendous burden of cardiovascular disease in the haemodialysis population. This study begins to lay the groundwork for clinical trials testing whether low-dose mineralocorticoid receptor blockade, a widely used and effective therapy in congestive heart failure, can reduce mortality in haemodialysis patients.

Acknowledgments

We are grateful to David Barrow, PhD, and the Bioanalytical Core Labs of the UNC Clinical and Translational Research Center for assistance with the aldosterone measurements. We also thank Stephen Marshall, PhD, for guidance with statistical analyses in this study.

Disclosures: Funding for this study was provided by a pilot grant from the Renal Research Institute, LLC (New York, NY, USA).

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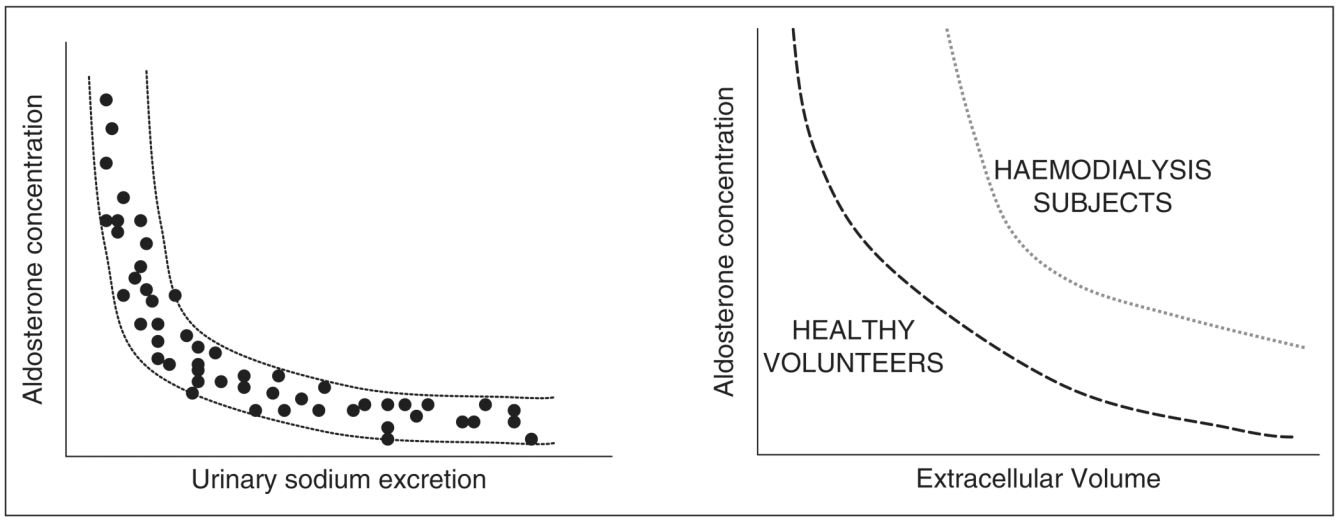

Figure 1.

The relationship between aldosterone and sodium intake predicts similar curves for aldosterone and extracellular volume (ECV) measurements. The aldosterone-sodium curves (A) are adapted from the study by Brunner *et al.*,[8] and serve as a model for our proposed aldosterone-volume curves (B). In healthy volunteers, a salt load should lead to expansion of ECV and resultant suppression of aldosterone. Poor or absent renal function, manifest in haemodialysis subjects, results in higher levels of ECV that are exacerbated by high inter-dialytic weight gain. We hypothesised that haemodialysis subjects would have a defective volume receptor, and thus not be able to appropriately suppress their aldosterone concentrations to levels befitting their degree of volume expansion. In other words, the aldosterone-volume curve shifts to the right in end-stage kidney disease.

