

Reduced Cardiovascular Reserve in Chronic Kidney Failure: A Matched Cohort Study

Stephen M.S. Ting^{1,8}, PhD, Thomas Hamborg⁷, PhD, Gordon McGregor¹, PhD, David Oxborough⁴, PhD, Nicolas Aldridge¹, Kenneth Lim⁵, MD, PhD, Sudheer Koganti², Chris Imray³, PhD, Rosemary Bland⁸, PhD, Simon Fletcher¹, MD, Nithya S. Krishnan¹, MD, Robert M. Higgins¹, MD, Jonathan Townend⁶, MD, Prithwish Banerjee², MD, Daniel Zehnder^{1,8}, MD, PhD

Divisions of Nephrology¹, Cardiology², Vascular and Renal Transplantation Surgery³, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK; Research Institutes of Sports and Exercise Sciences⁴, Liverpool John Moores University, Liverpool, UK; Division of Nephrology⁵, Brigham and Women's Hospital, Harvard Medical School, USA; Division of Cardiology, University Hospital Birmingham, Birmingham, UK⁶; Divisions of Health Sciences Statistics and Epidemiology⁷, Metabolic and Vascular Health⁸, The University of Warwick, Coventry, UK

Running Title: Reduced cardiovascular reserve in CKF

Abstract word count: 300

Main body word count: 3424

Keywords: cardiovascular reserve, oxygen consumption, exercise testing, chronic kidney failure, hypertension, left ventricular mass index

Corresponding authors:

Dr Daniel Zehnder and Dr Stephen Ting,
Division of Metabolic and Vascular Health,
Clinical Sciences Research Laboratory,
The University of Warwick,
Clifford Bridge Road,
Coventry CV2 2DX,
United Kingdom.
Phone: 044-2476965101
FAX: 044-2476965104
Email: d.zehnder@warwick.ac.uk; stephen_ting@yahoo.com

ABSTRACT

Background: Chronic kidney failure (CKF) patients experience impaired functional cardiovascular reserve with reduced oxygen consumption at peak exercise (VO_{2peak}). No studies have examined whether this is related to impaired cardiovascular compliance as a consequence of loss of adaptive structural alterations, resulting from chronic uremia or hypertension.

Study Design: Prospective matched cohort study.

Setting & Participants: We assessed CKF in parallel with patients with essential hypertension but without cardiovascular disease (CVD). The CKF subjects were either scheduled for kidney transplantation or transplant-waitlisted. 80 CKF and 80 essential hypertension subjects matched in age, sex and BMI were evaluated. 61 CKF patients (76.3%) were dialysis-dependent.

Predictor: CKF versus essential hypertension without CVD.

Measurements and outcomes: VO_{2peak} was measured during maximal exercise testing. 2D-echocardiography and arterial applanation tonometry were performed prior to exercise testing. To evaluate for the difference in VO_{2peak} between the study groups, statistically significant predictors of VO_{2peak} in multiple regression models were additionally assessed by fitting models comprising the interaction term of patient group with the predictor variable of interest.

Results: VO_{2peak} was significantly lower in CKF than essential hypertension subjects (18.8 vs. 24.5 ml/min/kg, $p < 0.001$). Independent predictors of VO_{2peak} for CKF included LV filling pressure (E/mean e') (unstandardized regression coefficient, $b = -5.1$) and pulse wave velocity (PWV) ($b = -4.0$); in essential hypertension, these were LV mass index ($b = 0.2$), LV end-diastolic volume index (LVEDVI) ($b = 0.4$), peak heart rate (HR) ($b = 0.2$) and PWV ($b = -8.8$). The interaction effect of VO_{2peak} between patient

groups with LV mass index ($\Delta B = -0.2$, $p < 0.001$), LVEDVI ($\Delta B = -0.4$, $p < 0.001$) and peak HR ($\Delta B = -0.1$, $p < 0.01$) were significantly stronger in the hypertension group whereby higher values led to greater VO_2 peak.

Limitations: Skeletal muscle strength was not assessed.

Conclusion: This study suggests that maladaptive LV changes as well as blunted chronotropic response are important mechanistic factors resulting in reduced cardiovascular reserve in CKF patients, beyond predominantly vascular changes associated with hypertension.

INTRODUCTION

Patients with chronic kidney failure (CKF) are at high risk of cardiovascular disease (CVD)¹. Complex changes in both the cardiac and vascular systems result in structural and functional changes that can lead to reduced exercise tolerance, quality of life, increased morbidity and ultimately premature death². CKF causes arterial stiffening resulting in reducing arterial cushioning of phasic pressure changes³. The resulting increase in left ventricular (LV) afterload combined with a host of metabolic stimuli including inflammation, oxidative stress, renin-angiotensin system activation, changes in phosphate metabolism and production of FGF-23 promotes an increase in LV mass and reduced myocardial perfusion^{4 5-7}. The hemodynamic sequelae of such morphological alterations imply a high cardiac energy expenditure and elevated oxygen consumption in the myocardium.

The LV abnormalities in CKF reflect both myocyte hypertrophy and ultra-structural changes such as myocardial fibrosis⁸. These changes result in impaired myocardial relaxation and elevation of LV filling pressure^{8,9}. This impairment in diastolic function along with more subtle changes in systolic function leads to a high incidence of heart failure (HF)^{3,6,10} with a reduction in exercise capacity¹¹. Oxygen consumption at peak exercise (VO_{2peak}) is a metric that provides an index of exercise capacity and represents the cardiovascular system's ability to take up, distribute and utilize oxygen at maximal exercise. Reduced values of VO_{2peak} have been shown to predict prognosis in the HF population^{12,13}. Several studies have also demonstrated a reduced VO_{2peak} in patients with CKF¹⁴⁻¹⁶ and this was also associated with poor survival^{14,17}. The precise relationship between adverse structural alterations of the cardiovascular system and VO_{2peak} in CKF patients is currently unknown.

In this study, we hypothesized that increased LV mass, filling pressure and

arterial stiffness are associated with reduced VO_2 peak in patients with CKF. Using a control group of patients with treated essential hypertension but without CVD we also investigated the hypothesis that the main determinants of structural and functional cardiovascular changes and VO_2 peak in CKF are a result of mechanisms other than hypertension.

