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Chinnappa, S, White, E orcid.org/0000-0002-3954-9792, Lewis, N et al. (6 more authors) (2018) Early and asymptomatic cardiac dysfunction in chronic kidney disease. Nephrology Dialysis Transplantation, 33 (3). pp. 450-458. ISSN 0931-0509

https://doi.org/10.1093/ndt/gfx064

Early and asymptomatic cardiac dysfunction in chronic kidney disease

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Running title: Peak cardiac power in CKD

Abstract

Background: Heart failure is highly prevalent and associated with high mortality in chronic kidney disease (CKD). However, the pathophysiology of cardiac dysfunction in CKD, especially in the early asymptomatic stage, is not well understood. We studied sub-clinical cardiac dysfunction in asymptomatic CKD patients without co-morbid cardiac disease or diabetes mellitus by evaluating peak cardiac performance.

Methods: In a cross-sectional study (n=130) we investigated 70 male non-diabetic CKD patients (21 CKD 2-3a, 27 CKD 3b-4 and 22 CKD 5) employing specialised cardiopulmonary exercise testing to measure peak cardiac output and cardiac power output non-invasively. Data from 35 age-matched healthy male volunteers were obtained for comparison. In addition, as a positive control, data from 25 age-matched male heart failure patients in NYHA class II & III were also obtained.

Results: The study subjects showed a graded reduction in peak cardiac power with 6.13±1.11 W in control, 5.02±0.78 W in CKD 2-3a, 4.59±0.53 W in CKD 3b-4 and 4.02±0.73 W in CKD 5 although not as impaired as in heart failure with 2.34±0.63 W (all $P<0.005$ vs control). The central haemodynamic characteristics of the cardiac impairment in CKD mirrored that of heart failure with reduced flow and pressure generating capacities, reduced chronotropic reserve and impaired contractility.

Conclusion: The study demonstrates for the first time, impaired peak cardiac performance and cardiac functional reserve in asymptomatic CKD patients. The evidence of myocardial dysfunction in the absence of co-morbid cardiac disease and diabetes warrants further evaluation of current pathophysiological concepts of cardiovascular disease in CKD.

Keywords: Cardiac reserve, cardiac power, CKD, heart failure, cardiorenal syndrome

Introduction

Heart failure (HF) is highly prevalent in chronic kidney disease (CKD) and confers a serious adverse prognosis.[1-3] Therefore, identification of early cardiac dysfunction and an understanding of the pathophysiology of such dysfunction are vital in preventing its emergence and progression in CKD.

However, significant gaps exist in our knowledge of HF in CKD. Whether HF is a complication of the common co-morbidities of CKD such as ischaemic heart disease (IHD) and diabetes mellitus (DM), or whether CKD per se can cause cardiac impairment remains to be answered. Furthermore, it is not known whether asymptomatic cardiac dysfunction, the precursor of heart failure,[4] is present in CKD.

Cardiac structural and ultrastructural changes in CKD have extensively been studied using techniques such as echocardiogram,[5] cardiac magnetic resonance imaging[6] and cardiac biopsy[7] offering valuable insights into uraemic cardiomyopathy by exposing abnormalities such as left ventricular hypertrophy (LVH), cardiac fibrosis and myocyte-capillary mismatch. However, attempts to detect cardiac dysfunction in asymptomatic CKD patients before they develop overt symptoms of heart failure have so far been unsuccessful. In a recent large echocardiographic study,[8] no relationship between *resting* measures of systolic and diastolic cardiac dysfunction and renal dysfunction in asymptomatic CKD patients was found.

Alternatively, functional measures of *peak* performance of the heart have the potential to reveal subclinical cardiac dysfunction as demonstrated by our proof of concept pilot study wherein we measured peak cardiac power output, non-invasively, during a cardiopulmonary exercise test (CPX).[9, 10]

In the present study, we tested the hypothesis that asymptomatic CKD patients have impaired peak cardiac power output and hence reduced cardiac functional reserve compared to healthy subjects. Moreover, we tested CKD patients without primary cardiac disease or DM to study the effect of CKD-specific factors in isolation.

Subjects and Methods

Study subjects

Asymptomatic male CKD patients (n=70) were recruited from the renal outpatient clinic of a tertiary UK referral center for cardiopulmonary exercise testing (CPX). The inclusion and exclusion criteria are listed in Table 1. The present study is limited to male gender alone to minimise confounders that arise due to the effect of gender and body composition on central haemodynamics.[11-13] Venous blood samples were taken at the time of recruitment to assay serum creatinine, urea, haemoglobin, serum calcium, inorganic phosphate and parathyroid hormone. Urine samples were assayed for urine protein-creatinine ratio. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable modification of diet in renal disease MDRD formula.[14] CPX data from contemporaneous healthy male volunteers (n=35) who participated in a previous study in the unit was obtained for comparison. For positive controls, the CPX data from age-matched male heart failure patients in New York Heart Association (NYHA) class II & III (n=25) who underwent CPX testing on clinical grounds were used for comparison. The control subjects and the HF patients were drawn from the same population as the CKD patients and all study participants underwent CPX tests using the same protocols and procedures. The study was approved by the Research Ethics Committee [Ref: 11/H1310/8 and 05/Q1205/151

(control)]. All subjects provided informed written consent before participation. These clinical investigations conformed with the Declaration of Helsinki.

Sample size

Based on the results of the pilot study,[9] to demonstrate 10% difference in CPO_{max} between study groups and healthy controls (with 90% power) a minimum of 11 patients per group was required.

Cardiopulmonary exercise tests (CPX)

Peak cardiac power output (CPO_{max}) was determined noninvasively during maximal cardiopulmonary exercise (CPX) testing. Full methodological details have been described in previous reports.[15, 16] The validity and reliability of the methods have been extensively studied in the past.[17-21] Furthermore, over the past 20 years several studies have been published using the same techniques.[11, 15, 16, 22, 23] A summary of the methodology is presented here.