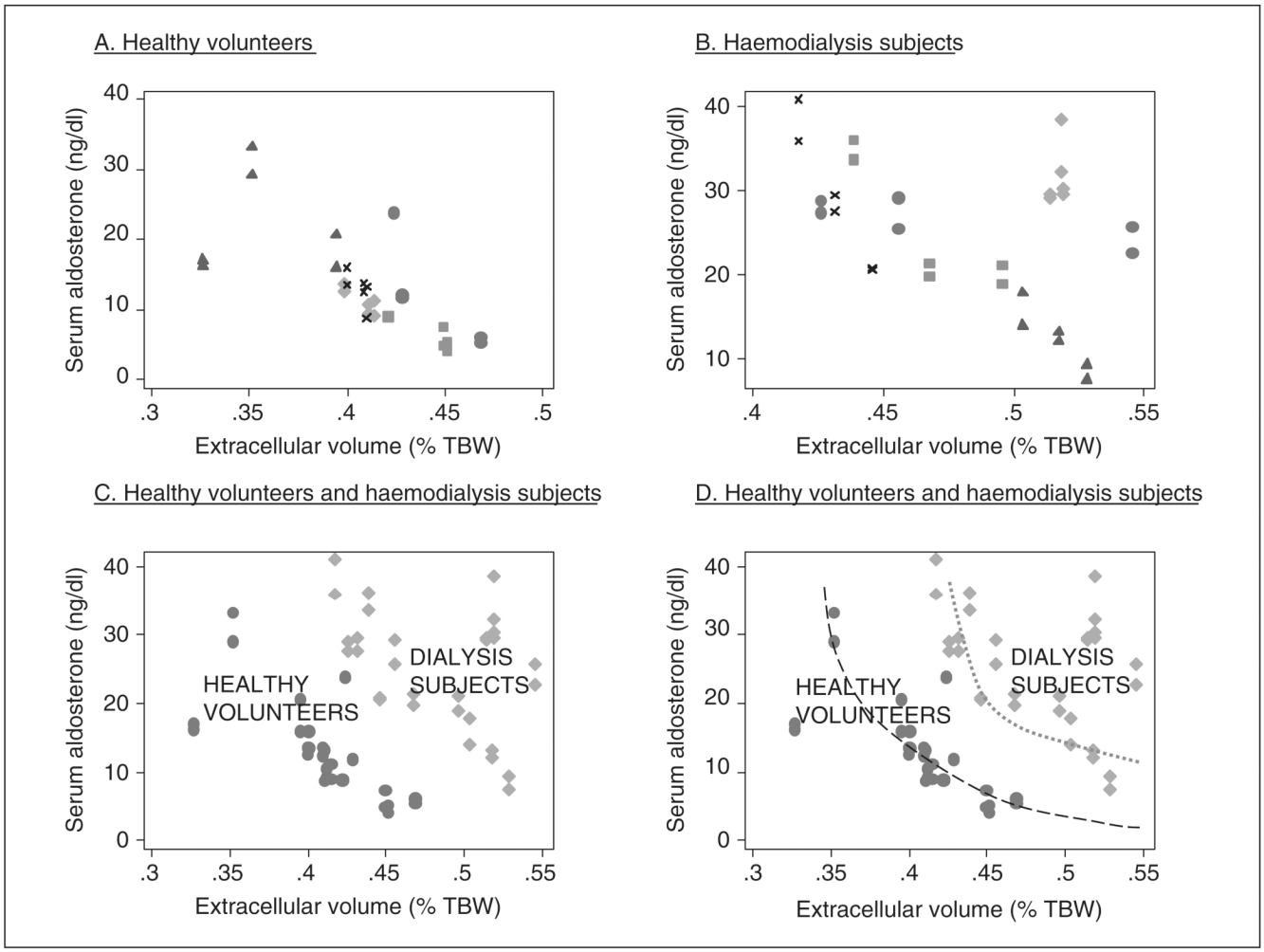

Figure 2.

Scatterplots of serum aldosterone levels and extracellular volume (ECV) measurements in healthy volunteers and haemodialysis subjects. Volume expansion during high-salt diets clearly suppressed aldosterone levels in the healthy volunteers (A), and a similar trend was seen in the haemodialysis subjects as their ECV increased with inter-dialytic weight gains (B). However, the haemodialysis subjects consistently demonstrated both higher levels of ECV and aldosterone (C), supporting our hypothesis that the aldosterone-volume curves in figure 1 would shift to the right in end-stage kidney disease. Unique symbols (×, •, ■, ▲, ◆) identify data from each healthy volunteer (A) and haemodialysis subject (B). TBW = total body water.

