Hypervolemia and blood pressure in prevalent kidney transplant recipients

Chan, Wing Lam Winnie; Bosch, Jos A; Jones, David; McTernan, Philip G; Inston, Nicholas; Moore, Sue; Kaur, Okdeep; Phillips, Anna C; Borrows, Richard

DOI:
10.1097/TP.0000000000000066

Document Version
Peer reviewed version

Citation for published version (Harvard):
Chan, WLW, Bosch, JA, Jones, D, McTernan, PG, Inston, N, Moore, S, Kaur, O, Phillips, AC & Borrows, R 2014, 'Hypervolemia and blood pressure in prevalent kidney transplant recipients', *Transplantation*, vol. 98, no. 3, pp. 320-327. https://doi.org/10.1097/TP.0000000000000066

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Title

Hypervolemia and Blood Pressure in Prevalent Kidney Transplant Recipients

Authors

Winnie Chan[1,2,3], Jos A Bosch[2], David Jones[4], Philip G McTernan[5], Nicholas Inston[1], Sue Moore[1], Okdeep Kaur[1], Anna C Phillips[2], Richard Borrows[1,6]

[1]Department of Nephrology & Kidney Transplantation, Queen Elizabeth Hospital Birmingham

[2]School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham

[3]Department of Nutrition & Dietetics, Queen Elizabeth Hospital Birmingham

[4]School of Healthcare Science, Manchester Metropolitan University

[5]Division of Metabolic and Vascular Health, Warwick Medical School, University of Warwick

[6]Centre for Translational Inflammation Research, University of Birmingham

Keywords

Hypervolemia; Sodium; Blood Pressure; NT-proBNP; Kidney Transplantation

Word Count

Abstract = 249 Main text = 3305

Tables, Figures & Supplementary Digital Content (SDC)

Tables = 1; Total Figures = 4 (2 full figures, 2 part figures); Colour Figures = 0; SDC Tables = 5; SDC Figures = 0.

Corresponding Author

Dr Richard Borrows

Department of Nephrology & Kidney Transplantation, Area 5, Level 7,

Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston,

Birmingham, B15 2WB, United Kingdom

Phone: +44 (0) 121 371 6099 Fax: +44 (0) 121 371 5858 Email:Richard.Borrows@uhb.nhs.uk

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Author's Contributions

Winnie Chan, Jos A Bosch, David Jones and Richard Borrows participated in research design. Winnie Chan, Jos A Bosch, David Jones, Phillip G McTernan, Nicholas Inston, Anna C Phillips and Richard Borrows participated in the writing of the paper. Winnie Chan, Nicholas Inston, Sue Moore, Okdeep Kaur, and Richard Borrows participated in the performance of the research. Winnie Chan, Anna Phillips and Richard Borrows participated in data analysis.

Financial Support

Winnie Chan is funded by the British Renal Society and the National Health Service West Midlands Strategic Health Authority.

Conflict of Interest

The authors declare no conflicts of interest.

Addresses for Each Author

[1]Department of Nephrology & Kidney Transplantation, Area 5, Level 7, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham B15 2WB, UK

[2]School of Sport, Exercise and Rehabilitation Sciences, The University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

[3]Department of Nutrition & Dietetics, Therapy Services South Suite, 1st Floor, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham B15 2WB, UK

[4]School of Healthcare Science, The Manchester Metropolitan University, John Dalton Building, Chester Street, Manchester M1 5GD, UK

[5]Division of Metabolic and Vascular Health, Clinical Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry CV2 2DX, UK

[6]Centre for Translational Inflammation Research, University of Birmingham Research Laboratories, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham B15 2WB, UK

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Abbreviations

Alpha-Adrenergic Blocker **(AAB)**

Analysis of Variance **(ANOVA)**

Angiotensin-Converting-Enzyme-Inhibitor **(ACEI)**

Angiotensin-Receptor Blocker **(ARB)**

Albumin **(Alb)**

Albumin : Creatinine Ratio **(ACR)**

B-type Natriuretic Peptide **(BNP)**

Blood Pressure **(BP)**

Body Composition Monitor **(BCM)**

Calcium Channel Blocker **(CCB)**

Chronic Kidney Disease **(CKD)**

Diastolic Blood Pressure **(DBP)**

Dietary Approach to Stop Hypertension **(DASH)**

End Stage Renal Disease **(ESRD)**

Estimated Glomerular Filtration Rate **(eGFR)**

European Renal Best Practice **(ERBP)**

Extracellular Fluid **(ECF)**

Fat Tissue Index **(FTI)**

Haemoglobin **(Hb)**

High-Sensitivity C-Reactive Protein **(hsCRP)**

Interquartile Range **(IQR)**

Kidney Disease: Improving Global Outcomes **(KDIGO)**

Kidney Transplant Recipients **(KTRs)**

Lean Tissue Index **(LTI)**

Mean Arterial Pressure **(MAP)**

N-terminal Fragment of Prohormone B-type Natriuretic Peptide **(NT-proBNP)**

New Onset Diabetes After Transplantation **(NODAT)**

Percentage Volume Expansion **(%VE)**

Presence of Diabetes Mellitus Pre-Transplantation **(Pre-DM)**

Prohormone B-type Natriuretic Peptide **(Pro-BNP)**

Standard Deviation **(SD)**

Systolic Blood Pressure **(SBP)**

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Abstract

Background: The prevalence and consequences of hypervolemia in kidney transplant recipients (KTRs) have not been investigated. Specifically, its impact on blood pressure (BP) and relationship with N-terminal fragment of prohormone B-type natriuretic peptide (NT-proBNP) are unknown. The objectives of this study were to establish the prevalence of hypervolemia among clinically stable KTRs, investigate the predictors of post-transplant hypervolemia, assess its impact on blood pressure, and determine its relationship with NT-proBNP.

Methods: This single-centre cross-sectional study enrolled 123 clinically stable KTRs. Extracellular volume status was determined by multi-frequency bioimpedance analysis. Mild and severe hypervolemia were defined as percentage volume expansion of >7% and >15% respectively. Systolic BP (SBP) and diastolic BP (DBP) were measured, with mean arterial pressure (MAP) calculated. Serum NT-proBNP was quantified using a non-competitive immunoluminometric assay. Potential demographic, nutritional and clinical predictors of extracellular volume status, BP and NT-proBNP levels were assessed.

Results: Hypervolemia was present in 30% of KTRs, with 5% classified as severe hypervolemia. Significant predictors of volume expansion were increased sodium intake, advancing age, and reduced fat mass ($p<0.01$ for all associations). Hypervolemia was the only independent predictor of elevated MAP, SBP and DBP ($p<0.001$ for all associations). Raised NT-proBNP levels were independently associated with both hypervolemia ($p=0.01$) and allograft dysfunction ($p=0.03$).

Conclusions: Hypervolemia is unexpectedly common among clinically stable KTRs. It is closely associated with elevated BP. The relationship with increased sodium intake signals

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

potential therapeutic focus. Further study is warranted to prospectively investigate objective measures of extracellular volume status among KTRs.

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Introduction

Hypervolemia (or volume expansion) represents isotonic expansion of the extracellular fluid compartment caused by abnormal retention of water and sodium, manifesting as fluid accumulation and swelling in the extremities or lung tissues. It is common among patients with end-stage renal disease (ESRD) requiring maintenance dialysis[1-4], and is associated with increased morbidity and mortality[1-3,5]. For many of these patients, kidney transplantation is a preferred option of renal replacement therapy to correct metabolic abnormalities. It is assumed that hypervolemia no longer represents a major problem following transplantation, but no study to date confirms or refutes this.

In addition, hypervolemia is associated with hypertension in patients on haemodialysis[2] and peritoneal dialysis[3], but this relationship has not been studied in kidney transplant recipients (KTRs) despite this complication arising in 75-90% of these patients[6].

B-type Natriuretic Peptide (BNP) is a cardiac hormone that is synthesized as an amino acid precursor protein and undergoes intracellular modification to a Prohormone BNP (pro-BNP)[7]. It is secreted predominately from the ventricles in response to increased stretch of the ventricular wall[7]. Upon release into the circulation, pro-BNP is cleaved into the biologically active 32-amino acid C-terminal fragment BNP, and the biologically inactive 76-amino acid N-terminal fragment (NT-proBNP)[7]. NT-proBNP possesses a longer half-life time than the biologically active counterpart, hence delivering a superior reflection of pathophysiological situation leading to raised BNP levels[8]. Due to renal metabolism of NT-proBNP,

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

concentrations also rise with the progression of chronic kidney disease (CKD)[9]. Recent studies have confirmed that it is a marker of extracellular volume overload rather than cardiac dysfunction *per se* in maintenance dialysis patients[10-13]. However, little research has examined this relationship following transplantation, with the 2 studies conducted to date highlighting the inverse relationship between NT-proBNP and allograft function[14,15].

The primary objectives of this study were to determine the prevalence and predictors for hypervolemia in a stable kidney transplant cohort, and to assess its association with post-transplant hypertension. Secondly, we sought to explore the utility of serum NT-proBNP as a correlate of hypervolemia and renal dysfunction in this cohort.

Results

Population characteristics

The characteristics of the studied population are shown in **Table 1**. The mean percentage volume expansion (%VE) ± standard deviation (SD) for the cohort was 2.6±7.7%, ranging from -17.0% to +25.0%. Based on denoted criteria (described in **Materials and Methods**), the prevalence of hypovolemia in KTRs was 11% (13 patients), normovolemia was 59% (73 patients), mild hypervolemia was 25% (31 patients displaying %VE between 7.1 and 15.0%), and 5% suffered from severe hypervolemia (6 patients displaying %VE >15.0%).