METHODS

Study Design and Clinical Data

Inclusion criteria were patients aged ≥ 18 who were either waitlisted or scheduled for kidney transplantation at our center, University Hospitals Coventry and Warwickshire NHS Trust, United Kingdom. In parallel, individuals with treated essential hypertension but without evidence of CVD (HF, ischemic heart disease, cerebrovascular disease), diabetes or secondary causes of hypertension were recruited at random from the community through primary care database. In both groups, patients with pre-existing chronic lung disease were excluded. All recruited patients underwent cardiopulmonary exercise testing (CPET), arterial applanation tonometry and a study-specified echocardiogram. For patients who were hemodialysis dependent, these assessments were carried out on the first non-dialysis day that was at least 12 hours after the last dialysis session in order to avoid the effects of hemodialysis-induced myocardial stunning¹⁸ and minimize the impact of volume load variability on the indices of cardiovascular structure and function¹⁹. Between April 2010 and December 2012, 150 CKF patients were screened and 136 individuals were included in the study (three unable to exercise due to physical limitations, eleven did not provide consent). Among the essential hypertension subjects, 80 individuals were recruited following the exclusion of 5 who had physical co-morbidities precluding

exercise testing. All blood samplings and clinical assessments (including office brachial blood pressure, echocardiography and vascular tonometry) were performed prior to exercise testing. The study was approved by the Black Country Research Ethics Committee (REC:09/H1202/113) and adhered to the Declaration of Helsinki. Written informed consent was obtained from all eligible participants.

Cardiopulmonary Exercise Testing

The CPET was conducted using an electronically braked, upright cycle ergometer to maximal tolerance incorporating an individualized work rate. An experienced blinded investigator carried out all exercise testing. Before each test, the equipment was calibrated using standard reference gases and a 3-litre syringe. Care was taken to ensure each study patient understood the maximal exercise test protocol. This included explanation of the anticipated early symptoms of lactic acid associated leg fatigue or discomfort that must not lead to premature cessation of pedaling or incremental loading. Each patient rested for 3 minutes followed by 3 minutes of unloaded pedaling prior to workload increments and continuous 12-lead ECG was recorded. Continuous breath-by-breath gas exchange analysis (VIASYS, MasterScreen CPX[®], Hoechberg, Germany) was performed. All patients were repeatedly encouraged to continue until symptom limited volitional fatigue.

The VO_2 at the point of anaerobic threshold (VO_{2AT}) was determined by the V-slope method in conjunction with analyses of the ventilatory equivalents and end-tidal gas tension plots²⁰. VO_{2peak} was measured as the highest VO_2 achieved during the final 20-second averaging of peak exercise. The predicted VO_{2peak} was determined by the Wasserman and Hansen equation²⁰.

Echocardiographic Study

2-dimensional, Doppler and tissue Doppler transthoracic echocardiography was

performed using Vivid 7, GE Healthcare, Horten, Norway ultrasound system according to a standardized study protocol. Calculations included LV ejection fraction according to quantitative biplane Simpson's method, LV end-diastolic volume, LV mass and left atrial (LA) volume. Mass and volume measures were indexed to body surface area. Tissue Doppler imaging of the mitral annulus, sequentially at the lateral and septal annular sites were obtained from the apical 4-chamber view. The ratio of early transmitral flow velocity to averaged annular (septal and lateral) mitral velocity ($E/\text{mean } e'$) was taken as an estimate of LV filling pressure. All measurements were undertaken according to the American Society of Echocardiography²¹ and analyzed offline (EchoPac, GE Healthcare) by a blinded investigator.

Evaluation of Vascular Compliance

Pulse wave analysis was performed on the radial artery and aortic (carotid-femoral) pulse wave velocity (PWV) was determined by sequential recording of ECG-gated carotid and femoral waveforms using the high fidelity micromanometer (SPC-301, Miller Instrument, Houston, Texas). As augmentation index is influenced by heart rate (HR), an index adjusted to a HR of 75 beats/minute (AIx_{75}) was recorded²². All measurements were derived using a validated radial-to-aortic transfer function (SphygmoCor, AtCor Medical Pty Ltd, Australia). An experienced operator, masked to the echocardiographic and CPET data, made all measurements in triplicate. Mean values of all tonometric measurements were used for analysis.

Statistical Methods

CKF patients were initially matched to the essential hypertension without CVD subjects in age, sex and body mass index (BMI) in a 1:1 ratio using a propensity score matching algorithm^{23,24}. The dataset of a study population consisting of 80 patients in each group was subsequently analyzed. Data were presented as mean, median or

frequencies depending on the distribution and type of the variable. VO_2 peak corrected for body weight ($ml\ VO_2, \min^{-1}\ kg^{-1}$) was the outcome variable of primary interest in this study and was therefore used as the dependent variable for regression modeling analyses.

To identify important predictors of VO_2 peak a sequence of regression modeling analyses were conducted. First CKF and essential hypertension participant data was analyzed separately to determine the variables that were predictive of VO_2 peak within each group. Variables that were statistically significant ($p < 0.05$) in the univariate analysis were included in the initial multiple linear regression modeling. Stepwise elimination, repeated with forward and backward variable selection techniques were performed to determine the most important predictors in a multiple regression model for each of the groups. Additional to the demographics (age, sex, and BMI), adjustments were also made for hemoglobin and duration of hypertension. Logarithmic transformation of non-normal distributed data was performed prior to regression analysis. Parameter estimate, standard error and 95% confidence interval (CI) were calculated for each variable.

To evaluate the potential adaptive functional cardiovascular changes that account for the difference in VO_2 peak between the two patient groups, variables that were statistically significant predictors of VO_2 peak in multiple regression models were additionally assessed by fitting models comprising the interaction term of patient group (binary variable) with the predictor variable of interest. The estimate of the interaction effect is denoted ΔB and may be interpreted as the difference of the slopes of the predictor between the groups. These models were adjusted for age, sex, BMI, hemoglobin, duration of hypertension and β -blocker usage. All hypothesis tests were two sided and a p -value < 0.05 was considered to indicate statistical significance. SAS software, version 9.3 (SAS Institute Inc.) was used. (See **Supplementary extended**

methods).

