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

Stephen M.S. Ting<sup>1,8</sup>, PhD, Thomas Hamborg<sup>7</sup>, PhD, Gordon McGregor<sup>1</sup>, PhD, David Oxborough<sup>4</sup>, PhD, Nicolas Aldridge<sup>1</sup>, Kenneth Lim<sup>5</sup>, MD, PhD, Sudheer Koganti<sup>2</sup>, Chris Imray<sup>3</sup>, PhD, Rosemary Bland<sup>8</sup>, PhD, Simon Fletcher<sup>1</sup>, MD, Nithya S. Krishnan<sup>1</sup>, MD, Robert M. Higgins<sup>1</sup>, MD, Jonathan Townend<sup>6</sup>, MD, Prithwish Banerjee<sup>2</sup>, MD, Daniel Zehnder<sup>1,8</sup>, MD, PhD

Divisions of Nephrology<sup>1</sup>, Cardiology<sup>2</sup>, Vascular and Renal Transplantation Surgery<sup>3</sup>, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK; Research Institutes of Sports and Exercise Sciences<sup>4</sup>, Liverpool John Moores University, Liverpool, UK; Division of Nephrology<sup>5</sup>, Brigham and Women's Hospital, Harvard Medical School, USA; Division of Cardiology, University Hospital Birmingham, Birmingham, UK<sup>6</sup>; Divisions of Health Sciences Statistics and Epidemiology<sup>7</sup>, Metabolic and Vascular Health<sup>8</sup>, The University of Warwick, Coventry, UK

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## **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)<sup>1</sup>. 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 death<sup>2</sup>. CKF causes arterial stiffening resulting in reducing arterial cushioning of phasic pressure changes<sup>3</sup>. 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<sup>4 5-7</sup>. 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 fibrosis<sup>8</sup>. These changes result in impaired myocardial relaxation and elevation of LV filling pressure<sup>8,9</sup>. This impairment in diastolic function along with more subtle changes in systolic function leads to a high incidence of heart failure (HF)<sup>3,6,10</sup> with a reduction in exercise capacity<sup>11</sup>. 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<sup>12,13</sup>. Several studies have also demonstrated a reduced  $VO_{2peak}$  in patients with CKF<sup>14-16</sup> and this was also associated with poor survival<sup>14,17</sup>. 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  $\geq 18$  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 stunning<sup>18</sup> and minimize the impact of volume load variability on the indices of cardiovascular structure and function<sup>19</sup>. 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<sup>®</sup>, 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 plots<sup>20</sup>.  $VO_{2peak}$  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 equation<sup>20</sup>.

### *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 Echocardiography<sup>21</sup> 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 recorded<sup>22</sup>. 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<sup>23,24</sup>. 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  $\Delta B$  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  $\beta$ -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/m<sup>2</sup>,  $p=0.6$ ). The use of  $\beta$ -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/m<sup>2</sup>,  $p<0.001$ ). LV end-diastolic volume index (LVEDVI, 48.3 vs. 44.8 ml/m<sup>2</sup>,  $p=0.1$ ) 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 CO<sub>2</sub> production to O<sub>2</sub> consumption) of  $>1.15$ . The mean of RER at the point of VO<sub>2</sub>AT for the study populations was  $0.9\pm 0.1$ . Relative to the essential

hypertension subjects, the CKF patients had a significantly lower  $\text{VO}_2\text{peak}$  (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  $\text{VO}_2\text{AT}$  (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 $\text{VO}_2\text{peak}$**

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  $\text{VO}_2\text{peak}$  onto individual cardiovascular measures are highlighted by **Figure 1**. Increasing LV mass index was positively associated with higher  $\text{VO}_2\text{peak}$  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  $\text{VO}_2\text{peak}$  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  $\text{VO}_2\text{peak}$  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  $\text{VO}_2\text{peak}$  in either group. Both  $\text{Alx}_{75}$  and PWV had an inverse relationship with  $\text{VO}_2\text{peak}$  in the CKF as well as the essential hypertension cohorts.

### **Cardiac structural variables and $\text{VO}_2\text{peak}$ 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  $\beta$ -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  $\beta$ -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 patients<sup>17</sup>. 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.*<sup>14,25</sup> 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 Sietsma *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/m<sup>2</sup>) and a lower number of male patients (56.3 vs. 65.0 %); each of these factors might result in a lower VO<sub>2</sub>peak. 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<sup>14,25</sup>.