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Factors predicting extracellular volume status

On univariate analysis, increasing values for %VE were associated with the following: higher sodium intake (relationship is shown in **Figure 1**), higher fluid intake, older age, pre-existing diabetes, male gender, the use of either an angiotensin-converting-enzyme-inhibitor (ACEI) or angiotensin-receptor blocker (ARB) (grouped as a single category), and the number of antihypertensive medications. The effect sizes for the univariate analyses are shown in **SDC, Table 1**. In the multivariate analysis, only increased sodium intake (beta coefficient, β = 1.7; 95% confidence interval, CI = 1.2, 2.4; p<0.001) and advancing age (β = 1.8; 95% CI = 1.0, 2.6; p<0.001) retained statistical significance. In addition, an association emerged in the multivariate analysis between increased %VE and reduced fat tissue index (FTI) (β = -1.4; 95% CI = -2.2, -0.5; p=0.002). A 51% of the variation in extracellular volume status (%VE) was explained by these variables (R^2: 51%; **SDC, Table 1**).

Extracellular volume status and blood pressure

Increasing volume status (higher %VE) was associated with progressive increases in all measures of blood pressure (BP) (systolic blood pressure, SBP, r=0.83, p <0.001; diastolic blood pressure, DBP, r=0.60, p<0.001; mean arterial pressure, MAP, r=0.78, p<0.001; **Figure 2a**). A significant difference across categories of volume status (“hypovolemia”; “normovolemia”; “mild hypervolemia”; “severe hypervolemia”) was seen, with increased BP at higher degrees of extracellular volume status (**Figure 2b**).

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

The univariate and adjusted analyses describing the predictors of MAP, SBP and DBP are shown in **SDC, Table 2**; **SDC, Table 3**; and **SDC, Table 4** respectively. The following predictor variables displayed univariate, unadjusted associations with higher values for all measures of BP (MAP, SBP and DBP): increasing %VE, increased sodium intake (associations shown in **Figure 3**), older age, diabetes (either pre-existing diabetes, pre-DM; or new onset diabetes after transplantation, NODAT), the use of either an ACEI or ARB, hypoalbuminaemia, male gender, and number of antihypertensive medications. In addition, higher fluid intake was associated with higher MAP and SBP readings, but not DBP. However, in the adjusted model, the only independent predictor of BP was a higher %VE, with this effect seen for MAP (β = 6.6; 95% CI = 5.6, 7.6; p<0.001), SBP (β = 9.8; 95% CI = 8.5, 11.0; p<0.001), and DBP (β = 4.9; 95% CI = 3.7, 6.2; p<0.001). Of note, a substantial proportion of BP variation could be explained by this single predictor variable (62%, 69% and 35% for MAP, SBP and DBP as shown in **SDC, Table 2**; **SDC, Table 3**; and **SDC, Table 4** respectively).

NT-proBNP as a marker of hydration status and allograft function

Median serum NT-proBNP level in this cohort of KTRs was 291.0 (interquartile range, IQR: 65.0-700.4) pmol/L. NT-proBNP levels demonstrated a positively skewed distribution and underwent logarithmic transformation prior to parametric analysis. On univariate analysis, higher %VE, lower estimated glomerular filtration rate (eGFR), and reduced haemoglobin (Hb) level were associated with higher values for NT-proBNP (**SDC, Table 5**). In the multivariate analysis, increasing %VE (Ratio, R = 1.16; 95% CI = 1.03, 1.29; p=0.01), decreasing eGFR (R = 0.95; 95% CI = 0.90, 0.99; p=0.03), and lower Hb level (R = 0.74; 95% CI = 0.58, 0.96; p=0.02) retained significant associations with NT-proBNP. In addition, the absence of a

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

dihydropyridine calcium channel blocker (CCB) prescription (R = 0.63; 95% CI = 0.45, 0.89; $p<0.01$) and either current or previous smoking history (R = 1.46; 95% CI = 1.04, 2.05; $p=0.03$) were significant predictors of raised NT-proBNP levels in the multivariate model. The relationships of NT-proBNP with %VE and renal allograft function are demonstrated in **Figure 4a** and **Figure 4b** respectively. A 21% of the variation in NT-proBNP was explained by the variables in the final multivariate model.

Discussion

This is the first study to address in detail the prevalence, predictors, and consequences of hypervolemia in KTRs. Based on the previously established definition of hypervolemia, 30% of KTRs were hypervolemic, of whom 5% suffered from severe hypervolemia. Despite a lower incidence when compared to continuous ambulatory peritoneal dialysis[3] or haemodialysis[16] populations, this degree of hypervolemia was unexpected, and is noteworthy in light of the specific selection of a clinically and biochemically stable kidney transplant cohort for this study. Hypervolemia was associated with increasing sodium intake, highlighting an important target for intervention. Dietary sodium restriction has not been formally examined in KTRs, but has gained attention in other contexts[17]. The daily sodium intake in the current cohort of KTRs was 2725mg (118mmol), lower than previously reported (3588 mg/156mmol per day)[18], but well above the recommendation of Dietary Approach to Stop Hypertension (DASH) guideline (1500-2300 mg/65-100 mmol per day)[19]. Collectively, these findings suggest that reducing sodium intake in line with the DASH diet should be recommended for KTRs presented with hypervolemia.

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

A recent study demonstrated a relationship between increased sodium intake and higher BP, although the contribution of extracellular volume status was not evaluated therein[18]. Whilst the results of the current study confirmed a univariate association between sodium intake and BP, this relationship did not hold when the effect of extracellular volume status was taken into account. Indeed, hypervolemia was identified as the only independent risk factor for elevated BP, which has a recognised impact upon long-term patient and graft outcomes[20-22]. Although this relationship between hypervolemia and elevated BP resonates with findings in dialysis patients[2,3,23], this has not been previously demonstrated in KTRs.

Pertinently, the American Society of Hypertension[24] acknowledges the possible role of volume expansion and potential therapeutic role of diuretics in post-transplant hypertension. Other expert review articles also recognise volume expansion as a potential risk factor, although remain guarded over the use of diuretic therapies[25,26]. In the current study, the prevalence of diuretic usage was only 15%, with furosemide being the only diuretic prescription. No association between furosemide usage and volume status was observed, but this may be a reflection of "confounding by indication". Furthermore, the median dosage of furosemide in this study cohort was 40mg, a dosage which may be insufficient to target hypervolemia in KTRs with a mean eGFR of 44mL/min[27]. Such confounding may also be responsible for the association between renin-angiotensin system blockers (ACEI and ARB), and volume overload, MAP, SBP and DBP, although these associations did not persist in the adjusted analysis.

In regard to other determinants of extracellular volume status, an inverse association between fat mass and volume status was observed in the current study. This phenomenon has been demonstrated in a non-transplanted population[28], which now extends to the kidney transplant

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

population. Interestingly renal dysfunction was not identified as one of the predictors of volume status and blood pressure in this study. However, based on the statistical point estimates, eGFR displayed inverse associations with volume overload, MAP, SBP and DBP, and the absence of statistical significance may reflect the study size and range of renal function encountered in this study, and certainly the current results do not exclude the importance of renal function in this setting.

Based on the findings from this study, a multi-modality approach involving the DASH diet and increased diuretic usage may be beneficial in the treatment of volume overload and hypertension in KTRs. Previous studies have shown that synergistic hypotensive effects were achieved when sodium restriction and diuretics were used in combination[29,30]. In particular, the DASH diet, comprising high fruits, vegetables, whole-grains, and low-fat dairy products; and low fat, refined carbohydrates and sodium, has been shown to substantially lower blood pressure in large, randomised, controlled trials[19,31,32]. It has also been proven to potentiate the benefits of antihypertensive medication treatment[31]. Diuretic therapy should be titrated in accordance with volume status and blood pressure. Crucially, meticulous monitoring of both volume status and blood pressure should be in place to ensure optimal management of hypertension in KTRs. In particular, increasing fluid intake is often promoted particularly in the early period post-transplantation, yet also displayed univariate association with volume overload, MAP and SBP, thereby highlighting the importance of judicious assessment of extracellular volume in these patients. Indeed, the findings from this study suggest that more widespread and accurate evaluation of extracellular volume status may facilitate the clinical management of KTRs, and sets the scene for interventional measures which have shown benefit in a recent haemodialysis-based trial[33]. It is hoped that the findings of this study will highlight the importance of extracellular volume status assessment in the management of hypertension, a

tool yet to be incorporated into international guidelines from Kidney Disease: Improving Global Outcomes (KDIGO)[34], European Renal Best Practice (ERBP) Work Group[35] and United Kingdom Renal Association (UKRA)[36].

The independent association between an objective measure of hypervolemia and raised NT-proBNP level is a novel and noteworthy finding of this study, confirming and extending findings from the non-transplanted populations, predominantly patients undergoing dialysis[10-13]. Additionally, reduced allograft function was independently associated with raised NT-proBNP levels, in keeping with findings from previous studies among KTRs[14,15], due to a reduced renal clearance of NT-proBNP. Although previous studies have suggested NT-proBNP as a marker of cardiac dysfunction in dialysis patients[37,38], interpretation of these studies is limited by a lack of concomitant and objective measurement of volume status, and by the variation in NT-proBNP levels depending on the timing of blood sampling relative to dialysis treatment. In fact, the most detailed study in dialysis which employed standardised sampling times, simultaneous echocardiography and bioimpedance-based extracellular fluid volume measurements, showed that NT-proBNP was dependent on volume overload *per se*, rather than the echocardiographic parameters of cardiac dysfunction[10,11]. The single study in KTRs addressing the relationship between echocardiography and NT-proBNP level likewise found no relationship between the two parameters[14]. Whilst cardiac function was not assessed in the current study, the findings from this study certainly support the concept that NT-proBNP levels reflect volume status. However, an important caveat is the high variability in the relationship between NT-proBNP levels and both %VE and eGFR. This suggests that although NT-proBNP may be a marker of volume expansion and renal dysfunction, it cannot yet be considered as an accurate surrogate for either. The utility of serial NT-proBNP measurements cannot be discerned by the current study.

Other factors independently associated with elevated NT-proBNP levels included smoking (current and/or ex- smoker), reduced level of Hb, and the absence of CCB prescription as an antihypertensive agent. Although the mechanisms behind these findings are not fully understood and were not the focus of the present study, these results are in keeping with previous observations in non-transplant cohorts[39-45], and reflecting the "face validity" of the current findings.