RESULTS

Clinical characteristics

Descriptive characteristics of all the study participants are presented in **Table 1**. CKF patients and subjects with essential hypertension without CVD were adequately matched in age (53.3 vs. 53.4 years, $p=0.8$), sex (male: 56.3 vs. 51.2%, $p=0.2$) and BMI (27.2 vs. 27.6 kg/m², $p=0.6$). The use of β -blockers was higher in the CKF patients (32.5 vs. 13.8%, $p<0.01$). Hemoglobin (11.8 vs. 14.2 g/dl, $p<0.001$), albumin (4.4 vs. 4.7 g/dl, $p<0.001$), LDL-cholesterol (92.8 vs. 112.1 mg/dl, $p<0.001$) and glycated hemoglobin (HbA1c, 5.4 vs. 5.6%, $p=0.02$) were lower in the CKF patients compared to the essential hypertension group.

Echocardiographic and applanation tonometric findings of the two groups are summarized in **Table 2**. LV mass index was significantly higher in the CKF than the essential hypertension group (109.1 vs. 87.5 g/m², $p<0.001$). LV end-diastolic volume index (LVEDVI, 48.3 vs. 44.8 ml/m², $p=0.1$) was not significantly different between the groups. Criteria for LV hypertrophy were present more frequently in CKF patients than the hypertensive subjects (45.0 vs. 18.7%, $p<0.001$). The latter group had a higher LV ejection fraction (66.2 vs. 62.6%, $p<0.01$) than the CKF patients. The measures of vascular compliance were not significantly different in both groups.

Functional cardiovascular reserve in CKF versus essential hypertension

The metabolic measures of CPET for the two groups are shown in **Table 3**. All patients performed exercise to a level accompanied by a respiratory exchange ratio (RER, ratio of CO₂ production to O₂ consumption) of >1.15 . The mean of RER at the point of VO₂AT for the study populations was 0.9 ± 0.1 . Relative to the essential

hypertension subjects, the CKF patients had a significantly lower VO_2peak (18.8 vs. 24.5 $\text{ml min}^{-1} \text{kg}^{-1}$, $p<0.001$; 73.4 vs. 92.9 % predicted, $p<0.001$) and VO_2AT (11.2 vs. 13.8 $\text{ml min}^{-1} \text{kg}^{-1}$, $p<0.001$; 43.9 vs. 52.9 % predicted, $p<0.001$). Essential hypertension subjects achieved a longer endurance time (11.9 vs. 10.8 minute, $p=0.001$), tolerated a greater workload (159.9 vs. 106.3 Watt, $p<0.001$) and more reached their predicted peak HR (92.2 vs. 79.7%, $p<0.001$) compared to CKF individuals.

Independent predictors of VO_2peak

Univariate linear regression analyses for the two groups are presented in **Table 4**. Differences between the CKF and essential hypertension populations in the unstandardized regression coefficients (b) and estimated regression lines for regressing VO_2peak onto individual cardiovascular measures are highlighted by **Figure 1**. Increasing LV mass index was positively associated with higher VO_2peak in the essential hypertension subjects ($b=0.21$, $p<0.001$) but not in the CKF population ($b=-0.01$, $p=0.9$). Higher LVEDVI was associated with a significantly higher VO_2peak in the hypertensives ($b=0.41$, $p<0.001$) but not in the CKF cohort ($b=0.01$, $p=0.7$). Higher LV filling pressure (E/mean e') was significantly negatively associated with VO_2peak in the CKF ($b=-5.10$, $p<0.001$) but not in the essential hypertension cohort ($b=-1.37$, $p=0.7$). LV ejection fraction had no association with VO_2peak in either group. Both Alx_{75} and PWV had an inverse relationship with VO_2peak in the CKF as well as the essential hypertension cohorts.

Cardiac structural variables and VO_2peak in the multiple regression models

Results of multiple linear regression models for the CKF and essential hypertension without CVD populations are presented in **Table 5**. In the CKF population (adjusted $R^2=0.45$), higher E/mean e' was significantly associated with a

lower VO_{2peak} ($b=-3.55$, $p=0.001$) after adjusting for demographics, hemoglobin and duration of hypertension. In the essential hypertension cohort (adjusted $R^2=0.66$), larger LVEDVI ($b=0.21$, $p=0.002$), LV mass index ($b=0.10$, $p=0.01$) and higher peak HR were significant predictors of higher VO_{2peak} ($b=0.12$, $p<0.001$).

Associations between cardiac structural variables and VO_{2peak}

The effects of the cardiac structural variables on VO_{2peak} in the two groups were compared in a model that included the group x predictor interaction terms, adjusting for demographics, hemoglobin and duration of hypertension. The regression slope for LV mass index predicting VO_{2peak} was steeply more positive in the essential hypertension population compared to that of the CKF cohort ($\Delta B=-0.17$, 95% CI -0.24 – -0.10, $p<0.001$) (**Figure 2A**). The regression slope for LVEDVI and VO_{2peak} in the essential hypertension subjects was also significantly more positive than the CKF population ($\Delta B=-0.36$, 95% CI -0.47 – -0.24, $p<0.001$) (**Figure 2B**).

Association of arterial stiffness and VO_{2peak}

PWV and AIx_{75} were significant independent predictors of VO_{2peak} in the CKF and the essential hypertension subjects (**Figure 1E-F; Table 4**). Importantly, the interaction effect between patient group and both measures of arterial stiffness was not significantly different adjusting for demographics, hemoglobin and duration of hypertension (**Figure 2C-D**). Therefore, there is no evidence to suggest that the association of arterial stiffness with VO_{2peak} differs between the groups.

Peak heart rate predicts VO_{2peak} but this relationship is blunted in CKF

HR at peak exercise and oxygen pulse were higher among the essential hypertension subjects than the CKF cohort (**Table 3**). HR at peak exercise was also a significant independent and adjusted predictor of VO_{2peak} in the essential hypertension but not among the CKF patients. The lower peak HR observed in the

CKF subjects could be related to a greater use of β -blocker (**Table 1**). Therefore, the effect of peak HR and oxygen pulse on VO_{2peak} were each directly compared between the groups in a model that included the group x peak HR or group x oxygen pulse interaction terms, adjusting for β -blocker, demographics, hemoglobin and duration of hypertension. The regression slope of peak HR was steeper in the essential hypertension cohort compared to that of the CKF group ($\Delta B = -0.11$, 95% CI -0.18 – -0.03, $p < 0.01$) (**Figure 3A**). A similar relationship of oxygen pulse with VO_{2peak} was also demonstrated by a steeper regression slope in the essential hypertension cohort than the CKF group ($\Delta B = -0.37$, 95% CI -0.68 – -0.06, $p = 0.02$) (**Figure 3B**).