Resting measures: The subjects had resting measurements for O_2 consumption and CO_2 production, respiratory rate, and cardiac output using a Medgraphics Cardio$_2$ Analytic System (Medgraphics Corp., St. Paul, MN, USA). Resting cardiac output was calculated using the Collier CO_2 rebreathing method.[17, 24] The Collier's equilibration method has been shown to have good correlation with thermodilution techniques at rest[18] and is easy to use, and therefore it was utilized for resting measurements.

Determination of aerobic capacity (VO_{2max}): Subjects then underwent an incremental exercise test on a treadmill according to a standard Bruce protocol, and every 3 minutes, the speed and incline of the treadmill were increased according to the protocol until the subjects reached volitional exhaustion. Throughout the treadmill

test, O_2 consumption, CO_2 production, end-tidal partial pressure of CO_2, tidal ventilation, and respiratory rate were measured using breath-to-breath analysis. Ventilatory ('anaerobic') threshold was measured by the V-slope method.[25] A 12-lead ECG was monitored throughout, and the subject's heart rate (HR) was obtained from this. Blood pressure (BP) was measured at rest and at 3-min intervals up to, and including, maximal exercise by auscultation and sphygmomanometry.

Determination of cardiac output: After resting at least 40 min, a second treadmill test was performed. The speed and incline of the treadmill were adjusted manually. The subjects exercised on the treadmill to 95% of their $VO_{2\ max}$ as established in the incremental exercise test. Two or three cardiac output measurements were made using the Defare's CO_2 rebreathing method.[26] The Defare's method was chosen as this method has been shown to correlate well with cardiac output obtained with thermodilution techniques during exercise.[19] The blood pressure was measured using a sphygmomanometer after each determination of cardiac output. The formulae used to calculate haemodynamic variables are listed in Table 2.

Statistical analysis

CPO_{max} was the primary outcome measure. Comparison of CPO_{max} among the study groups controlling for age was performed using analysis of covariance (ANCOVA). Difference between any 2 groups was tested using Bonferroni post-hoc test. Similar analyses were performed for peak cardiac output, peak mean blood pressure, heart rate reserve and cardiac reserve. Normality of data was verified using normal Q-Q plots and numerical methods (Shapiro-Wilk test). All data were normally distributed but for serum PTH. The association between CPO_{max} and biochemical parameters are tested using Pearson's correlation.

In order to determine the independent predictors of cardiac reserve in CKD, a step-wise multiple regression analysis was used incorporating the haemodynamic, demographic and biochemical variables with significant correlation ($P<0.05$) with cardiac reserve on a univariate analysis.

To evaluate the effect of beta blockers on the haemodynamic parameters, the CKD subjects were divided into two groups based on whether or not they were on beta blockers. A linear regression, controlling for eGFR, was employed to test the difference between the groups.

Results are presented as mean±SD. For Bonferroni post-hoc test, as there were 5 groups and 10 pairwise comparisons, a strict criterion for statistical significance, $P<0.005$, was employed. Fo all other analyes $P<0.05$ was considered statistically significant. SPSS 17.0 (IBM, USA) statistics software was used in the analysis.

Results

Subject characteristics

Anthropometric and biochemical characteristics of the study subjects are listed in Table 3 and the etiologies of CKD in Table 4. There were 70 male CKD patients with a mean age of 48.4±12.6 years covering the spectrum of CKD from stages 2 to 5 (CKD 2-5, pre-dialysis). None of the patients had a history of primary cardiac disease (ischaemic, arrhythmic or valvular) or diabetes mellitus. Patients had no cardiac symptoms and thus all were in New York Heart Association (NYHA) class I. No patient had electrocardiographic evidence or symptoms of angina pectoris, myocardial ischaemia or arrhythmia during exercise testing. None had uncontrolled hypertension (mean resting SBP was 113.9±12.5 and DBP was 72.3±8.1 mmHg). Of the 70 patients, 61.4% were receiving angiotensin converting enzyme inhibitors (ACE-I), 34.8% angiotensin receptor antagonists and 20.0% β-adrenoceptor antagonists. The average numbers of anti-hypertensive agents taken per patient in CKD 2-3a, CKD 3b-

4 and CKD 5 were 1.2, 1.6 and 1.7 respectively. For comparison, Table 3 also shows data from contemporaneous healthy male volunteers (n=35) and male patients with confirmed heart failure (HF) (n=25) in functional NYHA classes II & III.

Cardiopulmonary exercise test parameters

All CKD patients successfully performed *high intensity* cardiopulmonary exercise test (CPX) to volitional exhaustion with a mean duration of 10.5±2.9 min (Bruce protocol equivalent, P=NS vs Control), mean peak respiratory exchange ratio (RER) of 1.16±0.09, a peak end tidal pCO_2 ($ETpCO_2$) of 37.2±5.9 mmHg, and maximal aerobic capacity (VO_{2max}) was 2.51±0.53 l/min. The healthy volunteers exercised for 11.5±3.7 min (Bruce protocol) with a mean peak RER of 1.21±0.13, $ETpCO_2$ of 38.2±4.9 mmHg, and VO_{2max} was 3.10±0.62 l/min. The HF patients exercised for 5.5±2.8 min (Bruce protocol equivalent, $P<10^{-6}$ vs Control) with a mean RER of 1.1±0.2, $ETpCO_2$ of 29.9±8.7 mmHg, and VO_{2max} was 1.54±0.38 l/min.

Resting haemodynamics

The resting haemodynamic parameters of the study groups such as heart rate, mean blood pressure, cardiac output, systemic vascular resistance (SVR) and cardiac power output are presented in Table 5. The resting haemodynamic parameters were not significantly different between the study groups except for mean blood pressure between control and HF ($P<0.005$) and cardiac power output between control and HF ($P<0.005$). Significant differences were also demonstrated for cardiac power output between CKD2-3a and HF and cardiac output between CKD 2-3a and HF ($P<0.005$).