This study has limitations that should be acknowledged. It represents a single-centre experience, and validations of the findings are needed in other cohorts. Also, transplant renal artery stenosis is a potential cause for post-transplant hypertension and volume expansion. However, it was not systematically sought in this study due to an estimated prevalence of only 5-10%[46], and the lack of detection is unlikely to have confounded the results. The cross-sectional nature of this study is unable to establish the causal relationship between predictor and outcome variables. Long-term longitudinal follow-up and experimental interventions are now required to robustly evaluate the impact of extracellular volume status on relevant end-points in kidney transplantation.

In summary, this is the first study to investigate the prevalence, predictors, consequences, and biochemical markers of hypervolemia in KTRs. It points at potential targets for intervention, thereby expanding future avenues for basic and clinical research.

Materials and Methods

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Participants and study design

KTRs beyond 1 year post-transplantation, with stable graft function (<10% increase in serum creatinine over preceding 6 months), were recruited to this cross-sectional study between April 2010 and April 2013. Exclusion criteria included episodes of acute rejection within the last 6 months, evidence of sepsis in the last 6 weeks, known active malignancy or chronic infection, history of thyroid disease or adrenal insufficiency, and contra-indications for use of bio-impedance based body composition assessment (implanted or external electronic devices, metallic implants, amputations, pregnancy, and lactation). Of 133 patients approached, 10 did not participate (mainly due to work commitment). The study was approved by the local research ethics committee, and was conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection

Demographics and clinical parameters

Age, gender, ethnicity, and time post-transplantation were collected from patients' medical records. Smoking status (never smoked, current and ex- smoker) was collected by questionnaire. The following clinical parameters were retrieved from patients' medical records: 1) presence of diabetes, either pre-transplantation (pre-DM) or new onset diabetes

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

after transplantation (NODAT), 2) prior acute rejection episodes, 3) immunosuppressive medication usage, either prednisolone, calcineurin inhibitor or adjunctive antiproliferative agent, 4) use of anti-hypertensive medications, either angiotensin-converting-enzyme inhibitor (ACEI), angiotensin-receptor blocker (ARB), beta-adrenergic blocker (BAB), dihydropyridine calcium-channel blocker (CCB), or alpha-adrenergic blocker (AAB), and 5) use of diuretic.

Systolic BP (SBP) and diastolic BP (DBP) were measured semi-recumbent with a fully-automatic upper-arm digital blood-pressure monitor (Spot Vital Signs ® LXi, Welch Allyn). Six readings over an 8-10 minute period were taken, with the first reading ignored, and the mean of the remaining 5 used for analysis. This protocol for BP monitoring has been shown to produce measurements comparable to that derived from the 24-hour ambulatory blood pressure monitor, the "gold standard" for the diagnosis of hypertension[47]. Mean arterial pressure (MAP) was subsequently calculated using the formula (2DBP + SBP)/3[18].

Laboratory parameters

Blood samples were collected for measurement of high-sensitivity C-reactive protein (hsCRP), albumin (Alb), haemoglobin (Hb) and estimated glomerular filtration rate (eGFR) derived using 4-variable modification of diet in renal disease equation[48]. Morning urine was collected for assessment of albumin : creatinine ratio (ACR). Analyses were undertaken in accredited hospital haematology and biochemistry laboratories.

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Serum NT-proBNP was measured using a non-competitive immunoluminometric assay as described by Khan and colleagues[49]. This highly specific assay shows no cross-activity with atrial natriuretic peptide, BNP, or C-type natriuretic peptide[49]. The inter- and intra- assay coefficients of variation were 2.3 and 4.8% respectively[49].

Sodium and fluid intakes

Sodium and fluid intakes were estimated by a 3-day food diary. A multiple-day food diary provides a good estimate of individual's sodium intake[50], comparable to that derived from the mean 24-hour urinary sodium excretion[50,51], and produces a reliable and valid record of fluid intake in free-living humans[52]. Participants were given detailed written instructions on completing an accurate dietary record for a 3-day period, which included one weekend day, within one week prior to attending the research visit. These instructions were accompanied by verbal explanation from the researcher, which included training in portion size estimation and documentation for both dining in and eating out. The dietary records were reviewed by the researcher for accuracy and completeness at the research visit. Data was entered into Dietplan6 P3 (Forestfield Software Ltd) nutrition analysis program by the same researcher, avoiding inter-observer variation. Total daily intakes of fluid, energy, all macro- and micro- nutrients, were calculated by this program. No patients were prescribed sodium-containing oral medication at the time of the study.

Measurement of body composition and hydration status; definition of fluid overload

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Body composition and extracellular volume status were assessed by whole body bio-impedance spectroscopy ("body composition monitor" [BCM]; Fresenius Medical Care, Germany). This device has been used in dialysis patients extensively[5], and has been validated against reference methods for volume status and body composition[53]. The BCM utilises an algorithm based on a 3-compartment body model to evaluate extracellular and intracellular fluid volumes[28]. Absolute extracellular volume expansion was determined by calculating the difference between the actual amount of extracellular fluid in the body detected by the BCM and the expected amount of extracellular fluid (ECF) predicted by the BCM under normal physiological (i.e. normovolemia) conditions[5,54]. Percentage volume expansion (%VE) is therefore defined as: [(Absolute extracellular volume expansion × 100) / Expected ECF volume]. In a normal reference population, the 90th and the 10th percentiles of %VE is ±7%[5,55]. Increased mortality in haemodialysis patients is observed when %VE >15%[56,57]. Hence, established definitions (and those used in the current study) are based on %VE, <-7.0% representing "hypovolemia", within ±7.0% indicating "normovolemia", between 7.1% and 15.0% denoting "mild hypervolemia", and >15.0% demonstrating "severe hypervolemia".

Measurements were carried out in a standard manner while the patient was lying supine in a flat and non-conductive bed. The inbuilt physiological body composition model measures whole-body bioimpedance spectroscopy at 50 frequencies (5 to 1000 kHz) via electrodes placed on the wrist (proximal to the transverse) and the ankle (arch on the superior side of the foot) on the same side of the body. Results for %VE, together with Lean Tissue Index (LTI [kg/m^2]) and Fat Tissue Index (FTI [kg/m^2]), were displayed after each measurement.

Statistical analysis

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Statistical analyses were performed using STATA. Results were presented as mean ± standard deviation (SD) for normally distributed data or median (interquartile range, IQR) for non-normally distributed data. Unadjusted univariate relationships were evaluated with Pearson's correlation coefficients, and one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple-group comparisons.

Linear regression analysis was used to determine the associations between predictor variables and the continuously-distributed outcome variables, with logarithmic transformation of non-normally distributed data prior to analysis. The analyses were performed in two stages. Initially, the effect of each variable was examined in a series of univariate regression analyses. Subsequently, the joint effect of variables demonstrating some evidence of association on univariate analysis ($p<0.20$) was examined in a multivariable regression analysis, using a backwards selection procedure to derive the final model. A type 1 error rate ≤5% ($p\leq0.05$) was considered significant in the final model.

Acknowledgements

The research was carried out at the National Institute of Health Research (NIHR) / Wellcome Trust Clinical Research Facility Birmingham. The views expressed are those of the authors and not necessarily those of the NHS, and the NIHR of the Department of Health. The authors would like to acknowledge the staff in the Renal Outpatients Department and the Wellcome Trust Clinical Research Facility who has been involved in facilitating this study. Also, special

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

thanks to Golaleh McGinnell, Theresa Brady and Helen Houston for leading the nursing support of this research.

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

References

1. Kalantar-Zadeh K, Regidor DL, Kovesdy CP, et al. Fluid Retention Is Associated With Cardiovascular Mortality in Patients Undergoing Long-Term Hemodialysis. *Circulation.* 2009;119(5):671-679.
2. Arneson TJ, Liu J, Qiu Y, Gilbertson DT, Foley RN, Collins AJ. Hospital Treatment for Fluid Overload in the Medicare Hemodialysis Population. *Clinical Journal of the American Society of Nephrology.* 2010;5(6):1054-1063.
3. Guo Q, Yi C, Li J, Wu X, Yang X, Yu X. Prevalence and Risk Factors of Fluid Overload in Southern Chinese Continuous Ambulatory Peritoneal Dialysis Patients. *PLoS ONE.* 2013;8(1):e53294.
4. Ronco C, Kaushik M, Valle R, Aspromonte N, Peacock WF. Diagnosis and Management of Fluid Overload in Heart Failure and Cardio-Renal Syndrome: The “5B” Approach. *Seminars in nephrology.* 2012;32(1):129-141.
5. Van Biesen W, Williams JD, Covic AC, et al. Fluid Status in Peritoneal Dialysis Patients: The European Body Composition Monitoring (EuroBCM) Study Cohort. *PLoS ONE.* 2011;6(2):e17148.
6. Ojo AO. Cardiovascular Complications After Renal Transplantation and Their Prevention. *Transplantation.* 2006;82(5):603-611.
7. Wang AY-M, Lai K-N. Use of Cardiac Biomarkers in End-Stage Renal Disease. *Journal of the American Society of Nephrology.* 2008;19(9):1643-1652.
8. Locatelli F, Hannedouche T, Martin-Malo A, et al. The Relationship of NT-proBNP and Dialysis Parameters with Outcome of Incident Haemodialysis Patients: Results from the Membrane Permeability Outcome Study. *Blood Purification.* 2013;35(1-3):216-223.
9. Srisawasdi P, Vanavanan S, Charoenpanichkit C, Kroll MH. The Effect of Renal Dysfunction on BNP, NT-proBNP, and Their Ratio. *American Journal of Clinical Pathology.* 2010;133(1):14-23.
10. Papakrivopoulou E, Lillywhite S, Davenport A. Is N-terminal probrain-type natriuretic peptide a clinically useful biomarker of volume overload in peritoneal dialysis patients? *Nephrology Dialysis Transplantation.* 2012;27(1):396-401.
11. Booth J, Pinney J, Davenport A. N-terminal proBNP—Marker of Cardiac Dysfunction, Fluid Overload, or Malnutrition in Hemodialysis Patients? *Clinical Journal of the American Society of Nephrology.* 2010;5(6):1036-1040.
12. Paniagua R, Ventura M-d-J, Ávila-Díaz M, et al. NT-proBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients. *Nephrology Dialysis Transplantation.* 2010;25(2):551-557.
13. Jacobs LH, van de Kerkhof JJ, Mingels AM, et al. Inflammation, overhydration and cardiac biomarkers in haemodialysis patients: a longitudinal study. *Nephrology Dialysis Transplantation.* 2010;25(1):243-248.
14. Zbróg Z, Szuflet A, A R, et al. NT-proBNP plasma levels and echocardiographic assessment of cardiac function in patients after renal transplantation. *Kardiol Pol.* 2007;65(4):345-351.
15. Bodlaj G, Hubmann R, Saleh K, et al. Serum levels of N-terminal pro-B-type natriuretic peptide are associated with allograft function in recipients of renal transplants. *Wien Klin Wochenschr.* 2009;121(19-20):631-637.
16. Machek P, Jirka T, Moissl U, Chamney P, Wabel P. Guided optimization of fluid status in haemodialysis patients. *Nephrology Dialysis Transplantation.* 2010;25(2):538-544.
17. Agarwal R. Resistant hypertension and the neglected antihypertensive: sodium restriction. *Nephrol Dial Transplant.* 2012;27(11):4041-4045.
18. van den Berg E, Geleijnse JM, Brink EJ, et al. Sodium intake and blood pressure in renal transplant recipients. *Nephrology Dialysis Transplantation.* 2012;27(8):3352-3359.
19. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med.* 2001;344(1):3-10.