DISCUSSION

To our knowledge, this is the first prospective study to evaluate measures of arterial-ventricular structure and function and their association with functional cardiovascular reserve in subjects with CKF. While CPET has been used extensively in patients with HF, data on objective indices of cardiovascular reserve in patients with CKF are scarce. In this study, we have established that VO_{2peak} in ambulant patients with CKF was reduced to under 75% of the predicted value. We have previously demonstrated that reduced values of VO_{2peak} , VO_{2AT} and endurance time are associated with an increased risk of premature death among CKF patients¹⁷. The current study demonstrated that each of these parameters was significantly reduced in the CKF group compared to the cohort of essential hypertension without CVD. A comparable reduced value of VO_{2peak} at $18.6 \text{ ml min}^{-1} \text{ kg}^{-1}$ was documented in two prior cycle ergometric studies of patients with CKD by Sietsema *et al.*^{14,25} but data on the percent-predicted VO_{2peak} , VO_{2AT} and other measures of cardiovascular reserve were not available for comparison. In comparison to the patients of Sietsema *et al.*, the hemoglobin concentration of our patients was similar (11.8 vs. 11.2 g/dl), but our

patients were older (53.3 vs. 46.0 years), had a higher BMI (27.2 vs. 24.5 kg/m²) and a lower number of male patients (56.3 vs. 65.0 %); each of these factors might result in a lower VO₂peak. However, lower prevalence of diabetes (15.0 vs. 18.5 %) and the shorter dialysis vintage in our CKF cohort (32.0 vs. 41.5 months) could positively impact upon effort tolerance^{14,25}.

Because the prevalence of hypertension in patients with CKF is near universal, we compared the results on our patients with CKF with those of a similar group of essential hypertension but without CVD in an effort to differentiate the cardiovascular effects of CKF from those of hypertension alone. LV mass was significantly greater in the CKF population than the hypertensive controls confirming previous reports that hypertension alone does not lead to the myocardial disease known as 'uremic cardiomyopathy'⁸. The increase in LV mass although paralleled with the high prevalence of hypertension in CKF patients²⁶ is thought to be a compensatory response to both sustained pressure and volume overload. According to the paradigm of adaptive ventricular response to chronic pressure overload in essential hypertension, progressive increase in LV mass with thickening of the ventricular wall that serves to stabilize and maintain normal wall stress is associated with an increased cardiac output and preload^{27,28}. In this study, we demonstrated that incremental LV mass changes and end-diastolic volumes in the CKF subjects were not positively associated with increments in the VO₂peak which contrasted significantly with the essential hypertension controls. Even though myocardial growth and remodeling may be dynamic adaptive processes that occur early in the course of kidney failure, sustained cardiac afterloads exacerbated by uremia in CKF patients could therefore lead progressively to maladaptive hypertrophy. A plausible mechanism for this finding is that ultra-structural changes within the myocardium such as capillary deficit, fibrillar collagen accumulation, fibrosis and calcification alter the compliance and contractility

of the LV in patients with CKF to a greater extent than occurs in hypertension resulting in a reduced functional cardiovascular reserve^{5,29}

While the LV ejection fraction in the CKF patients was significantly lower than that of hypertensive subjects, this was not predictive of VO_2 peak. This finding is unsurprising as epidemiological data have shown that up to 50% of patients with HF in the absence of significant coronary artery disease have preserved LV ejection fraction³⁰. The underlying hemodynamic mechanism leading to exercise intolerance, dyspnea and thereby reduced VO_2 peak³¹ in these patients is probably mediated at least in part by the increased diastolic LV stiffness^{32,33}. A recent experimental study has also indicated that in uremia, the Na^+/Ca^{2+} exchanger mediated calcium extrusion from the cytosol of cardiac myocytes is abnormally reduced resulting in impaired myocyte relaxation³⁴. The uremic milieu itself may impact adversely on the functional cardiovascular reserve as the serum and ultrafiltrate of end-stage kidney disease patients have previously been shown to possess negative inotropic and chronotropic properties^{10,35}. The latter could explain the blunted HR response to maximal exercise in CKF (**Figure 3**). The suggestion that uremic-related factors may cause blunting of the cardiovascular reserve is also supported by published data, albeit from small studies which documented improvement in VO_2 peak following kidney transplantation^{36,37} or augmentation of uremic clearance by intensive nocturnal hemodialysis³⁸.

Higher LV filling pressure was a powerful independent determinant of a reduced VO_2 peak in subjects with CKF. The elevated LV filling pressure estimate provided by $E'/\text{mean } e'$ reflects the state of impaired cardiomyocyte relaxation³⁹. In CKF, the cumulative burden of myocardial fibrosis and LV hypertrophy could cause a reduction in the mean e' velocity which further decreases with age⁴⁰. The resulting impaired LV relaxation is a hallmark of diastolic dysfunction³³ which has been shown to cause a

similar reduction in VO_2 peak as with systolic dysfunction according to HF studies³¹. We observed an inverse relationship between LV filling pressure and VO_2 peak in the CKF group which differed markedly from the essential hypertension controls. However, the similar measure of LV filling pressure in the two cohorts (**Table 2**) and the lack of association between LV filling pressure and VO_2 peak in the hypertensives suggest that additional mechanistic factors are responsible for the reduced functional cardiovascular reserve in CKF.

Indices of arterial stiffness were similar between the CKF and hypertensive cohorts (**Table 2**). PWV and Alx_{75} were significant independent predictors of VO_2 peak (**Table 4**) in both cohorts. Analysis of individual group interaction with each of the arterial measures demonstrated an inverse relationship with VO_2 peak in both cohorts that were not significantly different (**Figure 2**). Besides being an indirect index of arterial stiffness, Alx_{75} is a measure of pulse wave reflection that calculates how much of the central pulse pressure is attributable to accelerated pressure wave reflection⁴¹. This pathological wave reflection increases cardiac loading and prejudices the diastolic coronary perfusion⁴¹⁻⁴³ which could aggravate the cardiovascular reserve. We postulate that the potential contribution of large artery compliance to functional cardiovascular reserve may, in part, be mediated by LV compliance^{44,45} and the loss of adaptive functional LV changes in the CKF.