Peak haemodynamics

Impaired peak cardiac power output (CPO_{max}) and cardiac reserve in CKD

CPO_{max} showed a graded decline across the study groups (Table 6 & Figure 1). Compared to healthy control all CKD groups and HF demonstrated statistically

significant (P<0.005) difference in CPO_{max} and in cardiac reserve (Figures 1&2). Furthermore, compared to CKD 2-3a the CPO_{max} and cardiac reserve were significantly impaired in CKD 5 and HF (P<0.005). The difference between CKD 2-3a and CKD 3b-4 did not reach statistical significance.

Impaired peak cardiac output and peak mean arterial pressure in CKD

Figure 3 shows the differences in peak cardiac output (CO) and peak mean arterial pressure (MAP), the flow and pressure generating capacities of the heart respectively, across the study groups. Peak CO was significantly lower in all study groups compared to control (P<0.005) and peak MAP was significantly lower in CKD 5 and HF compared to control (P<0.005).

Impaired peak heart rate and heart rate reserve in CKD

The peak heart rate of the study groups are presented in Table 6. The heart rate reserve, measured as the difference between peak and resting heart rate, and adjusted for age (AHRR)[27] was significantly lower in all study groups compared to control (P<0.005) (Fig 4).

Peak systemic vascular resistance across CKD groups

The peak systemic vascular resistance of the study groups are shown in Table 6.

Association between CPO_{max} and CKD related biochemical parameters

CPO_{max} had significant positive correlation with eGFR, haemoglobin and serum bicarbonate, and significant negative correlation with urea, parathyroid hormone and inorganic phosphate. No correlation existed with serum calcium and urine protein creatinine ratio (Figure 5). Independent association of individual biochemical variables with CPO_{max} could not be assessed because of strong collinearity among the biochemical parameters.

Effect of beta blockers on central haemodynamics in CKD patients

Linear regression was performed, controlling for eGFR, to compare haemodynamic parameters between CKD patients who were on beta blockers and those who were not. Results showed that there were no significant differences in peak CPO (Δ =0.03W, P=0.96), peak CO (Δ= 0.13 l/min, P=0.54) and peak MBP (Δ = 3.72 mmHg, P=0.23) between the two groups. However, significant differences were present between the mean peak HR and mean peak SV between the groups. The mean peak HR was lower in the beta blocker group by 26.85 min^{-1} ($P<10^{-3}$), whereas the mean peak SV was greater in the beta blocker group by 26.63 ml ($P<10^{-3}$) offsetting the reduction in peak HR.

Comparison between cardiac functional reserve measured by peak cardiac power output (CPO_{max}) and peak O_2 consumption (VO_{2max}) in CKD patients

Simultaneous measurements of CPO_{max} and VO_{2max} in CKD allowed evaluation of the determinants of these parameters in CKD. Furthermore, simultaneous measurements of VO_2 and cardiac output at rest and peak exercise enabled measurement of arterio-venous difference in O_2 concentration [$C(a\text{-}v)O_2$] at rest and peak exercise for the first time in CKD patients using Fick's equation $VO_2 = CO \times C(a\text{-}v)O_2$ (Tables 5&6).

Univariate and multivariate analyses

Tables 7 and 8 show the haemodynamic, biochemical and demographic parameters that are significantly associated with cardiac reserve determined by measuring CPO at rest and peak exercise (ΔCPO) and cardiac reserve determined by measuring VO_2 at rest and peak exercise (ΔVO_2) respectively on univariate analyses.

Table 9 show the independent predictors identified on a stepwise multiple regression analysis. For $CPO_{reserve}$, the increment in the pressure generating capacity of the heart (ΔMAP) was the strongest independent predictor. No independent

association was demonstrated with haemoglobin (Hb), systemic vasodilatory capacity (ΔSVR) or increment in peripheral O_2 extraction [$\Delta C(a\text{-}v)O_2$]. Whereas, $\Delta C(a\text{-}v)O_2$ was the strongest predictor of the $VO_{2reserve}$. No independent association was demonstrated with ΔMAP or eGFR.

Discussion

The present study significantly advances our knowledge of the impact of CKD on cardiac pump function. The results of the study support the hypothesis that cardiac performance, as represented by CPO_{max} and cardiac reserve, is significantly impaired in CKD compared to healthy control. Moreover, the impairment was proportional to the severity of CKD. The cardiac performance of CKD patients was shown to lie between that of healthy control and patients with symptomatic heart failure. As we studied asymptomatic, non-diabetic CKD patients with no overt cardiac disease and with controlled blood pressure, our results show that CKD per se is associated with cardiac dysfunction even at early CKD and when asymptomatic. This dysfunction is only revealed under conditions of peak exercise, suggesting that in CKD patients, like conventional cardiac failure, compensatory mechanisms maintain resting cardiac performance within normal limits. Although cardiac *structural* changes have been studied in the past in asymptomatic CKD patients, the present study has demonstrated *functional* impairment for the first time in such patients, thereby offering a potential tool to study early, subclinical cardiac dysfunction in CKD.

The central haemodynamic alterations underlying the impaired peak cardiac performance in CKD mirror the changes in symptomatic heart failure patients albeit of lesser magnitude. The study shows cardiac power, an index of *myocardial contractility*, is impaired in CKD. The study also shows the impairment in cardiac power results from impairment in both flow and pressure generating capacities of the

heart akin to HF. Furthermore, the study also revealed impaired *chronotropic reserve* in CKD not unlike HF. In summary, the central haemodynamic changes seen in symptomatic heart failure appears to be evolving in asymptomatic CKD patients even in the absence of any primary cardiac disease.

Heart failure and CKD share several common pathophysiological mediators with the potential to cause progressive myocardial dysfunction. These include renin angiotensin aldosterone system (RAAS) activation, sympathetic activation, pro-inflammatory cytokines and myocardial wall stress.[28-33] In heart failure, these mediators were shown to cause direct cardiomyocyte toxicity by inducing apoptosis and necrosis, and pathological hypertrophy resulting in progressive myocardial dysfunction.[34-39] The existence of the above mediators in the uremic milieu raises the possibility of similar pathogenesis of myocardial dysfunction in CKD.