20. Kasiske BL, Anjum S, Shah R, et al. Hypertension after kidney transplantation. *American Journal of Kidney Diseases.* 2004;43(6):1071-1081.

21. El-Amm J-M, Haririan A, Crook E. The Effects of Blood Pressure and Lipid Control on Kidney Allograft Outcome. *American Journal of Cardiovascular Drugs* 2006;6(1):1-7.

22. Mangray M, Vella JP. Hypertension After Kidney Transplant. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2011;57(2):331-341.

23. Kovacic V, Roguljic L, Bacic B, Bosnjak T. Ultrafiltration volume is associated with changes in blood pressure in chronically hemodialyzed patients. *Ren Fail.* 2003;25(6):945-951.

24. Weir MR, Salzberg DJ. Management of hypertension in the transplant patient. *J Am Soc Hypertens.* 2011;5(5):425-432.

25. Arias M, Fernandez-Fresnedo G, Gago M, et al. Clinical characteristics of resistant hypertension in renal transplant patients. *Nephrol Dial Transplant.* 2012;27(4):iv36-iv38.

26. Zbroch E, Malyszko J, Mysliwiec M, Przybylowski P, Durlik M. Hypertension in solid organ transplant recipients. *Ann Transplant.* 2012;17(1):100-107.

27. Wilcox CS. New Insights into Diuretic Use in Patients with Chronic Renal Disease. *Journal of the American Society of Nephrology.* 2002;13(3):798-805.

28. Chamney PW, Wabel P, Moissl UM, et al. A whole-body model to distinguish excess fluid from the hydration of major body tissues. *The American Journal of Clinical Nutrition.* 2007;85(1):80-89.

29. Wing LM, Arnolda LF, Harvey PJ, et al. Low-dose diuretic and/or dietary sodium restriction when blood pressure is resistant to ACE inhibitor. *Blood Press.* 1998;7(5-6):299-307.

30. Ram CV, Garrett BN, Kaplan NM. Moderate sodium restriction and various diuretics in the treatment of hypertension. *Arch Intern Med.* 1981;141(8):1015-1019.

31. Craddick S, Elmer P, Obarzanek E, Vollmer W, Svetkey L, Swain M. The DASH diet and blood pressure. *Curr Atheroscler Rep.* 2003;5(6):484-491.

32. Moore TJ, Conlin PR, Ard J, Svetkey LP, Group ftDCR. DASH (Dietary Approaches to Stop Hypertension) Diet Is Effective Treatment for Stage 1 Isolated Systolic Hypertension. *Hypertension.* 2001;38(2):155-158.

33. Hur E, Usta M, Toz H, et al. Effect of fluid management guided by bioimpedance spectroscopy on cardiovascular parameters in hemodialysis patients: a randomized controlled trial. *Am J Kidney Dis.* 2013;61(6):957-965.

34. Kasiske BL, Zeier MG, Chapman JR, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Kidney Int.* 2010;77(4):299-311.

35. Heemann U, Abramowicz D, Spasovski G, Vanholder R. Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on kidney transplantation: a European Renal Best Practice (ERBP) position statement. *Nephrol Dial Transplant.* 2011;26(7):2099-2106.

36. Mactier R, Davies S, Dudley C, et al. Summary of the 5th Edition of the Renal Association Clinical Practice Guidelines (2009–2012). *Nephron Clinical Practice.* 2011;118(1):c27-c70.

37. David S, Kumpers P, Seidler V, Biertz F, Haller H, Fliser D. Diagnostic value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) for left ventricular dysfunction in patients with chronic kidney disease stage 5 on haemodialysis. *Nephrol Dial Transplant.* 2008;23(4):1370-1377.

38. Goldfarb-Rumyantzev AS, Chelamcharla M, Bray BE, et al. Volume indicators and left ventricular mass during aggressive volume management in patients on thrice-weekly hemodialysis. *Nephron Clin Pract.* 2009;113(4):c270-280.

39. Desai AS, Bibbins-Domingo K, Shlipak MG, Wu AHB, Ali S, Whooley MA. Association between anaemia and N-terminal pro-B-type natriuretic peptide (NT-proBNP): Findings from the Heart and Soul Study. *European Journal of Heart Failure.* 2007;9(9):886-891.

40. Hogenhuis J, Voors AA, Jaarsma T, et al. Anaemia and renal dysfunction are independently associated with BNP and NT-proBNP levels in patients with heart failure. *European Journal of Heart Failure.* 2007;9(8):787-794.

41. Willis MS, Lee ES, Grenache DG. Effect of anemia on plasma concentrations of NT-proBNP. *Clin Chim Acta.* 2005;358(1-2):175-181.

42. Anand IS, Chandrashekhar Y, Ferrari R, Poole-Wilson PA, Harris PC. Pathogenesis of oedema in chronic severe anaemia: studies of body water and sodium, renal function, haemodynamic variables, and plasma hormones. *British Heart Journal.* 1993;70(4):357-362.

43. Allanore Y, Borderie D, Meune C, et al. N-terminal pro-brain natriuretic peptide as a diagnostic marker of early pulmonary artery hypertension in patients with systemic sclerosis and effects of calcium-channel blockers. *Arthritis Rheum.* 2003;48(12):3503-3508.

44. Mirjafari H, Welsh P, Verstappen SM, et al. N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) and mortality risk in early inflammatory polyarthritis: results from the Norfolk Arthritis Registry (NOAR). *Ann Rheum Dis.* 2013;0:1-7.

45. Otsuka T, Kawada T, Seino Y, Ibuki C, Katsumata M, Kodani E. Relation of smoking status to serum levels of N-terminal pro-brain natriuretic peptide in middle-aged men without overt cardiovascular disease. *Am J Cardiol.* 2010;106(10):1456-1460.

46. Kasiske BL, Vazquez MA, Harmon WE, et al. Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation. *J Am Soc Nephrol.* 2000;11(15):S1-86.

47. Brothwell S, Dutton M, Ferro C, Stringer S, Cockwell P. Optimising the accuracy of blood pressure monitoring in chronic kidney disease: the utility of BpTRU. *BMC Nephrology.* 2013;14(1):218.

48. Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. *Clinical Chemistry.* 2007;53(4):766-772.

49. Khan SQ, Kelly D, Quinn P, Davies JE, Ng LL. Myotrophin is a more powerful predictor of major adverse cardiac events following acute coronary syndrome than N-terminal pro-B-type natriuretic peptide. *Clin Sci.* 2007;112(4):251-256.

50. Caggiula AW, Wing RR, Nowalk MP, Milas NC, Lee S, Langford H. The measurement of sodium and potassium intake. *The American Journal of Clinical Nutrition.* 1985;42(3):391-398.

51. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on Blood Pressure of Reduced Dietary Sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet. *New England Journal of Medicine.* 2001;344(1):3-10.

52. De Castro JM. Methodology, Correlational Analysis, and Interpretation of Diet Diary Records of the Food and Fluid Intake of Free-living Humans. *Appetite.* 1994;23(2):179-192.

53. Wabel P, Chamney P, Moissl U, Jirka T. Importance of Whole-Body Bioimpedance Spectroscopy for the Management of Fluid Balance. *Blood Purification.* 2009;27(1):75-80.

54. Gallar-Ruiz P, Digioia C, Lacalle C, et al. Body composition in patients on haemodialysis: relationship between the type of haemodialysis and inflammatory and nutritional parameters. *Nefrologia.* 2012;32(4):467-476.

55. Wieskotten S, Moissl U, Chamney P, Wabel P. Reference Ranges for Human Body Composition and Fluid Overload. http://www.bcm-fresenius.com/mediafiles/information_on_reference_ranges.pdf.

56. Wizemann V, Wabel P, Chamney P, et al. The mortality risk of overhydration in haemodialysis patients. *Nephrology Dialysis Transplantation.* 2009;24(5):1574-1579.

57. Wabel P, Moissl U, Chamney P, et al. Towards improved cardiovascular management: the necessity of combining blood pressure and fluid overload. *Nephrology Dialysis Transplantation.* 2008;23(9):2965-2971.