Limitations

Exercise training has been shown to improve VO_2 peak⁴⁶ but data on muscle mass or strength were not collected in this study. Despite these, extensive evaluation of the ventricular-vascular function and dynamics were carried out resulting in novel and important information on how these cardiovascular alterations could adversely impact the VO_2 peak in CKF. Also, Painter *et al.*⁴⁷ had previously shown that muscle

conditioning through supervised five-month exercise training and normalization of hematocrit improved but failed to normalize VO_2 peak in hemodialysis-dependent patients, indicating other physiological contributors to the reduced cardiovascular reserve in these patients.

In conclusion, our study shows that there are complex cardiovascular alterations in CKF that are associated with reduced functional cardiovascular reserve. Our findings provide a pathophysiological background for appreciating the association between the maladaptive ventricular-vascular dynamics and reduced VO_2 peak in CKF.

Acknowledgements

We would like to thank the Reading family and University Hospital Coventry and Warwickshire NHS Trust Charity for funding the CPET machine used in this study. We thank the National Institute of Health Research (NIHR) for clinical staffing support providing assistance in the administrative work and data collection.

Funding: The British Heart Foundation (BHF) Grant (PG/11/66/28982). BHF did not have any role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

Contributions: Research idea and study design: SMST, CI, RMH, JT, RB, SF, NK, PB, DZ; data acquisition: SMST, GM, DO, SK, NA, DZ; data analysis/interpretation: SMST, TH, KL, PB, DZ; statistical analysis: SMST, TH, DZ; supervision or mentorship: DZ. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately

investigated and resolved. SMST, TH, PB, DZ take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflict of Interest: None declared

REFERENCES

1. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. *Journal of the American Society of Nephrology : JASN*. Dec 1998;9(12 Suppl):S16-23.
2. Beddhu S, Baird BC, Zitterkoph J, Neilson J, Greene T. Physical activity and mortality in chronic kidney disease (NHANES III). *Clinical journal of the American Society of Nephrology : CJASN*. Dec 2009;4(12):1901-1906.
3. Raggi P, Boulay A, Chasan-Taber S, et al. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *Journal of the American College of Cardiology*. Feb 20 2002;39(4):695-701.
4. London GM, Guerin AP, Marchais SJ, et al. Cardiac and arterial interactions in end-stage renal disease. *Kidney international*. Aug 1996;50(2):600-608.
5. London GM. Cardiovascular calcifications in uremic patients: clinical impact on cardiovascular function. *Journal of the American Society of Nephrology : JASN*. Sep 2003;14(9 Suppl 4):S305-309.
6. London GM. Left ventricular hypertrophy: why does it happen? *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. Nov 2003;18 Suppl 8:viii2-6.
7. Moody WE, Edwards NC, Chue CD, Ferro CJ, Townend JN. Arterial disease in chronic kidney disease. *Heart*. Mar 2013;99(6):365-372.
8. Gross ML, Ritz E. Hypertrophy and fibrosis in the cardiomyopathy of uremia--beyond coronary heart disease. *Seminars in dialysis*. Jul-Aug 2008;21(4):308-318.
9. Mall G, Huther W, Schneider J, Lundin P, Ritz E. Diffuse intermyocardiocytic fibrosis in uraemic patients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 1990;5(1):39-44.
10. Aoki J, Ikari Y, Nakajima H, et al. Clinical and pathologic characteristics of dilated cardiomyopathy in hemodialysis patients. *Kidney international*. Jan 2005;67(1):333-340.
11. Edwards NC, Ferro CJ, Townend JN, Steeds RP. Aortic distensibility and arterial-ventricular coupling in early chronic kidney disease: a pattern resembling heart failure with preserved ejection fraction. *Heart*. Aug 2008;94(8):1038-1043.
12. O'Neill JO, Young JB, Pothier CE, Lauer MS. Peak oxygen consumption as a predictor of death in patients with heart failure receiving beta-blockers. *Circulation*. May 10 2005;111(18):2313-2318.
13. Benjaminovitz A, Mancini DM. The role of exercise-based prognosticating algorithms in the selection of patients for heart transplantation. *Current opinion in cardiology*. Mar 1999;14(2):114-120.
14. Sietsema KE, Amato A, Adler SG, Brass EP. Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. *Kidney international*. Feb 2004;65(2):719-724.
15. Johansen KL. Physical functioning and exercise capacity in patients on dialysis. *Advances in renal replacement therapy*. Apr 1999;6(2):141-148.
16. Sezer S, Elsurur R, Ulubay G, Ozdemir FN, Haberal M. Factors associated with peak oxygen uptake in hemodialysis patients awaiting renal transplantation. *Transplantation proceedings*. May 2007;39(4):879-882.
17. Ting SM, Iqbal H, Kanji H, et al. Functional cardiovascular reserve predicts survival pre-kidney and post-kidney transplantation. *Journal of the American Society of Nephrology : JASN*. Jan 2014;25(1):187-195.
18. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clinical journal of the American Society of Nephrology : CJASN*. Dec 2009;4(12):1925-1931.
19. Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray D, Barre PE. Outcome and risk factors of ischemic heart disease in chronic uremia. *Kidney international*. May 1996;49(5):1428-1434.
20. Wasserman K, Hansen J.E., Sue D.Y., Stringer W.W., Whipp B.J. *Principles of exercise testing and interpretation : including pathophysiology and clinical applications*. 4 ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
21. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. Dec 2005;18(12):1440-1463.
22. Wilkinson IB, Mohammad NH, Tyrrell S, et al. Heart rate dependency of pulse pressure amplification and arterial stiffness. *American journal of hypertension*. Jan 2002;15(1 Pt 1):24-30.
23. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41-55.