The above similarities between CKD and HF in the biomechanics of myocardial dysfunction and the mediators of such dysfunction draw our attention to potential therapies to attenuate or reverse the process. Whereas in heart failure the benefits of RAAS blockade and beta blockade in preventing the progression of myocardial dysfunction has been shown consistently,[40-42] the evidence for such treatments in uraemic cardiomyopathy is still lacking.

A standard CPX is normally employed to measure the exercise capacity, VO_{2max}. We used physical exercise as a physiological, non-invasive stimulus to drive the heart to its peak performance to measure cardiac output and CPO_{max}. As CPX is the study tool it is natural to draw comparison between CPO_{max} and VO_{2max}. Indeed, VO_{2max} has recently been proposed as a measure of "functional cardiac reserve" in CKD.[43] However, evidence from heart failure research demonstrate that VO_{2max} can be influenced by non-cardiac factors such as muscle deconditioning, age, gender,

anaemia and motivation.[44] Instead, it has been shown that a more direct assessment of cardiac performance can be achieved by measuring CPX-derived haemodynamic variables rather than just the VO_{2max}.[44, 45] Indeed, on head-to-head comparison CPO_{max} has repeatedly been shown to be the best predictor of prognosis in HF compared VO_{2max}.[16, 46] In the present study, the simultaneous measurement of cardiac output and VO_{2max} had enabled us to compare the determinants of cardiac reserve in CKD as measured by CPO_{max} or VO_{2max}. Our detailed analysis undermines the assumption that VO_{2max} serves as a convenient measure of "functional cardiac reserve". Our data showed that the increment in arterio-venous O_2 difference was the strongest predictor of VO_2 reserve. This limitation in increasing peripheral O_2 extraction is likely to be related to anaemia, plus possible uremic skeletal myopathy, though further studies would be required to fully elucidate the role of central, peripheral and biochemical determinants of VO_{2max} in CKD.

Our analysis demonstrated that haemoglobin is an independent predictor of VO_{2max} but not of CPO_{max}. Studies that simultaneously measured peak cardiac output and VO_{2max} before and after erythropoietin therapy/haemodilution had also shown that altered haemoglobin affected VO_{2max} measures but not peak cardiac output.[47] Though it must be acknowledged our evaluation is limited to statistical analysis of a cross sectional study. Further longitudinal studies in CKD may be worthwhile in the future to evaluate the effect of anaemia correction on central haemodynamics.

A criticism of employing CPX in the evaluation of cardiac performance is that inadequate patient effort could be a confounder. In our study, all CKD patients exercised above the anaerobic threshold with a mean respiratory exchange ratio (RER) of > 1.1 in all three CKD groups. All patients were encouraged to exercise until volitional exhaustion. Furthermore, the exercise duration was comparable

between the control and CKD patients. This makes it less likely that the impairment in cardiac functional reserve is attributable to inadequate effort.

Cardiac power output and cardiac reserve were not shown to be influenced by beta blockade therapy in the present study. The reduction in peak heart rate associated with beta blockade was shown to be offset by the increase in SV and hence there was no net effect on the cardiac performance. Almost all CKD patients were treated with RAAS blockade and if this has affected the results the effect is uniform. Furthermore, as cardiac output and afterload have a linear inverse relationship,[48] and CPO_{max} is an index that incorporates measures of both volume and pressure, the changes in arterial pressure are offset by changes in the volume generated. Hence CPO_{max} remains afterload-independent akin to other pressure-volume indices such as stroke work, stroke work index etc.[48]

As the first ever study exploring the impact of CKD directly on peak cardiac power, we utilised a cross-sectional study design. A longitudinal study design in the same patients as the disease progresses would be better suited to demonstrate a causal relationship between uraemia and cardiac dysfunction. However, most etiologies of CKD (especially in the absence of co-morbid CVD or DM) run an indolent course progressing over many years making such a study challenging to undertake. Alternatively, a longitudinal study design testing interventions such as kidney transplantation or novel dialysis strategies would be highly pertinent in the future.

In conclusion, the study has demonstrated that cardiac functional reserve is impaired in asymptomatic CKD patients and the dysfunction appears to be associated with CKD alone in the absence of cardiovascular co-morbidities. The haemodynamic characteristics of such impairment demonstrate a failing myocardium in CKD thus highlighting the existence of cardiomyopathic component in the pathophysiology of

cardio-vascular disease of CKD. As the current concepts of pathogenesis of cardiovascular disease in CKD do not adequately explain this phenomenon, further investigation into the etiology and its management is paramount.

Acknowledgements

We thank Yorkshire Kidney Research Fund and Sheffield Kidney Research Foundation. We thank Prof LB Tan for reports on cardiopulmonary exercise tests. We also thank Ms Wanda McDonald for assistance with cardiopulmonary exercise testing.

Financial & competing interest disclosure

The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilised in the production of this manuscript. The manuscript represents an original work, was not invited for a special issue, is not under consideration elsewhere for publication in whole or in part, and has not been published in another form or in another country, except in abstract format.

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Table 1: Inclusion and exclusion criteria

Inclusion Criteria
• Age > 18 years • Male sex • CKD stages 2 to 5 (pre-dialysis) stable for 3 months
Exclusion Criteria
• Diabetes mellitus • Any known cardiac diseases (ischaemic, arrhythmic or valvular) • Limitation of exercise ability due to significant musculoskeletal, cardiovascular, pulmonary, hepatic, neurological or other non-renal medical disorders • Clinical hypervolemia.

Table 2: List of formulae used in the study

Parameter	Formula
MAP (mmHg)	MAP=DBP+0.412(SBP–DBP)
CPO (W)	CPO = (CO×MAP)×*K*
Cardiac reserve (ΔCPO) (W)	CPO_{max} - CPO_{rest}
SVR dyn.sec.cm^{-5}	SVR = (MAP/CO)x80.
VDC dyn.sec.cm^{-5}	SVR_{rest} – SVR_{peak}

MAP: mean arterial pressure, DBP: diastolic blood pressure, SBP: systolic blood pressure, CPO: cardiac power output, CO: cardiac output, SVR: systemic vascular resistance, VDC: vasodilatory capacity.

K (2.22×10^{-3}) is the conversion factor to convert CPO into the SI unit of power, Watt.