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Table Legends

Table 1. Population Characteristics

Figure Legends

Figure 1. Association between Sodium Intake and Extracellular Volume Status (Percentage Volume Expansion, %VE)

Figure 2a. Relationship between Extracellular Volume Status (Percentage Volume Expansion, %VE) and Blood Pressure

Figure 2b. Comparisons of Blood Pressure among Kidney Transplant Recipients with Different Extracellular Volume Status

Figure 3. Association between Sodium Intake and Blood Pressure

Figure 4a. Association between Extracellular Volume Status (Percentage Volume Expansion, %VE) and level of NT-proBNP

Figure 4b. Association between Renal Function and level of NT-proBNP

Supplemental Digital Content (SDC) Legends

SDC, Table 1. Predictors of Extracellular Volume Status (Percentage Volume Expansion, %VE)

SDC, Table 2. Predictors of Mean Arterial Pressure (MAP)

SDC, Table 3. Predictors of Systolic Blood Pressure (SBP)

SDC, Table 4. Predictors of Diastolic Blood Pressure (DBP)

SDC, Table 5. Predictors of N-Terminal of prohormone B-type Natriuretic Peptide (NT-proBNP)

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Table 1. Population Characteristics

	Characteristics
Sample size	n = 123
Gender (%)	Male = 56 Female = 44
[*]Ethnicity (%)	Caucasian = 77 Asian = 16 Afro-Caribbean = 5 Others = 2
[†]Mean age (years)	50 ± 15
[‡]Median time post-transplantation (years)	5 (2-11)
[§]Smoking status (%)	Non-smoker = 63 Current smoker = 8 Ex-smoker = 29
[†]Mean extracellular volume status: %VE (%)	2.6 ± 7.7
[‡]Median level of NT-proBNP (pmol/L)	291.0 (65.0-700.4)
Blood pressure	
[†]Mean systolic blood pressure (mmHg)	141 ± 19
[†]Mean diastolic blood pressure (mmHg)	82 ± 13
[†]Mean arterial pressure (mmHg)	101 ± 13
Immunosuppressive medication usage	
Calcineurin inhibitor (%)	79
Adjunctive antiproliferative agent (%)	87
Prednisolone (%)	77
Dosage of immunosuppressive medications	
[‡]Median dose of Tacrolimus (mg/day)	4.0 (2.5-6.0)
[‡]Median dose of Cyclosporin (mg/day)	150 (150-200)
[†]Mean dose of Mycophenolate Mofetil (mg/day)	987 ± 392
[†]Mean dose of Azathioprine (mg/day)	77 ± 36
[‡]Median dose of Prednisolone (mg/day)	5 (5-5)
Anti-hypertensive medication usage	
ACEI / ARB (%)	43
BAB (%)	21
CCB (%)	48
AAB (%)	39
Diuretic medication usage	
Furosemide, exclusively (%)	15
[‡]Median dosage of Furosemide (mg)	40 (30-40)
Presence of diabetes (%)	Non-diabetic = 75 NODAT = 15 Pre-DM = 10
Previous episodes of acute rejection (%)	Yes = 23 No = 77
[‡]Median hsCRP (mg/L)	2.4 (1.0-4.9)
[†]Mean Hb (g/dL)	12.6 ± 1.6
[†]Mean Alb (g/L)	44.5 ± 3.2
[†]Mean eGFR (mL/min)	44.2 ± 17.3
[‡]Median ACR (mg/mmol)	4.4 (1.6-14.7)
[‡]Median sodium intake (mg)	2725 (2131-3248)
[‡]Median fluid intake (mL)	2567 (2100-3672)
Body Composition	
Body mass index, BMI (kg/m^2)	27.4 ± 5.8
Lean Tissue Index, LTI (kg/m^2)	13.9 ± 3.0
Fat Tissue Index, FTI (kg/m^2)	13.3 ± 6.3

[*]For the purpose of statistical analysis, the ethnicity of patients classified as "Afro-Caribbean", "Asian" and "Others" was grouped as "Non-Caucasian", 77% "Caucasian" versus 23% "Non-Caucasian".
[†]Normally distributed data, results expressed as mean ± standard deviation (SD).
[‡]Non-normally distributed data, results expressed as median (interquartile range, IQR).
[§]For the purpose of statistical analysis, smoking status was arranged into 2 categories, "non-smoker" versus "current smoker and ex-smoker", 63% and 37% of patients respectively.
Abbreviations: %VE=Percentage Volume Expansion; NT-proBNP=N-Terminal pro B-type Natriuretic Peptide; ACEI=Angiotensin-Converting-Enzyme Inhibitor; ARB=Angiotensin-Receptor Blocker; Beta-Adrenergic Blocker; CCB=Calcium Channel Blocker; AAB=Alpha-Adrenergic Blocker; hsCRP=high-sensitivity C-Reactive Protein; Hb=Haemoglobin; Alb=Albumin; eGFR=estimated Glomerular Filtration Rate; ACR=Albumin : Creatinine Ratio; BMI=Body Mass Index; LTI= Lean Tissue Index; FTI=Fat Tissue Index; NODAT=New Onset Diabetes After Transplantation; Pre-DM=Presence of Diabetes Mellitus pre-transplantation.

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

SDC, Table 1. Predictors of Extracellular Volume Status (Percentage Volume Expansion, %VE)

	Univariate Analysis		Multivariate Analysis[§]	
	Regression Coefficient (95% CI[∝])	***p*-value**	**Regression Coefficient (95% CI[∝])**	***p*-value**
[(***)] Sodium intake (mg)	1.8 (1.3, 2.3)	<0.001	1.7 (1.2, 2.4)	<0.001
[(***)] Fluid intake (mL)	1.4 (0.6, 2.0)	<0.001		
[(**)] Age (years)	1.9 (0.9, 2.8)	<0.001	1.8 (1.0, 2.6)	<0.001
Presence of diabetes				
Non-diabetic	0	<0.001		
NODAT	2.4 (-1.2, 5.9)			
Pre-DM	10.3 (6.0, 14.7)			
Gender				
Female	0	0.002		
Male	4.3 (1.6, 7.0)			
Use of ACEI / ARB				
No	0	0.01		
Yes	3.6 (0.9, 6.3)			
Number of antihypertensive medications	1.6 (0.1, 3.2)	0.04		
Alb (g/L)	-0.4 (-0.8, 0.1)	0.11		
Use of diuretic (furosemide)				
No	0	0.11		
Yes	3.5 (-0.8, 7.8)			
[(*)] FTI (kg/m^2)	-1.0 (-2.0, 0.5)	0.12	-1.4 (-2.2, -0.5)	0.002
[(*)] eGFR (mL/min)	-0.3 (-0.6, 0.1)	0.19		
[(ℓ)] ACR (mg/mmol)	0.5 (-0.4, 1.4)	0.27		
[‡]**Ethnicity**				
Caucasian	0	0.29		
Non-Caucasian	-1.8 (-5.1, 1.5)			
Use of prednisolone				
No	0	0.29		
Yes	-1.8 (-5.1, 1.6)			
[(*)] LTI (kg/m^2)	-0.2 (-0.7, 0.2)	0.31		
[†]**Smoking status**				
Never smoked	0	0.32		
Ex-smoker / Current smoker	0.1 (-1.4, 4.3)			
Use of BAB				
No	0	0.34		
Yes	0.2 (-1.3, 3.9)			
Use of CCB				
No	0	0.34		
Yes	0.1 (-1.5, 4.1)			
Hb (g/dL)	-0.4 (-1.3, 0.5)	0.44		
Use of AAB				
No	0	0.52		
Yes	0.1 (-2.0, 3.9)			
[(*)] Time post transplantation (years)	0.2 (-0.9, 1.3)	0.76		
Use of calcineurin inhibitor				
No	0	0.85		
Yes	-0.3, (-3.7, 3.1)			
[(ℓ)] hsCRP (mg/L)	0.1 (-1.3, 1.4)	0.94		
Previous episodes of acute rejection				
No	0	0.95		
Yes	-0.1 (-3.4, 3.2)			
Use of adjunctive antiproliferative agents				
No	0	0.99		
Yes	-0.0 (-4.6, 4.5)			
R^2 value from final model			51%	

[§]Results in the final multivariate regression model were presented.
[∝]CI = Confidence Interval.
[†]For the purpose of statistical analysis, smoking status was arranged into 2 categories, "non-smoker" versus "the combination of current smoker and ex-smoker", 63% and 37% of patients respectively.
[‡]For the purpose of statistical analysis, the ethnicity of patients classified as "Afro-Caribbean", "Asian" and "Others" was grouped as "Non-Caucasian", 77% "Caucasian" versus 23% "Non-Caucasian".
[(*)] Coefficients reported for a 5-unit increase in explanatory variable.
[(**)] Coefficients reported for a 10-unit increase in explanatory variable.
[(***)] Coefficients reported for a 50-unit increase in explanatory variable.

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

(l) Variable analysed on the log scale (base 10).

Abbreviations: %VE=Percentage Volume Expansion; NODAT=New Onset Diabetes After Transplantation; Pre-DM=Presence of Diabetes Mellitus pre-transplantation; ACEI=Angiotensin-Converting-Enzyme Inhibitor; ARB=Angiotensin-Receptor Blocker; Alb=Albumin; FTI=Fat Tissue Index; eGFR=estimated Glomerular Filtration Rate; ACR=Albumin : Creatinine Ratio; LTI= Lean Tissue Index; BAB=Beta-Adrenergic Blocker; CCB=Calcium Channel Blocker; Hb=Haemoglobin; AAB=Alpha-Adrenergic Blocker; hsCRP=high-sensitivity C-Reactive Protein.