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'<sup>8</sup>. The increase in LV mass although paralleled with the high prevalence of hypertension in CKF patients<sup>26</sup> 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<sup>27,28</sup>. 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 VO<sub>2</sub>peak 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<sup>5,29</sup>

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 fraction<sup>30</sup>. The underlying hemodynamic mechanism leading to exercise intolerance, dyspnea and thereby reduced  $VO_2$ peak<sup>31</sup> in these patients is probably mediated at least in part by the increased diastolic LV stiffness<sup>32,33</sup>. 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 relaxation<sup>34</sup>. 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<sup>10,35</sup>. 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<sup>36,37</sup> or augmentation of uremic clearance by intensive nocturnal hemodialysis<sup>38</sup>.

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 relaxation<sup>39</sup>. In CKF, the cumulative burden of myocardial fibrosis and LV hypertrophy could cause a reduction in the mean  $e'$  velocity which further decreases with age<sup>40</sup>. The resulting impaired LV relaxation is a hallmark of diastolic dysfunction<sup>33</sup> which has been shown to cause a



similar reduction in  $VO_2$ peak as with systolic dysfunction according to HF studies<sup>31</sup>. 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 reflection<sup>41</sup>. This pathological wave reflection increases cardiac loading and prejudices the diastolic coronary perfusion<sup>41-43</sup> 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<sup>44,45</sup> and the loss of adaptive functional LV changes in the CKF.

## Limitations

Exercise training has been shown to improve  $VO_2$ peak<sup>46</sup> 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.*<sup>47</sup> 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.

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**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

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## 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. <sup>a</sup>Log-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

$\Delta B$  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. <sup>a</sup>Log-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

$\Delta B$  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  $\beta$ -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  $\chi^2$  (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 $\text{VO}_2\text{peak}$ in the CKF and the essential hypertension populations

<sup>a</sup>All models adjusted for demographic variables age, sex, BMI, hemoglobin and duration of hypertension. <sup>b</sup>Log-transformed prior to analysis. *b*, unstandardized regression coefficient: change in ml  $\text{VO}_2\text{peak}$ ,  $\text{min}^{-1} \text{kg}^{-1}$  per one unit change of variable. <sup>†</sup>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 <sup>2</sup>	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
<b>Antihypertensives</b>			
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*
<b>Co-morbidities</b>			
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	-	
<b>Biochemical</b>			
Creatinine, mg/dl	-	0.8 ± 0.2	
eGFR, ml/min/1.73m <sup>2</sup>	-	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  $\chi^2$  (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  $\mu$ 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
<b>Cardiac</b>			
LV mass index, g/m <sup>2</sup>	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 <sup>2</sup>	48.3 ± 18.1	44.8 ± 10.1	0.1
LA volume index, ml/m <sup>2</sup>	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
<b>Vascular</b>			
Tr, ms	135.7 ± 11.8	137.4 ± 12.2	0.4
Alx <sub>75</sub> , %	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  $\chi^2$  (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; Alx<sub>75</sub>, 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

<b>Variables</b>	<b>CKF (n=80)</b>	<b>HTN (n=80)</b>	<b>p-value</b>
<b>VO<sub>2</sub>peak, ml min<sup>-1</sup> kg<sup>-1</sup></b>	18.8 ± 4.1	24.5 ± 7.1	<0.001*
<b>VO<sub>2</sub>peak, % predicted</b>	73.4 ± 15.0	92.9 ± 20.4	<0.001*
<b>VO<sub>2</sub>AT, ml min<sup>-1</sup> kg<sup>-1</sup></b>	11.2 ± 2.1	13.8 ± 3.6	<0.001*
<b>VO<sub>2</sub>AT, % predicted VO<sub>2</sub>peak</b>	43.9 ± 8.7	52.9 ± 11.4	<0.001*
<b>VE-VCO<sub>2</sub> slope</b>	29.3 (27.4 – 33.9)	28.5 (26.7 – 30.9)	0.06
<b>Maximal work load, Watt</b>	106.4 ± 38.8	159.3 ± 59.9	<0.001*
<b>Endurance time, min</b>	10.8 (9.2 – 12.1)	11.9 (10.5 – 12.8)	0.003*
<b>RER at VO<sub>2</sub>AT</b>	0.9 ± 0.1	0.9 ± 0.1	0.7
<b>RER at peak exercise</b>	1.3 ± 0.1	1.2 ± 0.1	<0.001*
<b>HR at peak exercise, beat min<sup>-1</sup></b>	132.8 ± 22.5	155.4 ± 19.4	<0.001*
<b>HR at peak exercise,% predicted</b>	79.7 ± 12.9	92.2 ± 14.1	<0.001*
<b>Oxygen pulse, ml O<sub>2</sub> min<sup>-1</sup></b>	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. VO<sub>2</sub>peak, oxygen consumption at peak exercise; VO<sub>2</sub>AT, oxygen consumption at the point of anaerobic threshold; VE-VCO<sub>2</sub>, ventilatory equivalent for carbon dioxide; RER, respiratory exchange ratio of CO<sub>2</sub> production to O<sub>2</sub> consumption; HR, heart rate. \*p-value<0.05.