Table 3: Body composition and biochemical characteristics of study subjects

	Control (n=35)	CKD 2-3a (n=21)	CKD 3b-4 (n=27)	CKD 5 (n=22)	P	HF (n=25)
Age (years)	59.1±7.0	42.5±11.0	49.4±11.5	52.9±13.6	<0.05	49.4±14.6
BMI (kg/m^2)	27.2±3.6	27.5±3.8	27.6±4.0	28.4±3.9	NS	25.1±3.2
BSA (m^2)	1.98±0.15	2.07±0.15	1.99±0.18	2.03±0.17	NS	1.93±0.18
eGFR (ml/min)	--	65.8±13.1	26.5±7.8	12.3±2.3	<0.05	69.3±16.9
Creatinine (µmol/l)	--	114.9±18.6	254.9±67.9	504.5±174.5	<0.05	110.4±22.8
Urea (mmol/l)	--	8.3±2.4	17.9±5.0	25.9±7.1	<0.05	7.9±2.0
Hemoglobin (g/dl)	--	15.0±1.2	13.2±1.5	11.9±1.2	<0.05	14.4±1.13
Calcium (mmol/l)	--	2.34±0.08	2.34±0.11	2.29±0.17	NS	--
Phosphate (mmol/l)	--	1.08±0.18	1.22±0.15	1.53±0.55	<0.05	--
Bicarbonate (mmol/l)	--	27.24±3.02	23.74±3.15	21.32±2.97	<0.05	--
PTH (pmol/l)	--	12.28±24.17	20.81±15.23	43.18±30.39	<0.05	--
Urine PCR (mg/mmol)	--	25.99±28.9	96.44± 112.52	130.94± 140.94	<0.05	--

BMI: body mass index, BSA: body surface area, CKD: chronic kidney disease, HF: heart failure, PTH: parathyroid hormone, PCR: protein creatinine ratio. P value is for ANOVA across the study groups.

Table 4: Etiologies of CKD

Etiologies	Number of patients
IgA Nephropathy	19
Polycystic kidney disease	15
Reflux nephropathy & chronic pyelonephritis	15
Membranoproliferative glomerulonephritis	3
Focal segmental glomerulosclerosis	3
Alport's nephropathy	2
Interstitial nephritis	1
Hypertensive nephropathy	1
Minimal change disease	1
Uncertain etiology	10

Table 5: Resting cardiopulmonary exercise parameters of study subjects

Variables	Control (n=35)	CKD 2-3a (n=21)	CKD 3b-4 (n=27)	CKD 5 (n=22)	HF (n=25)
HR_{rest} (beats/min)	69.9±9.5	76.7±14.3	76.7±14.2	76.0±11.8	78.5±16.4
SBP_{rest} (mmHg)	119.6±8.4	110.5±11.2	114.4±13.1	116.5±12.6	100.8±19.4*
DBP_{rest} (mmHg)	75.2±7.3	71.9±8.1	73.3±6.8	71.6±9.5	66.8±11.6
MAP_{rest} (mmHg)	93.5±6.9	87.8±7.8	90.3±8.3	90.1±9.4	80.8±14.1*
CO_{rest} (l/min)	4.6±0.9	5.3±1.3	4.6±0.7	4.4±0.9	4.05±1.17
SV_{rest} (ml/min)	66.3±18.4	71.1±14.3	63.5±13.7	60.8±13.1	56.3±21.1
SVR_{rest} dyn.sec.cm^{-5}	1706.1±508.7	1406.4±347.8	1634.2±346.1	1739.5±450.5	1694.3± 435.3
CPO_{rest} (W)	0.94±0.19	1.05±0.29	0.92±0.15	0.87±0.21	0.72±0.26*
VO_{2rest} (ml/min)	277.3±85.6	309.5±89.1	344.4±122.4	320.8±119.0	302.4±92.5
$C(a\text{-}v)O_{2rest}$ ml/dl	6.1±1.6	6.3±2.6	7.7±2.7	7.5±2.5	7.7±2.4

CKD: chronic kidney disease, HF: heart failure, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, CO: cardiac output, SV; stroke volume, SVR: systemic vascular resistance, CPO: peak cardiac power output, VO_2: O_2 consumption, $C(a\text{-}v)O_2$: peripheral O_2 extraction

*P<0.005 vs Control on Bonferroni post-hoc test.

Table 6: Peak cardiopulmonary exercise parameters of study subjects

Variables	Control	CKD 2-3a (n=21)	CKD 3b-4 (n=27)	CKD 5 (n=22)	HF (n=25)
RER	1.21±0.13	1.15±0.09	1.15±0.11	1.16±0.06	1.1±0.29
Measures of peak haemodynamics					
Peak HR (beats/min)	173.6±13.4	171.3±19.7	158.7±17.9*	148.7±24.9*	128.9±40.1*
Peak SBP (mmHg)	161.1±21.7	153.3±12.4	155.2±17.3	144.2±16.3*	112.8±29.6*
Peak DBP (mmHg)	77.4±11.6	74.5±7.4	72.8±7.5	67.3±9.4*	65.8±13.8*
Peak MAP (mmHg)	111.9±13.1	107.0±8.2	106.7±10.0	98.9±9.9*	82.7±18.0*
Peak SVR dyn.sec.cm^{-5}	369.7±75.6	430.6±60.1	464.1±77.1	465.9±67.6	593.2±237.6 *
Peak CO (l/min)	24.75±3.59	21.50±2.31*	19.44±2.07*	18.26±2.60*	12.52±2.37*
CPO_{max} (W)	6.13±1.11	5.02±0.78*	4.59±0.53*	4.02±0.73*	2.34±0.63*
Cardiac reserve ΔCPO (W)	5.19±1.09	3.98±0.82*	3.66±0.5*	3.15±0.68*	1.62±0.6*
Measures of exercise capacity					
Exercise duration[§] (min)	11.5±3.7	12.2±3.0	10.2±2.6	9.1±2.6	5.5±2.8*
MET[ς]	11.7±2.3	12.0±2.0	10.6±1.6	9.8±2.0	7.3±3.1*
AT (l/min)	2.23±0.49	2.12±0.50	1.75±0.44*	1.58±0.28*	1.11±0.35*
AT as percentage of VO_{2max} (%)	73.2±14.3	72.9±12.8	72.4±12.7	73.6±11.1	72.8±14.3
VO_{2max} (l/min)	3.10±0.62	2.91±0.46	2.48±0.43*	2.17±0.43*	1.54±0.38*
VO_{2max} (ml/min/kg)	37.7±7.8	33.5±6.5*	29.9±5.5*	24.9±3.5*	19.9±3.9*
$C(a\text{-}v)O_{2peak}$ ml/dl	13.4±1.5	14.3±1.9	13.5±2.0	12.7±1.6	12.9±2.1
$\Delta C(a\text{-}v)O_2$ ml/dl	7.3±2.4	8.0±3.3	5.9±3.2	5.2±3.1	5.1±2.6