SDC, Table 2. Predictors of Mean Arterial Pressure (MAP)

	Univariate Analysis		**Multivariate Analysis**[§]	
	Regression Coefficient (95% CI[≈]**)**	***p*-value**	**Regression Coefficient (95% CI**[≈]**)**	***p*-value**
(*) %VE	6.6 (5.6, 7.5)	<0.001	6.6 (5.6, 7.6)	<0.001
(***) Sodium intake (mg)	0.3 (0.2, 0.4)	<0.001		
(**) Age (years)	2.5 (0.9, 4.1)	<0.01		
Presence of diabetes				
Non-diabetic	0	<0.01		
NODAT	5.6 (2.1, 9.0)			
Pre-DM	11.2 (2.8, 19.5)			
Use of ACEI / ARB				
No	0	<0.01		
Yes	6.7 (2.1, 11.3)			
Alb (g/L)	-0.9 (-1.7, -0.2)	0.01		
Gender				
Female	0	0.02		
Male	5.8 (1.1, 10.4)			
(***) Fluid intake (mL)	0.2 (0.0, 0.3)	0.03		
Number of antihypertensive medications	2.7 (0.0, 5.4)	0.05		
‡**Ethnicity**				
Caucasian	0	0.08		
Non-Caucasian	5.0 (-0.5, 11.0)			
(*) Time post transplantation (years)	1.2 (-0.6, 2.9)	0.18		
(*) FTI (kg/m^2)	1.3 (-3.1, 0.6)	0.19		
Use of calcineurin inhibitor				
No	0	0.22		
Yes	3.6 (-2.2, 9.3)			
Use of diuretic (furosemide)				
No	0	0.23		
Yes	4.0 (-2.5, 10.5)			
Use of prednisolone				
No	0	0.38		
Yes	-2.5 (-8.1, 3.1)			
Use of CCB				
No	0	0.39		
Yes	2.1 (-2.7, 6.8)			
Use of BAB				
No	0	0.41		
Yes	3.2 (-2.9, 6.2)			
(*) eGFR (mL/min)	-0.2 (-0.9, 0.5)	0.54		
Hb (g/dL)	-0.5 (-2.0, 1.1)	0.56		
Use of adjunctive antiproliferative agents				
No	0	0.56		
Yes	2.2 (-5.3, 9.7)			
Use of AAB				
No	0	0.56		
Yes	1.5 (-3.5, 6.5)			
†**Smoking status**				
Never smoked	0	0.57		
Ex-smoker / Current smoker	1.4 (-3.5, 6.3)			
LTI (kg/m^2)	-0.2 (-1.0, 0.6)	0.63		
(l) hsCRP (mg/L)	1.1 (-3.8, 5.9)	0.66		
(l) ACR (mg/mmol)	0.6 (-3.0, 4.3)	0.72		
Previous episodes of acute rejection				
No	0	0.86		
Yes	-0.5 (-6.1, 5.1)			
R^2 value from final model			62%	

[§]Results in the final multivariate regression model were presented.

[≈]CI = Confidence Interval.

†For the purpose of statistical analysis, smoking status was arranged into 2 categories, “non-smoker” versus “the combination of current smoker and ex-smoker”, 63% and 37% of patients respectively.

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

‡For the purpose of statistical analysis, the ethnicity of patients classified as "Afro-Caribbean", "Asian" and "Others" was grouped as "Non-Caucasian", 77% "Caucasian" versus 23% "Non-Caucasian".
(*) Coefficients reported for a 5-unit increase in explanatory variable.
(**) Coefficients reported for a 10-unit increase in explanatory variable.
(***) Coefficients reported for a 50-unit increase in explanatory variable.
(l) Variable analysed on the log scale (base 10).
Abbreviations: %VE=Percentage Volume Expansion; NODAT=New Onset Diabetes After Transplantation; Pre-DM=Presence of Diabetes Mellitus pre-transplantation; ACEI=Angiotensin-Converting-Enzyme Inhibitor; ARB=Angiotensin-Receptor Blocker; Alb=Albumin; FTI=Fat Tissue Index; CCB=Calcium Channel Blocker; BAB=Beta-Adrenergic Blocker; eGFR=estimated Glomerular Filtration Rate; Hb=Haemoglobin; AAB=Alpha-Adrenergic Blocker; LTI= Lean Tissue Index; hsCRP=high-sensitivity C-Reactive Protein; ACR=Albumin : Creatinine Ratio.

SDC, Table 3. Predictors of Systolic Blood Pressure (SBP)

	Univariate Analysis		**Multivariate Analysis§**	
	Regression Coefficient (95% CI∞)	***p*-value**	**Regression Coefficient (95% CI∞)**	***p*-value**
(***) Sodium intake (mg)	0.4 (0.3, 0.6)	<0.001		
(***) Fluid intake (mL)	0.2 (0.1, 0.4)	<0.001		
(**) Age (years)	4.2 (2.0, 6.3)	<0.001		
(*) %VE	9.7 (8.4, 11.0)	<0.001	9.8 (8.5, 11.0)	<0.001
Presence of diabetes				
Non-diabetic	0	<0.001		
NODAT	9.2 (4.3, 14.0)			
Pre-DM	23.9 (12.7, 35.0)			
Use of ACEI / ARB				
No	0	<0.01		
Yes	9.3 (2.8, 15.8)			
Gender				
Female	0	0.02		
Male	8.1 (1.5, 14.6)			
Alb (g/L)	-1.1 (-2.2, -0.1)	0.03		
Number of antihypertensive medications	3.3 (-0.5, 7.0)	0.09		
‡Ethnicity				
Caucasian	0	0.20		
Non-Caucasian	5.2 (2.7, 13.1)			
(*) FTI (kg/m^2)	-1.6 (-4.2, 1.1)	0.24		
(l) ACR (mg/mmol)	2.9 (-2.1, 8.0)	0.25		
Use of diuretic (furosemide)				
No	0	0.28		
Yes	-4.4 (-12.3, 3.5)			
Use of prednisolone				
No	0	0.28		
Yes	-4.4 (-12.3, 3.5)			
LTI (kg/m^2)	-0.6 (-1.8, 0.5)	0.28		
(*) Time post transplantation (years)	1.2 (-1.2, 3.7)	0.31		
Hb (g/dL)	-0.9 (-3.1, 1.3)	0.42		
Use of calcineurin inhibitor				
No	0	0.53		
Yes	2.6 (-5.6, 10.7)			
Use of BAB				
No	0	0.55		
Yes	-2.1 (-4.4, 7.2)			
Previous episodes of acute rejection				
No	0	0.56		
Yes	-2.4 (-10.3, 5.6)			
Use of CCB				
No	0	0.62		
Yes	1.7 (-5.0, 8.4)			
†Smoking status				
Never smoked	0	0.69		
Ex-smoker / Current smoker	1.4 (-5.5, 8.3)			
(*) eGFR (mL/min)	-0.2 (-1.2, 0.8)	0.71		
Use of AAB				
No	0	0.74		
Yes	1.2 (-5.9, 8.3)			
(l) hsCRP (mg/L)	0.9 (-6.0, 7.8)	0.80		
Use of adjunctive antiproliferative agents				
No	0	0.95		
Yes	0.4 (-10.2, 11.0)			

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

R^2 value from final model	69%

[§]Results in the final multivariate regression model were presented.
[∝]CI = Confidence Interval.
[†]For the purpose of statistical analysis, smoking status was arranged into 2 categories, "non-smoker" versus "the combination of current smoker and ex-smoker", 63% and 37% of patients respectively.
[‡]For the purpose of statistical analysis, the ethnicity of patients classified as "Afro-Caribbean", "Asian" and "Others" was grouped as "Non-Caucasian", 77% "Caucasian" versus 23% "Non-Caucasian".
(*) Coefficients reported for a 5-unit increase in explanatory variable.
(**) Coefficients reported for a 10-unit increase in explanatory variable.
(***) Coefficients reported for a 50-unit increase in explanatory variable.
(l) Variable analysed on the log scale (base 10).
Abbreviations: %VE=Percentage Volume Expansion; NODAT=New Onset Diabetes After Transplantation; Pre-DM=Presence of Diabetes Mellitus pre-transplantation; ACEI=Angiotensin-Converting-Enzyme Inhibitor; ARB=Angiotensin-Receptor Blocker; Alb=Albumin; FTI=Fat Tissue Index; ACR=Albumin : Creatinine Ratio; LTI= Lean Tissue Index; Hb=Haemoglobin; BAB=Beta-Adrenergic Blocker; CCB=Calcium Channel Blocker; eGFR=estimated Glomerular Filtration Rate; AAB=Alpha-Adrenergic Blocker; hsCRP=high-sensitivity C-Reactive Protein.

SDC, Table 4. Predictors of Diastolic Blood Pressure (DBP)

	Univariate Analysis		**Multivariate Analysis[§]**	
	Regression Coefficient (95% CI[∝])	***p*-value**	**Regression Coefficient (95% CI[∝])**	***p*-value**
(*) %VE	5.0 (3.7, 6.2)	<0.001	4.9 (3.7, 6.2)	<0.001
(***) Sodium intake (mg)	0.2 (0.1, 0.3)	<0.01		
Use of ACEI / ARB				
No	0	0.02		
Yes	5.3 (0.7, 9.9)			
Alb (g/L)	-0.8 (-1.5, -0.1)	0.03		
(**) Age (years)	1.7 (0.1, 3.3)	0.04		
Presence of diabetes				
Non-diabetic	0	0.04		
NODAT	3.7 (0.2, 7.2)			
Pre-DM	4.9 (-3.6, 13.4)			
Gender				
Female	0	0.05		
Male	4.7 (0.0, 9.3)			
[‡]**Ethnicity**				
Caucasian	0	0.08		
Non-Caucasian	4.9 (-0.6, 10.4)			
Number of antihypertensive medications	2.4 (-0.3, 5.0)	0.08		
(***) Fluid intake (mL)	0.1 (-0.1, 0.2)	0.16		
Use of BAB				
No	0	0.16		
Yes	2.8 (-3.1, 4.8)			
Use of calcineurin inhibitor				
No	0	0.16		
Yes	4.0 (-1.7, 9.6)			
(*) Time post transplantation (years)	1.1 (-0.6, 5.6)	0.21		
[†]**Smoking status**				
Never smoked	0	0.23		
Ex-smoker / Current smoker	2.9 (-1.9, 7.7)			
(*) FTI (kg/m^2)	-1.1 (-3.0, 0.7)	0.24		
Use of CCB				
No	0	0.34		
Yes	2.3 (-2.4, 7.0)			
Use of adjunctive antiproliferative agents				
No	0	0.39		
Yes	3.2 (-4.1, 10.6)			
(*) eGFR (mL/min)	-0.2 (-0.9, 0.5)	0.50		
Use of AAB				
No	0	0.53		
Yes	1.6 (-3.3, 6.5)			
Use of diuretic (furosemide)				
No	0	0.58		
Yes	1.8 (-4.6, 8.2)			
Use of prednisolone				
No	0	0.59		
Yes	-1.5 (-7.1, 4.0)			
(l) hsCRP (mg/L)	1.2 (-3.6, 6.0)	0.62		
(l) ACR (mg/mmol)	-0.6 (-4.1, 3.0)	0.75		
Hb (g/dL)	-0.2 (-1.7, 1.3)	0.77		