24. An Introduction to Implementing Propensity Score Matching with SAS. 2010.
25. Sietsema KE, Hiatt WR, Esler A, Adler S, Amato A, Brass EP. Clinical and demographic predictors of exercise capacity in end-stage renal disease. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. Jan 2002;39(1):76-85.
26. Rao MV, Qiu Y, Wang C, Bakris G. Hypertension and CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES), 1999-2004. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. Apr 2008;51(4 Suppl 2):S30-37.
27. Campus S, Malavasi A, Ganau A. Systolic function of the hypertrophied left ventricle. *Journal of clinical hypertension*. Mar 1987;3(1):79-86.
28. de Simone G, Di Lorenzo L, Moccia D, Costantino G, Buonissimo S, De Divitiis O. Hemodynamic hypertrophied left ventricular patterns in systemic hypertension. *The American journal of cardiology*. Dec 1 1987;60(16):1317-1321.
29. London GM. Cardiovascular disease in chronic renal failure: pathophysiologic aspects. *Seminars in dialysis*. Mar-Apr 2003;16(2):85-94.
30. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *Journal of the American College of Cardiology*. Jun 1999;33(7):1948-1955.
31. Farr MJ, Lang CC, Lamanca JJ, et al. Cardiopulmonary exercise variables in diastolic versus systolic heart failure. *The American journal of cardiology*. Jul 15 2008;102(2):203-206.
32. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. *Circulation*. Apr 17 2007;115(15):1982-1990.
33. Westermann D, Kasner M, Steendijk P, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. *Circulation*. Apr 22 2008;117(16):2051-2060.
34. McMahon AC, Naqvi RU, Hurst MJ, Raine AE, MacLeod KT. Diastolic dysfunction and abnormality of the Na⁺/Ca²⁺ exchanger in single uremic cardiac myocytes. *Kidney international*. Mar 2006;69(5):846-851.
35. Vanholder R, Glorieux G, Lameire N, European Uremic Toxin Work G. Uraemic toxins and cardiovascular disease. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. Mar 2003;18(3):463-466.
36. Painter P, Hanson P, Messer-Rehak D, Zimmerman SW, Glass NR. Exercise tolerance changes following renal transplantation. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. Dec 1987;10(6):452-456.
37. Painter P, Krasnoff JB, Kuskowski M, Frassetto L, Johansen KL. Effects of modality change and transplant on peak oxygen uptake in patients with kidney failure. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. Jan 2011;57(1):113-122.
38. Chan CT, Notarius CF, Merlocco AC, Floras JS. Improvement in exercise duration and capacity after conversion to nocturnal home haemodialysis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. Nov 2007;22(11):3285-3291.
39. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *Journal of the American College of Cardiology*. Nov 15 1997;30(6):1527-1533.
40. De Sutter J, De Backer J, Van de Veire N, Velghe A, De Buyzere M, Gillebert TC. Effects of age, gender, and left ventricular mass on septal mitral annulus velocity (E') and the ratio of transmitral early peak velocity to E' (E/E'). *The American journal of cardiology*. Apr 15 2005;95(8):1020-1023.
41. O'Rourke MF, Gallagher DE. Pulse wave analysis. *Journal of hypertension. Supplement : official journal of the International Society of Hypertension*. Dec 1996;14(5):S147-157.
42. Nichols WW, O'Rourke, M.F. *Vascular Impedance and Wave Reflections. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*. 4th ed1998.
43. O'Rourke MF, Kelly RP. Wave reflection in the systemic circulation and its implications in ventricular function. *Journal of hypertension*. Apr 1993;11(4):327-337.
44. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation*. May 11 1999;99(18):2434-2439.
45. Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, London GM. Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney international*. May 2003;63(5):1852-1860.
46. Kouidi EJ, Grekas DM, Deligiannis AP. Effects of exercise training on noninvasive cardiac measures in patients undergoing long-term hemodialysis: a randomized controlled trial. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. Sep 2009;54(3):511-521.
47. Painter P, Moore G, Carlson L, et al. Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. Feb 2002;39(2):257-265.

Figure Legends

Figure 1: Scatterplots of cardiovascular measures with VO_2 peak among the CKF and essential hypertension (HTN) cohorts

Grey circles represent the HTN cohort and the black circles represent the CKF cohort. The dashed and straight lines are unadjusted regression lines for the CKF and the HTN cohorts respectively. *b*, unstandardized regression coefficient: change in ml VO_2 peak, $\text{min}^{-1} \text{kg}^{-1}$ per one unit change of variable. ^aLog-transformed. **p*-value<0.05.

Figure 2: Difference of changes in VO_2 peak with LV mass index (A), LVEDVI (B) and arterial stiffness (C, D) between the CKF and essential hypertension (HTN) cohorts

ΔB is the difference in the parameter estimates between the regression lines for the HTN and CKF groups. Group interaction with LV mass index (A), LVEDVI (B), PWV (C) and AIx_{75} (D) were adjusted for demographics, hemoglobin and duration of hypertension. Dash line=HTN, straight line=CKF. ^aLog-transformed. **p*-value<0.05.

Figure 3: Changes in VO_2 peak with peak HR (A) and oxygen pulse (B) differ between the CKF and essential hypertension (HTN) cohorts

ΔB is the difference in the parameter estimates between the regression lines for HTN and CKF groups. Group interaction with peak HR (A) and oxygen pulse (B) were adjusted for β -blocker usage, demographics, hemoglobin and duration of hypertension. Dash line=HTN, straight line=CKF. **p*-value<0.05.

Supplementary Materials

Supplementary extended methods

- Clinical Data
- Evaluation of Vascular Compliance
- Statistical Methods

Table S1: Characteristics of the CKF cohort

Data are mean \pm SD, median (IQR) or frequencies (%). P-value by independent-samples t-test or Mann-Whitney U (continuous variables) and χ^2 (categorical variables). BMI, body mass index; BP, blood pressure; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LDL, low density lipoprotein (in mg/dl to mmol/l, $\times 0.02586$). Phosphate in mg/dl to mmol/l, $\times 0.3229$; creatinine in mg/dl to $\mu\text{mol/l}$, $\times 88.4$. *p-value<0.05.

Table S2: Multiple regression analysis of VO_2peak in the CKF and the essential hypertension populations

^aAll models adjusted for demographic variables age, sex, BMI, hemoglobin and duration of hypertension. ^bLog-transformed prior to analysis. *b*, unstandardized regression coefficient: change in ml VO_2peak , $\text{min}^{-1} \text{kg}^{-1}$ per one unit change of variable. [†]Final model derived through variable selection process from variables in models. *p-value<0.05.