CKD: chronic kidney disease, HF: heart failure, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, CO: cardiac output, SV; stroke volume, RER: respiratory exchange ratio, SVR: systemic vascular resistance, AT: anaerobic threshold, VO_{2max}: peak oxygen consumption, CPO_{max}: peak cardiac power output, $C(a\text{-}v)O_2$: peripheral O_2 extraction.
*P<0.005 vs Control on Bonferroni post-hoc test. [§]Bruce protocol equivalent exercise duration
[ς]Metabolic equivalent corresponding to the maximum stage achieved on bruce protocol

Table 7: Haemodynamic, demographic and biochemical correlates of $CPO_{reserve}$

Variable	Correlation Coefficient	P value
$HR_{reserve}$	0.33	0.007
$SV_{reserve}$	0.29	0.021
$MAP_{reserve}$	0.69	$<10^{-3}$
$C(a\text{-}v)O_{2reserve}$	-0.02	0.88
ΔSVR	0.09	0.45
Age	-0.36	0.003
BMI	0.16	0.20
Haemoglobin	0.49	$<10^{-3}$
eGFR	0.45	$<10^{-3}$

HR: heart rate, SV: stroke volume, MAP: mean arterial pressure, $C(a\text{-}v)O_2$: peripheral O_2 extraction, SVR: systemic vascular resistance, BMI: body mass index.

Table 8: Haemodynamic, demographic and biochemical correlates of $VO_{2reserve}$

Variable	Correlation Coefficient	P value
$HR_{reserve}$	0.55	$<10^{-3}$
$SV_{reserve}$	0.36	$<10^{-3}$
$MAP_{reserve}$	0.35	0.003
$C(a\text{-}v)O_{2reserve}$	0.62	$<10^{-3}$
ΔSVR	0.41	0.001
Age	-0.40	0.001
BMI	0.31	0.01
Haemoglobin	0.59	$<10^{-3}$
eGFR	0.53	$<10^{-3}$

HR: heart rate, SV: stroke volume, MAP: mean arterial pressure, $C(a\text{-}v)O_2$: peripheral O_2 extraction, SVR: systemic vascular resistance, BMI: body mass index.

Table 9: Independent predictors of $CPO_{reserve}$ and $VO_{2reserve}$

Variable	Standardised co-efficient (β)	P value
$CPO_{reserve}$		
$MAP_{reserve}$	0.51	$<10^{-4}$
$SV_{reserve}$	0.49	$<10^{-4}$
$HR_{reserve}$	0.42	$<10^{-4}$
eGFR	0.23	0.003
$VO_{2reserve}$		
$C(a\text{-}v)O_{2reserve}$	0.53	$<10^{-6}$
$SV_{reserve}$	0.32	$<10^{-3}$
$HR_{reserve}$	0.28	0.002
Hb	0.31	$<10^{-3}$
Age	0.28	$<10^{-3}$
BMI	0.20	0.003

HR: heart rate, SV: stroke volume, MAP: mean arterial pressure, $C(a\text{-}v)O_2$: peripheral O_2 extraction, BMI: body mass index.

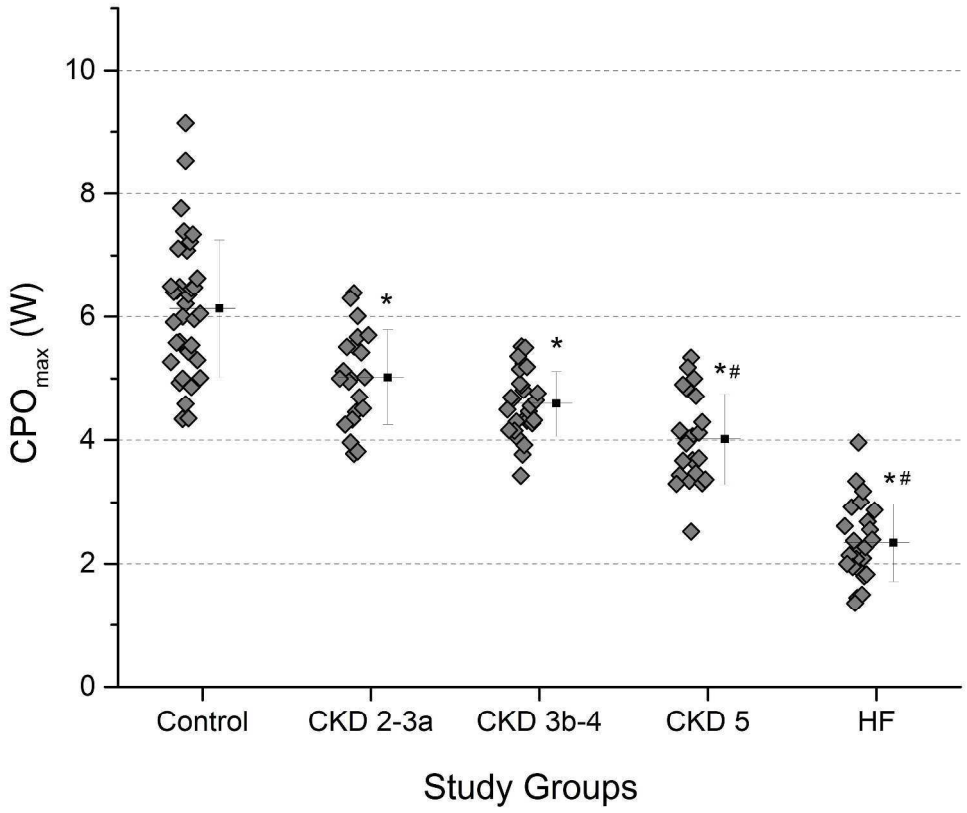

Figure 1: CPO_{max} showing graded decline across the study groups.
CKD: chronic kidney disease, HF: heart failure.
*P<0.005 vs Control, #P<0.005 vs CKD 2-3a on Bonferroni post hoc test