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Previous episodes of acute rejection No Yes	 0 0.4 (-5.1, 6.0)	 0.87		
LTI (kg/m^2)	0.0 (-0.8, 0.8)	0.91		
		R^2 value from final model	35%	

[§]Results in the final multivariate regression model were presented.
[∞]CI = Confidence Interval.
[†]For the purpose of statistical analysis, smoking status was arranged into 2 categories, "non-smoker" versus "the combination of current smoker and ex-smoker", 63% and 37% of patients respectively.
[‡]For the purpose of statistical analysis, the ethnicity of patients classified as "Afro-Caribbean", "Asian" and "Others" was grouped as "Non-Caucasian", 77% "Caucasian" versus 23% "Non-Caucasian".
(*) Coefficients reported for a 5-unit increase in explanatory variable.
(**) Coefficients reported for a 10-unit increase in explanatory variable.
(***) Coefficients reported for a 50-unit increase in explanatory variable.
(l) Variable analysed on the log scale (base 10).
Abbreviations: %VE=Percentage Volume Expansion; ACEI=Angiotensin-Converting-Enzyme Inhibitor; ARB=Angiotensin-Receptor Blocker; Alb=Albumin; NODAT=New Onset Diabetes After Transplantation; Pre-DM=Presence of Diabetes Mellitus pre-transplantation; BAB=Beta-Adrenergic Blocker; FTI=Fat Tissue Index; CCB=Calcium Channel Blocker; eGFR=estimated Glomerular Filtration Rate; AAB=Alpha-Adrenergic Blocker; hsCRP=high-sensitivity C-Reactive Protein; ACR=Albumin : Creatinine Ratio; Hb=Haemoglobin; LTI= Lean Tissue Index.

SDC, Table 5. Predictors of N-Terminal of prohormone B-type Natriuretic Peptide (NT-proBNP)

	Univariate Analysis		**Multivariate Analysis[§]**	
	Ratio (95% CI[∞])	***p*-value**	**Ratio (95% CI[∞])**	***p*-value**
(*) %VE	1.38 (1.07, 1.78)	0.01	1.16 (1.03, 1.29)	0.01
(*) eGFR (mL/min)	0.89 (0.80, 0.99)	0.03	0.95 (0.90, 0.99)	0.03
Hb (g/dL)	0.74 (0.57, 0.96)	0.03	0.74 (0.58, 0.96)	0.02
Use of CCB No Yes	 1 0.84 (0.53, 1.05)	 0.09	 1 0.63 (0.45, 0.89)	 <0.01
(l) ACR (mg/mmol)	1.24 (0.96, 1.60)	0.10		
Use of adjunctive antiproliferative agents No Yes	 1 0.85 (0.40, 1.10)	 0.11		
[†]Smoking status Never smoked Ex-smoker / Current smoker	 1 1.16 (0.93, 1.84)	 0.12	 1 1.46 (1.04, 2.05)	 0.03
LTI (kg/m^2)	0.96 (0.91, 1.02)	0.20		
(**) Age (years)	1.20 (0.91, 1.59)	0.20		
(*) Time post transplantation (years)	1.20 (0.91, 1.60)	0.20		
[‡]Ethnicity Caucasian Non-Caucasian	 1 0.56 (0.23, 1.40)	 0.21		
Use of prednisolone No Yes	 1 0.17 (0.01, 4.75)	 0.29		
(l) hsCRP (mg/L)	0.83 (0.58, 1.19)	0.31		
Gender Female Male	 1 0.68 (0.32, 1.47)	 0.33		
Use of AAB No Yes	 1 1.09 (0.82, 1.64)	 0.41		
Presence of diabetes Non-diabetic NODAT Pre-DM	 1 2.02 (0.69, 5.96) 1.32 (0.37, 4.70)	 0.42		
Use of BAB No Yes	 1 0.98 (0.81, 1.28)	 0.45		
Use of calcineurin inhibitor No Yes	 1 1.44 (0.52, 4.01)	 0.48		
(***) Fluid intake (mL)	1.07 (0.86, 1.33)	0.53		
Number of antihypertensive medications	0.95 (0.79, 1.16)	0.63		
Alb (g/L)	1.03 (0.91, 1.17)	0.67		
Use of diuretic (furosemide) No Yes	 1 1.02 (0.67, 1.67)	 0.81		

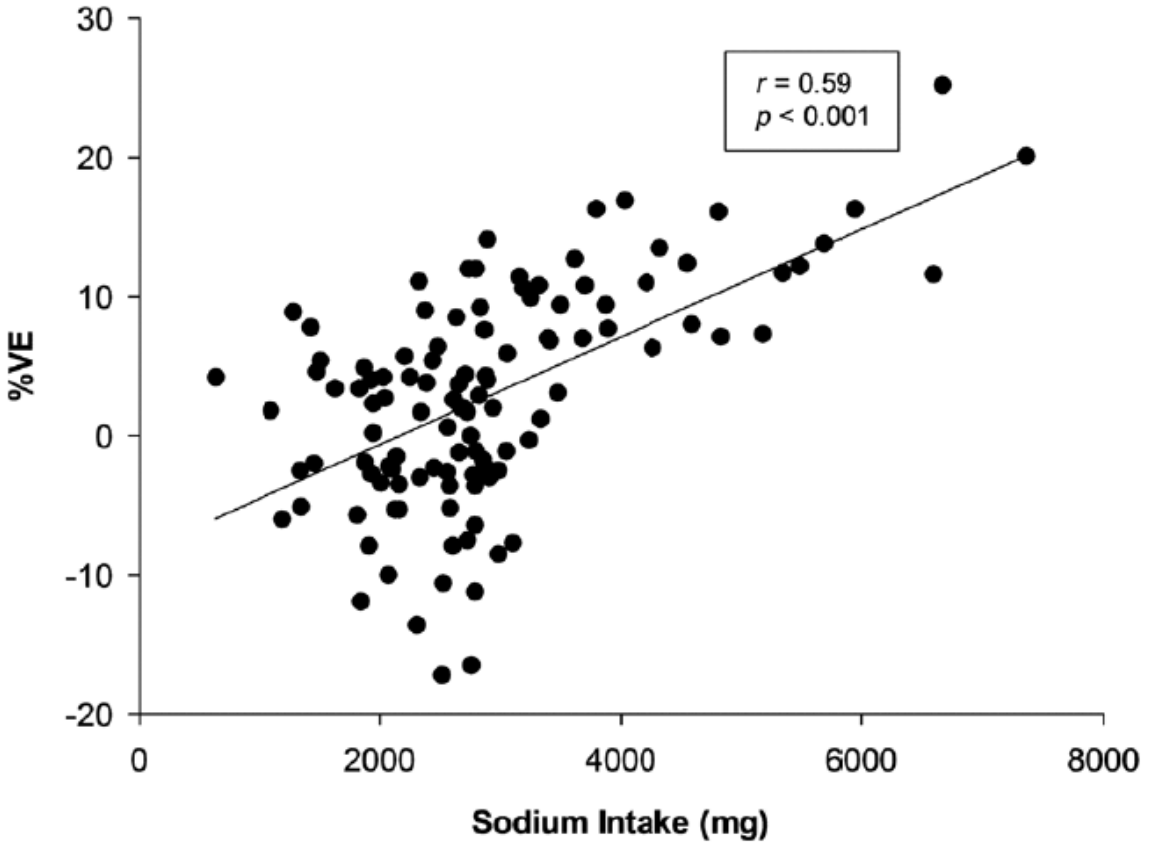
Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Use of ACEI / ARB No Yes	 1 1.05 (0.48, 2.28)	 0.90		
(*) FTI (kg/m^2)	1.01 (0.88, 1.15)	0.95		
(***) Sodium intake (mg)	1.01 (0.84, 1.20)	0.95		
Previous episodes of acute rejection No Yes	 1 1.01 (0.36, 2.89)	 0.98		
		R^2 value from final model	21%	

[§]Results in the final multivariate regression model were presented.
[α]CI = Confidence Interval.
[†]For the purpose of statistical analysis, smoking status was arranged into 2 categories, "non-smoker" versus "the combination of current smoker and ex-smoker", 63% and 37% of patients respectively.
[‡]For the purpose of statistical analysis, the ethnicity of patients classified as "Afro-Caribbean", "Asian" and "Others" was grouped as "Non-Caucasian", 77% "Caucasian" versus 23% "Non-Caucasian".
(*) Coefficients reported for a 5-unit increase in explanatory variable.
(**) Coefficients reported for a 10-unit increase in explanatory variable.
(***) Coefficients reported for a 50-unit increase in explanatory variable.
(l) Variable analysed on the log scale (base 10).
Abbreviations: NT-proBNP=N-Terminal pro B-type Natriuretic Peptide; %VE=Percentage Volume Expansion; eGFR=estimated Glomerular Filtration Rate; Hb=Haemoglobin; CCB=Calcium Channel Blocker; ACR=Albumin : Creatinine Ratio; LTI= Lean Tissue Index; hsCRP=high-sensitivity C-Reactive Protein; AAB=Alpha-Adrenergic Blocker; NODAT=New Onset Diabetes After Transplantation; Pre-DM=Presence of Diabetes Mellitus pre-transplantation; BAB=Beta-Adrenergic Blocker; Alb=Albumin; ACEI=Angiotensin-Converting-Enzyme Inhibitor; ARB=Angiotensin-Receptor Blocker; FTI=Fat Tissue Index.