Table 1: Characteristics of the study population

| Variables | †CKF (n=80) | HTN (n=80) | p-value |
|-------------------------------------|-----------------|-----------------|---------|
| Age, years | 53.3 ± 9.1 | 53.4 ± 8.2 | 0.8 |
| Male, n (%) | 45 (56.3) | 41 (51.2) | 0.2 |
| BMI, kg/m ² | 27.2 ± 4.7 | 27.6 ± 3.6 | 0.6 |
| Smoking, n (%) | 41 (51.3) | 43 (53.7) | 0.8 |
| Hypertension, n (%) | 71 (88.8) | 80 (100.0) | <0.01* |
| Duration of hypertension, months | 120 (48 – 228) | 60 (36 -120) | 0.02* |
| Systolic BP, mm Hg | 135.8 ± 23.9 | 140.9 ± 12.8 | 0.1 |
| Diastolic BP, mm Hg | 79.1 ± 11.6 | 85.4 ± 9.8 | 0.001* |
| Pulse pressure, mm Hg | 57.0 ± 18.3 | 55.5 ± 12.1 | 0.5 |
| Antihypertensives | | | |
| ACEi/ARB, n (%) | 25 (31.3) | 47 (58.8) | <0.001* |
| Calcium antagonist, n (%) | 42 (52.5) | 34 (42.5) | 0.2 |
| β-blocker, n (%) | 26 (32.5) | 11 (13.8) | <0.01* |
| Diuretics, n (%) | 12 (15.0) | 35 (43.8) | <0.001* |
| Co-morbidities | | | |
| Diabetes mellitus, n (%) | 12 (15.0) | 0 | |
| Prior cardiovascular disease, n (%) | 10 (12.5) | 0 | |
| Dialysis, n (%) | 61 (76.3) | 0 | |
| Dialysis vintage, months | 32 (15 – 60) | - | |
| Urea reduction ratio, % | 69.8 ± 8.6 | - | |
| Biochemical | | | |
| Creatinine, mg/dl | - | 0.8 ± 0.2 | |
| eGFR, ml/min/1.73m ² | - | 92.6 ± 15.2 | |
| Hemoglobin, g/dl | 11.8 ± 1.3 | 14.2 ± 1.2 | <0.001* |
| C-reactive protein, mg/dl | 0.3 (0.0 – 0.7) | 0.3 (0.3 – 0.4) | 0.8 |
| Albumin, g/dl | 4.4 (4.2 – 4.5) | 4.7 (4.6 – 4.8) | <0.001* |
| Phosphate, mg/dl | 4.6 (3.7 – 5.3) | 3.4 (3.1 – 3.7) | <0.001* |
| HbA1c, % | 5.4 (5.2 – 5.9) | 5.6 (5.4 – 5.9) | 0.02* |
| LDL cholesterol, mg/dl | 92.8 ± 38.7 | 112.1 ± 34.8 | <0.001* |

Data are mean ± SD, median (IQR) or frequencies (%). P-value by paired-samples t-test or Wilcoxon (continuous variables) and χ^2 (categorical variables). BMI, body mass index; BP, blood pressure; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LDL, low density lipoprotein (in mg/dl to mmol/l, x0.02586). Phosphate in mg/dl to mmol/l, x0.3229; creatinine in mg/dl to μ mol/l, x88.4. †For clinical characteristics of dialysis-dependent and

non-dialysis CKF cohort, please refer to Table S1 (supplementary). *p-value<0.05.

Table 2: Measures of cardiac function and vascular compliance

| Variables | CKF (n=80) | HTN (n=80) | p-value |
|------------------------------------|--------------------|--------------------|---------|
| Cardiac | | | |
| LV mass index, g/m ² | 109.1 ± 33.4 | 87.5 ± 17.1 | <0.001* |
| LV geometry, n (%) | | | <0.001* |
| Normal geometry | 12 (15.0) | 27 (33.7) | |
| Concentric remodeling | 32 (40.0) | 38 (47.6) | |
| Concentric hypertrophy | 24 (30.0) | 6 (7.5) | |
| Eccentric hypertrophy | 12 (15.0) | 9 (11.2) | |
| LVEDVI, ml/m ² | 48.3 ± 18.1 | 44.8 ± 10.1 | 0.1 |
| LA volume index, ml/m ² | 25.4 (18.6 – 31.6) | 25.7 (19.8 – 30.5) | 0.7 |
| LV ejection fraction, % | 62.6 ± 7.9 | 66.2 ± 5.7 | <0.01* |
| Transmitral E/A | 0.8 (0.7 – 1.0) | 1.0 (0.8 – 1.2) | <0.001* |
| Deceleration time, ms | 222.4 ± 64.6 | 202.0 ± 50.4 | 0.03* |
| Mean e', m/s | 8.6 ± 2.2 | 8.9 ± 2.2 | 0.4 |
| E/mean e' | 8.3 (6.6 – 10.5) | 8.3 (7.0 – 9.1) | 0.2 |
| Vascular | | | |
| Tr, ms | 135.7 ± 11.8 | 137.4 ± 12.2 | 0.4 |
| Alx ₇₅ , % | 26.9 ± 11.8 | 25.4 ± 11.9 | 0.5 |
| PWV (m/s) | 8.4 (7.3 – 9.7) | 8.5 (7.9 – 9.6) | 0.4 |
| Ea, mmHg/ml | 2.6 ± 1.2 | 2.4 ± 0.7 | 0.09 |

Data are mean ± SD, median (IQR) or frequencies (%). P-value by paired-samples t-test or Wilcoxon (continuous variables) and χ^2 (categorical variables). LV, left ventricular; LVEDVI, LV end-diastolic volume index; LA, left atrium; E/A, the ratio of peak early to late transmitral ventricular filling velocities; mean e', averaged septal and lateral annular mitral velocity; Tr, time to reflection; Alx₇₅, augmentation index adjusted to heart rate of 75 beats/min; PWV, pulse wave velocity; Ea, arterial elastance. *p-value<0.05.