Figure 1
1383x1163mm (96 x 96 DPI)

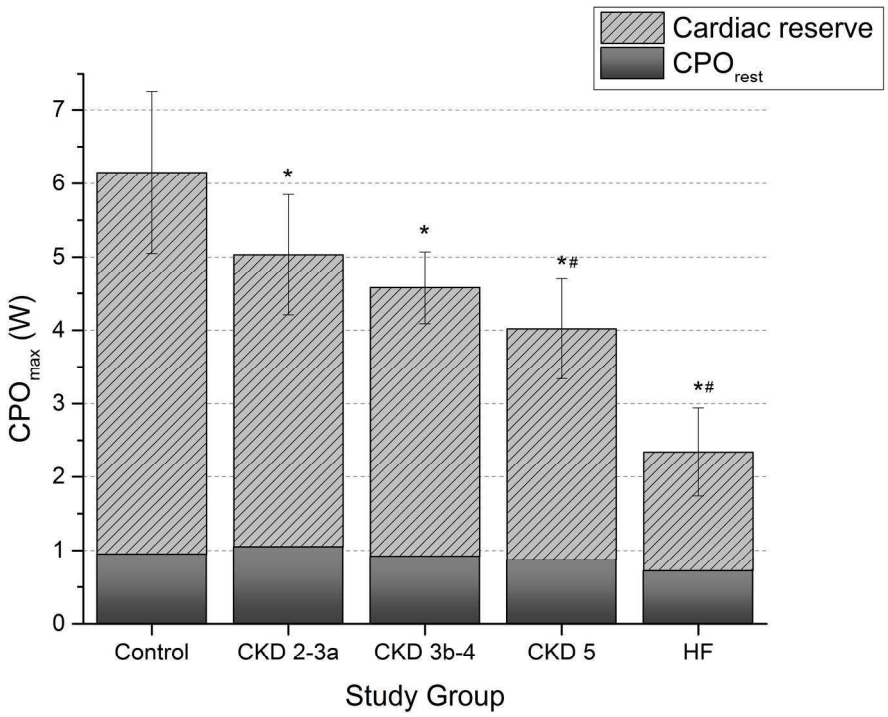

Figure 2: Cardiac reserve (ΔCPO) showing graded decline across the study groups. The peak performance (CPO_{max}) of the heart is more discriminatory among different groups than the resting measure (CPO_{rest}).
CKD: chronic kidney disease, HF: heart failure.
*P<0.005 vs Control, #P<0.005 vs CKD 2-3a on Bonferroni post hoc test

Figure 2
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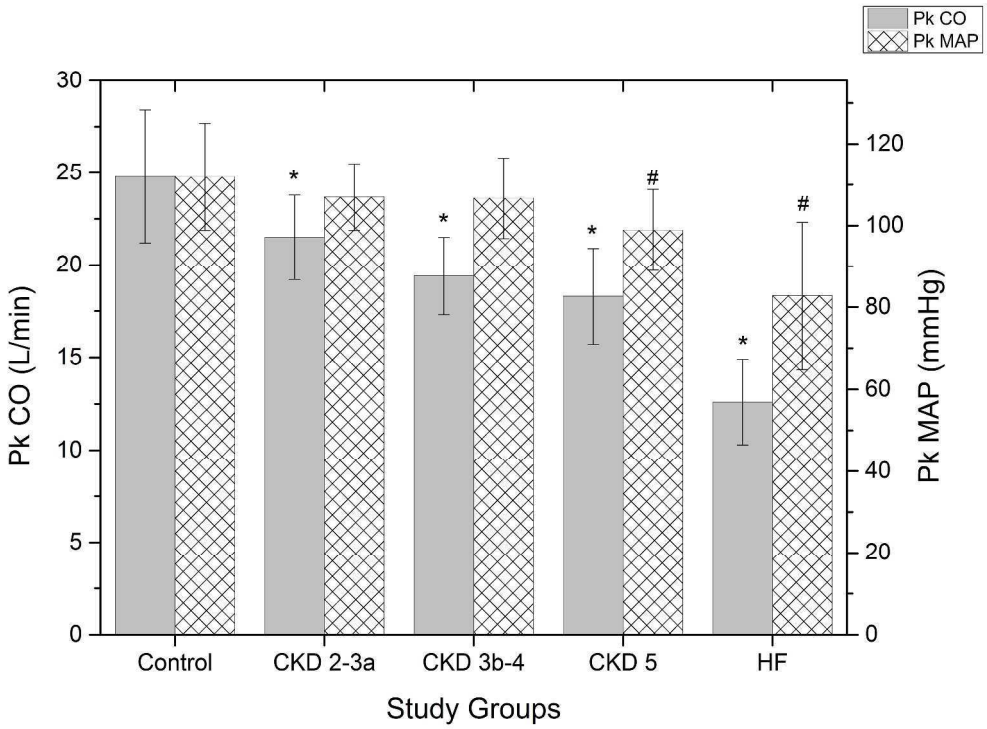

Figure 3: Peak cardiac output (Pk CO) and peak mean arterial pressure (Pk MAP) across the study groups showing graded decline in flow and pressure generating capacities of the heart respectively. CKD: chronic kidney disease, HF: heart failure.
*P<0.005 for Pk CO and #P<0.005 for Pk MAP vs Control on Bonferroni post hoc test.