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Figure 1. Association between Sodium Intake and Extracellular Volume
(Percentage Volume Expansion, %VE)



Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Figure 2a. Relationship between Extracellular Volume Status (Percentage Volume Expansion, %VE) and Blood Pressure

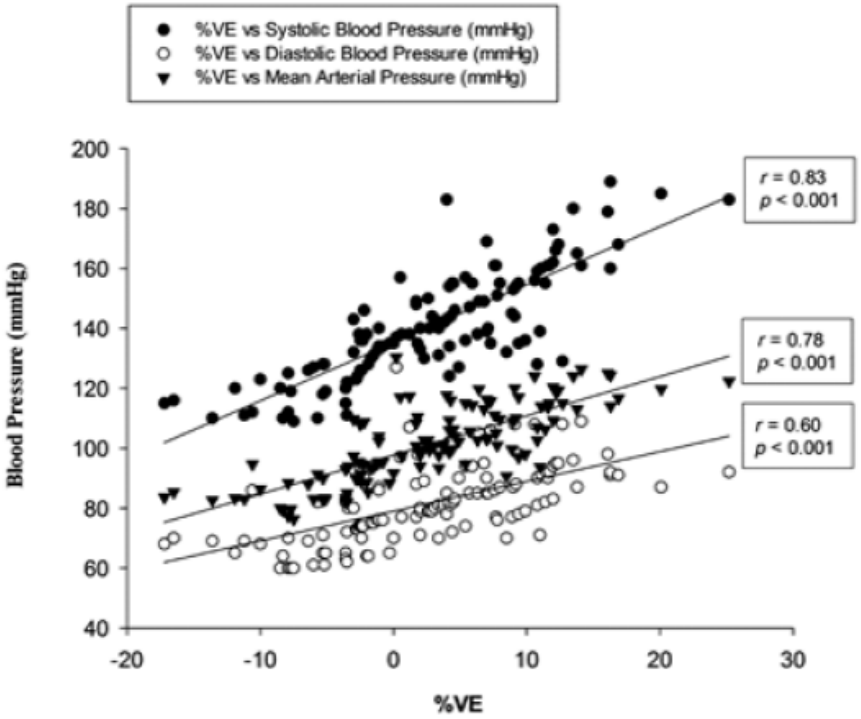
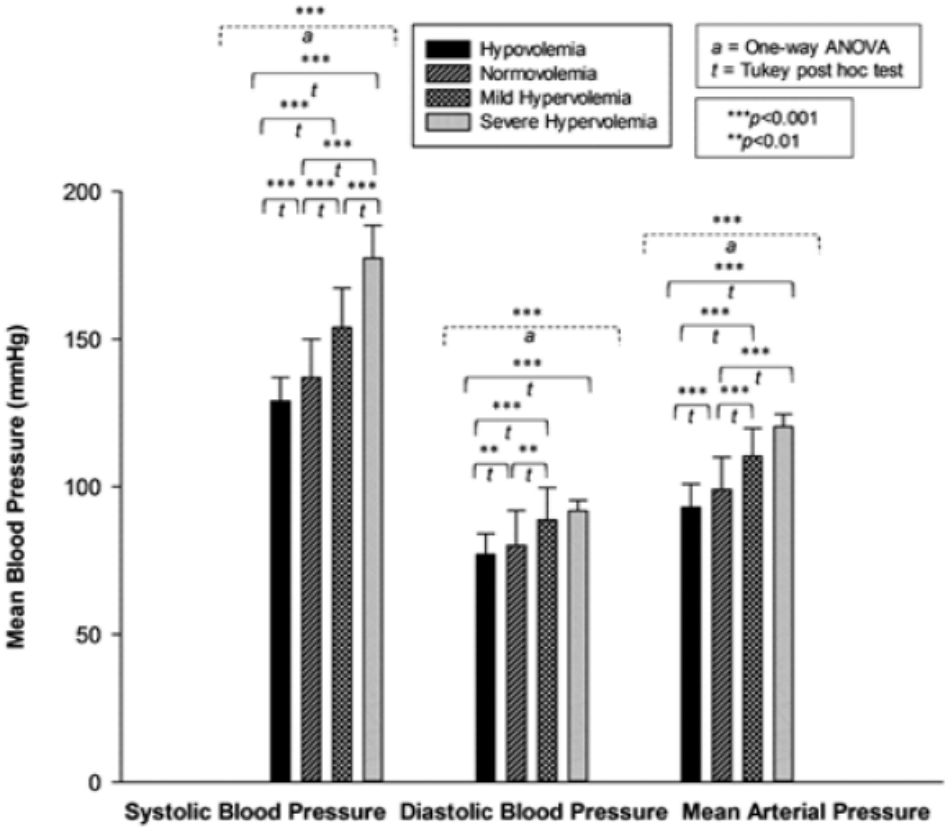


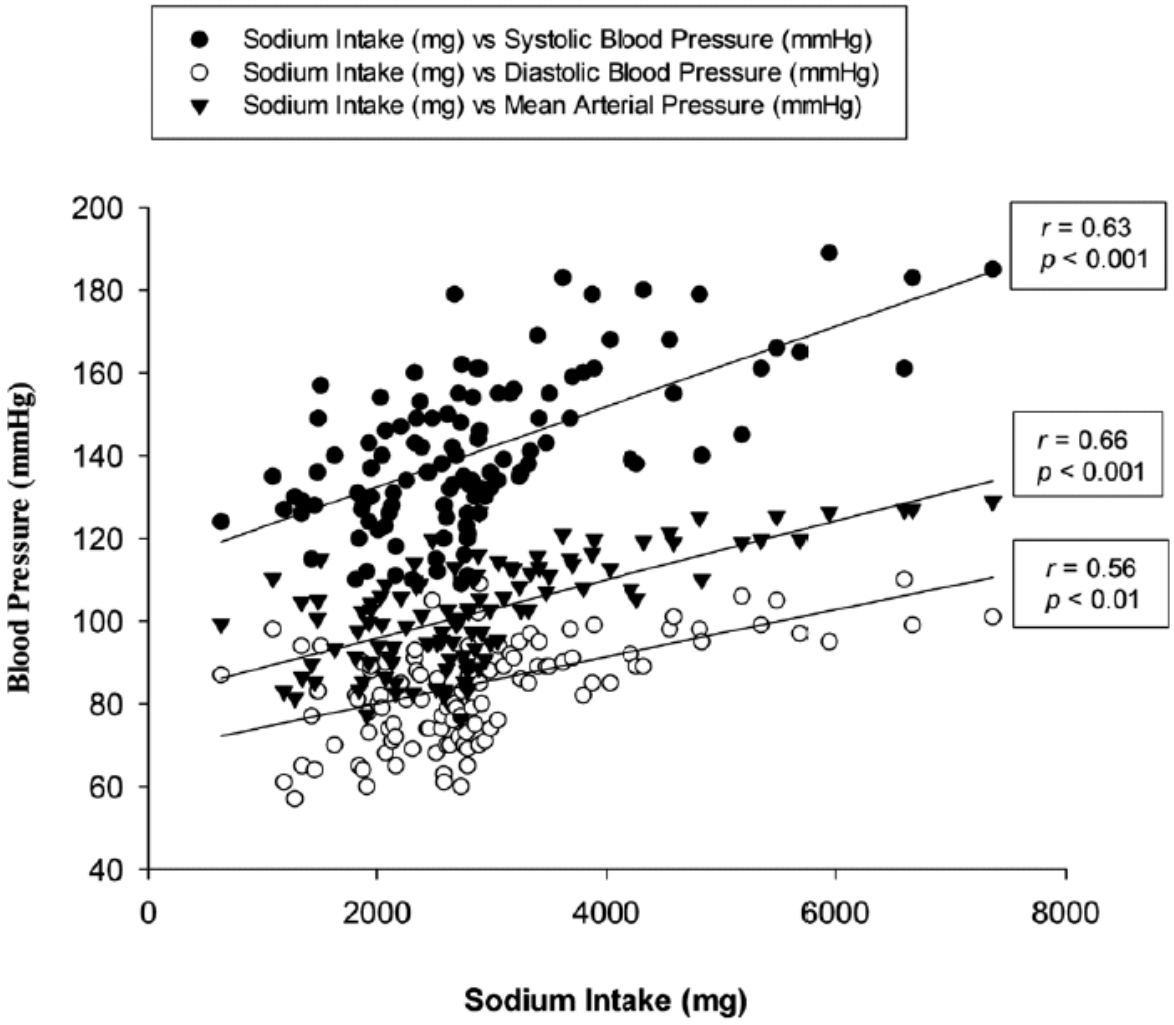
Figure 2b. Comparisons of Blood Pressure among Kidney Transplant Recipients with Different Extracellular Volume Status



Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Figure 3. Association between Sodium Intake and Blood Pressure



Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. http://dx.doi.org/10.1097/TP.0000000000000066

Figure 4a. Association between Extracellular Volume Status (Percentage Volume Expansion, %VE) and level of NT-proBNP

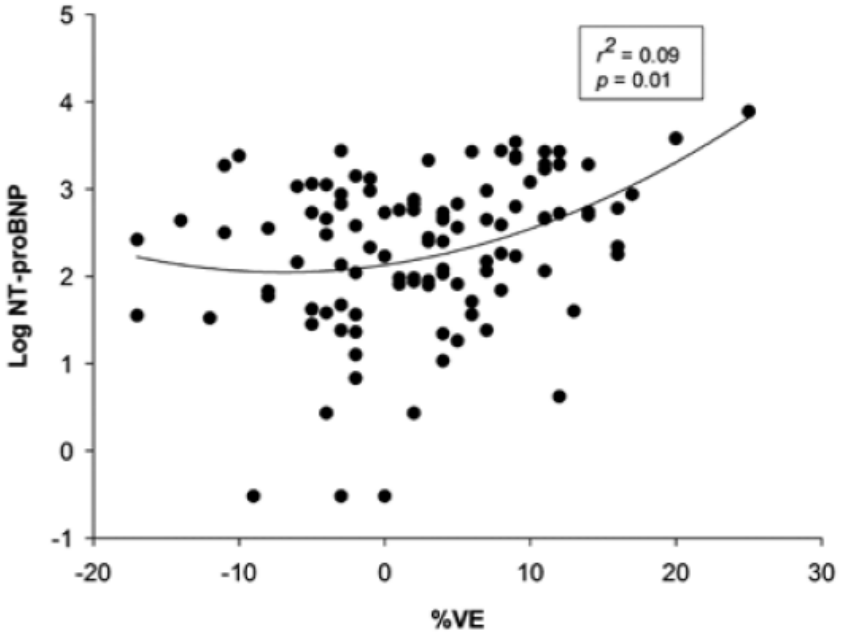


Figure 4b. Association between Renal Function and level of NT-proBNP