Table 3: Measures of functional cardiovascular reserve

| Variables | CKF (n=80) | HTN (n=80) | p-value |
|--|--------------------|--------------------|----------------|
| VO₂peak, ml min⁻¹ kg⁻¹ | 18.8 ± 4.1 | 24.5 ± 7.1 | <0.001* |
| VO₂peak, % predicted | 73.4 ± 15.0 | 92.9 ± 20.4 | <0.001* |
| VO₂AT, ml min⁻¹ kg⁻¹ | 11.2 ± 2.1 | 13.8 ± 3.6 | <0.001* |
| VO₂AT, % predicted VO₂peak | 43.9 ± 8.7 | 52.9 ± 11.4 | <0.001* |
| VE-VCO₂ slope | 29.3 (27.4 – 33.9) | 28.5 (26.7 – 30.9) | 0.06 |
| Maximal work load, Watt | 106.4 ± 38.8 | 159.3 ± 59.9 | <0.001* |
| Endurance time, min | 10.8 (9.2 – 12.1) | 11.9 (10.5 – 12.8) | 0.003* |
| RER at VO₂AT | 0.9 ± 0.1 | 0.9 ± 0.1 | 0.7 |
| RER at peak exercise | 1.3 ± 0.1 | 1.2 ± 0.1 | <0.001* |
| HR at peak exercise, beat min⁻¹ | 132.8 ± 22.5 | 155.4 ± 19.4 | <0.001* |
| HR at peak exercise,% predicted | 79.7 ± 12.9 | 92.2 ± 14.1 | <0.001* |
| Oxygen pulse, ml O₂ min⁻¹ | 10.4 (9.0 – 14.0) | 11.7 (9.1 – 14.8) | 0.04* |

Data are mean ± SD and median (IQR). P-value by paired-samples t-test or Wilcoxon test. VO₂peak, oxygen consumption at peak exercise; VO₂AT, oxygen consumption at the point of anaerobic threshold; VE-VCO₂, ventilatory equivalent for carbon dioxide; RER, respiratory exchange ratio of CO₂ production to O₂ consumption; HR, heart rate. *p-value<0.05.

Table 4: Univariate regression analysis of VO₂peak in the study population

| Variables | CKF | | HTN | |
|--------------------------|--------------|----------------------------------|--------------|-----------------------------------|
| | <i>b</i> | 95% CI | <i>b</i> | 95% CI |
| Age | -0.08 | -0.18 – 0.02 | -0.34 | -0.53 – -0.16[†] |
| Sex (Female) | -2.89 | -4.61 – -1.17[†] | -6.48 | -9.35 – -3.61[†] |
| BMI | -0.16 | -0.35 – 0.03 | -0.11 | -0.56 – 0.34 |
| Smoking (Ever) | -0.73 | -2.54 – 1.09 | -1.40 | -4.62 – 1.81 |
| Duration of hypertension | -0.01 | -0.02 - -0.01[‡] | -0.01 | -0.02 – 0.02 |
| Diabetes (Present) | -1.64 | -4.16 – 0.89 | - | - |
| Dialysis vintage | -0.01 | -0.04 – 0.01 | - | - |
| HR at peak exercise | 0.02 | -0.02 – 0.07 | 0.17 | 0.10 – 0.25[†] |
| Alx ₇₅ | -0.10 | -0.17 – -0.02[‡] | -0.23 | -0.35 – -0.10[†] |
| ^a PWV | -3.96 | -7.53 – -0.40[‡] | -8.77 | -16.77 – -0.78[‡] |
| LV mass index | -0.01 | -0.03 – 0.03 | 0.21 | 0.13 – 0.30[†] |
| LA volume index | -0.05 | -0.13 – 0.03 | 0.07 | -0.15 – 0.28 |
| LV ejection fraction | 0.05 | -0.07 – 0.16 | -0.22 | -0.50 – 0.06 |
| LVEDVI | 0.01 | -0.04 – 0.06 | 0.41 | 0.28 – 0.54[†] |
| Transmitral E/A | -2.90 | -5.76 – 0.04 | 6.45 | 0.95 – 11.94[‡] |
| ^a E/mean e' | -5.10 | -7.40 – -2.81[†] | -1.37 | -8.97 – 6.22 |
| Hemoglobin | 0.72 | 0.05 – 1.39[‡] | 1.45 | 0.14 – 2.76[‡] |
| C-reactive protein | -0.05 | -0.13 – 0.03 | -0.55 | -1.55 – 0.46 |
| Albumin | 0.26 | -0.03 – 0.56 | 0.91 | 0.18 – 1.64[‡] |
| Phosphate | -1.49 | -3.68 – 0.69 | -4.25 | -10.10 – 1.61 |
| HbA1c | -0.56 | -1.55 – 0.43 | -4.00 | -8.32 – 0.32 |
| LDL cholesterol | -0.27 | -1.21 – 0.66 | -0.47 | -2.35 – 1.41 |
| Urine PCR | 0.00 | -0.01 – 0.01 | -0.06 | -0.15 – 0.04 |

^aLog-transformed prior to analysis. *b*, unstandardized regression coefficient: change in ml VO₂peak, min⁻¹ kg⁻¹ per one unit change of variable. Statistical significance of the regression coefficient as determined by p-value: ≤0.001[†], ≤0.01[‡], <0.05[‡].

Table 5: Multiple regression analysis of VO₂peak in the CKF and the essential hypertension populations

| ^a Models | <i>b</i> | Standard Error | 95% CI | p-value |
|--|----------|----------------|----------------|---------|
| CKF (n = 80); (unadjusted R² = 0.51, adjusted R² = 0.45) | | | | |
| Intercept | 33.18 | 5.64 | 21.90 – 44.46 | <0.001* |
| ^b E/mean e' | -3.55 | 1.05 | -5.66 – -1.45 | 0.001* |
| Alx ₇₅ | -0.07 | 0.04 | -0.15 – 0.02 | 0.1 |
| ^b PWV | -1.31 | 1.67 | -4.66 – 2.03 | 0.4 |
| Essential hypertension (n = 80); (unadjusted R² = 0.71, adjusted R² = 0.66) | | | | |
| Intercept | -12.02 | 18.26 | -48.52 – 24.47 | 0.5 |
| Transmitral E/A | 1.76 | 2.12 | -2.47 – 5.99 | 0.4 |
| LVEDVI | 0.21 | 0.07 | 0.09 – 0.34 | 0.002* |
| LV mass index | 0.10 | 0.04 | 0.02 – 0.17 | 0.01* |
| Alx ₇₅ | -0.06 | 0.06 | -0.17 – 0.05 | 0.3 |
| ^b PWV | -1.97 | 3.03 | -8.02 – 4.09 | 0.5 |
| HR at peak exercise | 0.12 | 0.03 | 0.07 – 0.18 | <0.001* |
| Albumin | 0.24 | 0.27 | -0.30 – 0.79 | 0.4 |

^aAll models including final models (see Table S2 - supplementary) adjusted for demographic variables age, sex, BMI, hemoglobin and duration of hypertension. ^bLog-transformed prior to analysis. *b*, unstandardized regression coefficient: change in ml VO₂peak, min⁻¹ kg⁻¹ per one unit change of variable. *p-value<0.05.