**Table 4:** Univariate regression analysis of VO<sub>2</sub>peak in the study population

Variables	CKF		HTN	
	<i>b</i>	95% CI	<i>b</i>	95% CI
Age	-0.08	-0.18 – 0.02	<b>-0.34</b>	<b>-0.53 – -0.16<sup>†</sup></b>
Sex (Female)	<b>-2.89</b>	<b>-4.61 – -1.17<sup>†</sup></b>	<b>-6.48</b>	<b>-9.35 – -3.61<sup>†</sup></b>
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	<b>-0.01</b>	<b>-0.02 - -0.01<sup>‡</sup></b>	-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	<b>0.17</b>	<b>0.10 – 0.25<sup>†</sup></b>
Alx <sub>75</sub>	<b>-0.10</b>	<b>-0.17 – -0.02<sup>‡</sup></b>	<b>-0.23</b>	<b>-0.35 – -0.10<sup>†</sup></b>
<sup>a</sup> PWV	<b>-3.96</b>	<b>-7.53 – -0.40<sup>‡</sup></b>	<b>-8.77</b>	<b>-16.77 – -0.78<sup>‡</sup></b>
LV mass index	-0.01	-0.03 – 0.03	<b>0.21</b>	<b>0.13 – 0.30<sup>†</sup></b>
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	<b>0.41</b>	<b>0.28 – 0.54<sup>†</sup></b>
Transmitral E/A	-2.90	-5.76 – 0.04	<b>6.45</b>	<b>0.95 – 11.94<sup>‡</sup></b>
<sup>a</sup> E/mean e'	<b>-5.10</b>	<b>-7.40 – -2.81<sup>†</sup></b>	-1.37	-8.97 – 6.22
Hemoglobin	<b>0.72</b>	<b>0.05 – 1.39<sup>‡</sup></b>	<b>1.45</b>	<b>0.14 – 2.76<sup>‡</sup></b>
C-reactive protein	-0.05	-0.13 – 0.03	-0.55	-1.55 – 0.46
Albumin	0.26	-0.03 – 0.56	<b>0.91</b>	<b>0.18 – 1.64<sup>‡</sup></b>
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

<sup>a</sup>Log-transformed prior to analysis. *b*, unstandardized regression coefficient: change in ml VO<sub>2</sub>peak, min<sup>-1</sup> kg<sup>-1</sup> per one unit change of variable. Statistical significance of the regression coefficient as determined by p-value: ≤0.001<sup>†</sup>, ≤0.01<sup>‡</sup>, <0.05<sup>‡</sup>.

**Table 5:** Multiple regression analysis of VO<sub>2</sub>peak in the CKF and the essential hypertension populations

<sup>a</sup> Models	<i>b</i>	Standard Error	95% CI	p-value
<b>CKF (n = 80); (unadjusted R<sup>2</sup> = 0.51, adjusted R<sup>2</sup> = 0.45)</b>				
Intercept	33.18	5.64	21.90 – 44.46	<0.001*
<sup>b</sup> E/mean e'	-3.55	1.05	-5.66 – -1.45	0.001*
Alx <sub>75</sub>	-0.07	0.04	-0.15 – 0.02	0.1
<sup>b</sup> PWV	-1.31	1.67	-4.66 – 2.03	0.4
<b>Essential hypertension (n = 80); (unadjusted R<sup>2</sup> = 0.71, adjusted R<sup>2</sup> = 0.66)</b>				
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 <sub>75</sub>	-0.06	0.06	-0.17 – 0.05	0.3
<sup>b</sup> 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

<sup>a</sup>All models including final models (see Table S2 - supplementary) adjusted for demographic variables age, sex, BMI, hemoglobin and duration of hypertension. <sup>b</sup>Log-transformed prior to analysis. *b*, unstandardized regression coefficient: change in ml VO<sub>2</sub>peak, min<sup>-1</sup> kg<sup>-1</sup> per one unit change of variable. \*p-value<0.05.