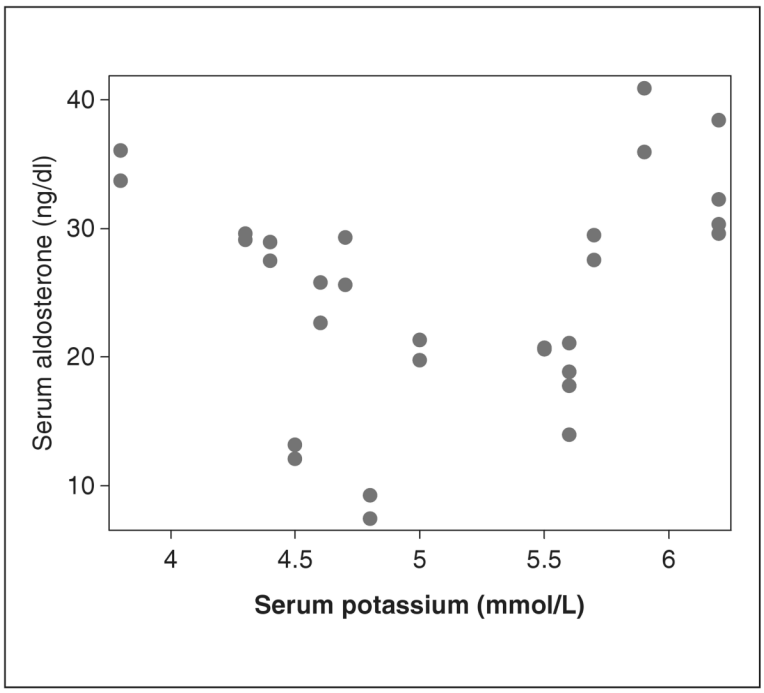

Figure 3.
In haemodialysis subjects, serum potassium did not appear to influence serum aldosterone levels.

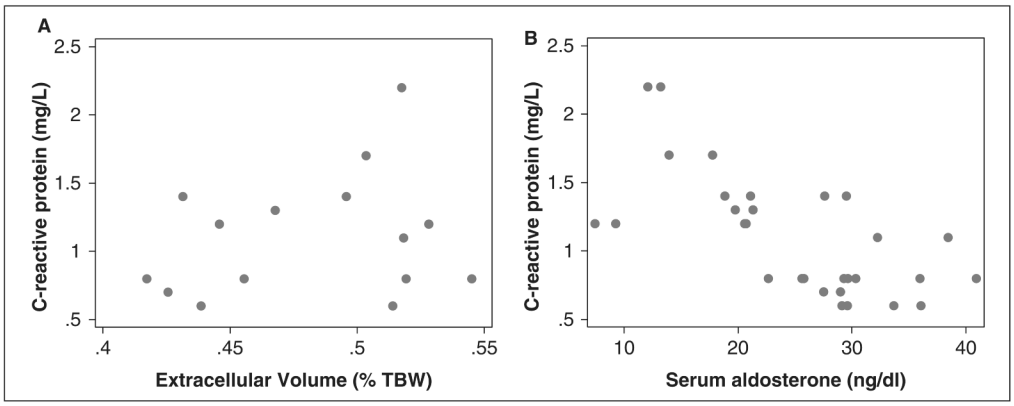

Figure 4.

In haemodialysis subjects, C-reactive protein tended to increase with volume expansion but decrease with elevations in aldosterone. In the setting of expanded volume, aldosterone's actions at non-epithelial mineralocorticoid receptors are pro-inflammatory. However, C-reactive protein levels clearly decreased with elevations in aldosterone concentration. Speculatively, these data suggest that aldosterone concentration plays a lesser role than volume status in end-stage kidney disease in determining the pro-inflammatory activation of non-epithelial mineralocorticoid receptors. TBW = total body water.

J Renin Angiotensin Aldosterone Syst. Author manuscript; available in PMC 2010 March 31.

Table 1

Whole body bioimpedance measurements of healthy volunteers (A) and haemodialysis subjects (B) at time of aldosterone measurements.

	(A) HEALTHY VOLUNTEERS									
	Volunteer 1		**Volunteer 2**		**Volunteer 3**		**Volunteer 4**		**Volunteer 5**	
	Dietary salt intake	**ECV (%TBW)**	**Dietary salt intake**	**ECV (%TBW)**	**Dietary salt intake**	**ECV (%TBW)**	**Dietary salt intake**	**ECV (%TBW)**	**Dietary salt intake**	**ECV (%TBW)**
Visit 1	Low	42.3	Low	39.9	Low	42.1	Low	32.6	Low	39.9
Visit 2	Normal	42.8	Normal	41.1	Normal	44.9	Normal	35.1	Normal	40.9
Visit 3	High	46.8	High	41.4	High	45.0	High	39.5	High	41.0
	(B) HAEMODIALYSIS SUBJECTS									
	Subject 1		Subject 2		Subject 3		Subject 4		Subject 5	
	Kg above EDW	ECV (%TBW)	Kg above EDW	ECV (%TBW)	Kg above EDW	ECV (%TBW)	Kg above EDW	ECV (%TBW)	Kg above EDW	ECV (%TBW)
Visit 1	4.0	42.6	3.4	51.9	4.1	46.8	1.2	52.8	2.7	43.1
Visit 2	3.3	54.5	3.1	51.8	3.2	49.6	1.1	51.8	2.2	44.6
Visit 3	2.5	45.6	3.0	51.4	2.5	43.9	0.7	50.3	2.0	41.7

Key: ECV = extracellular volume; EDW = estimated dry weight; TBW = total body water.