Figure 3
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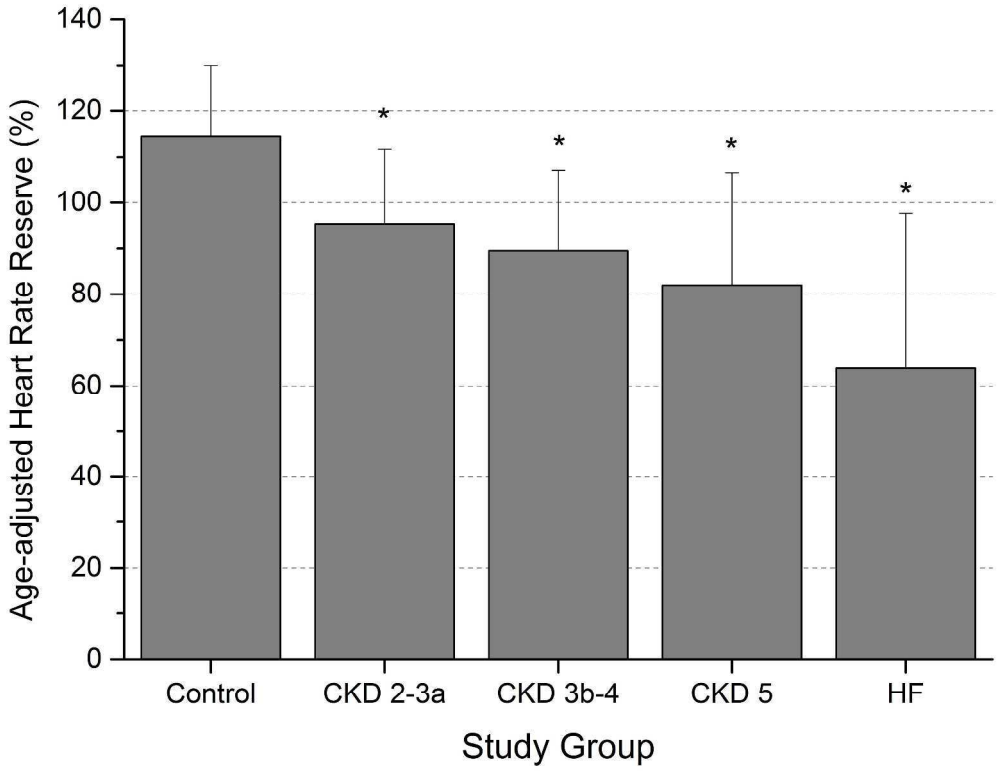

Figure 4: Age adjusted heart rate reserve across the study groups showing graded reduction in chronotropic reserve. CKD: chronic kidney disease, HF: heart failure.
* P<0.005 Vs Control on Bonferroni post hoc test.

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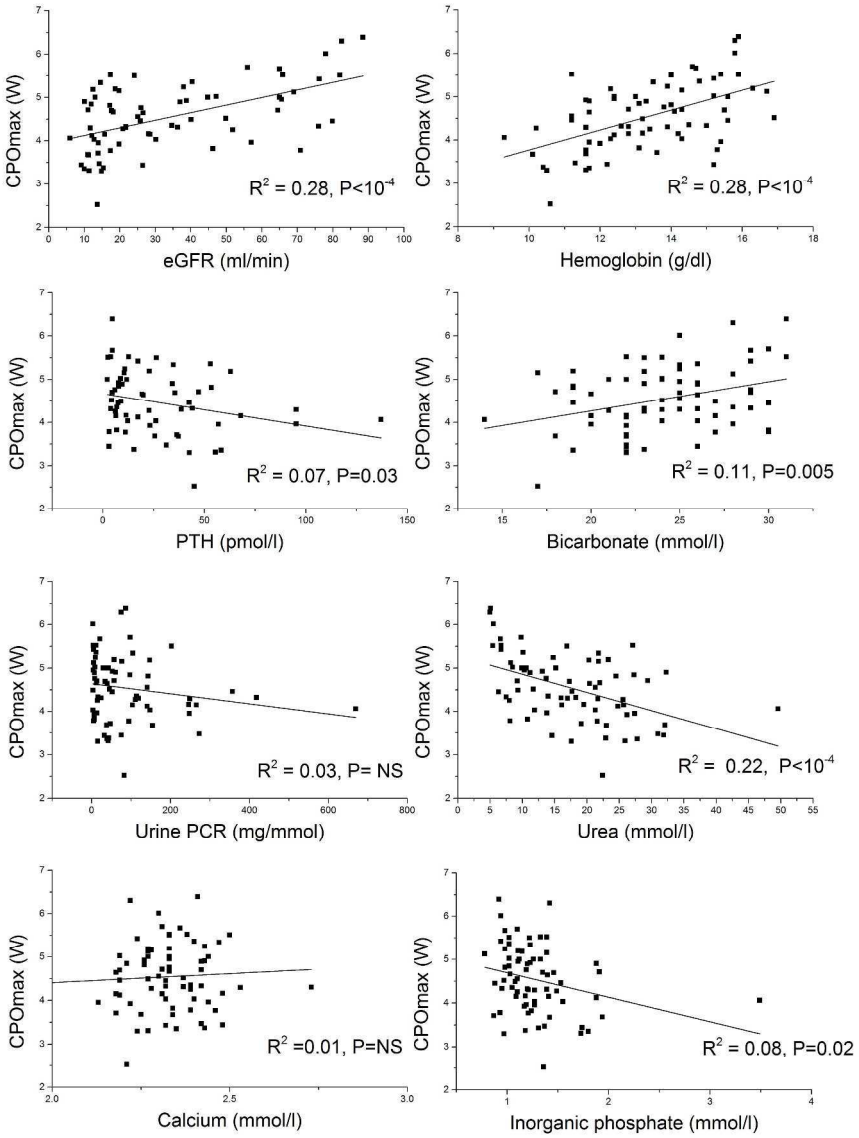

Figure 5: Association between CPO_{max} and CKD-related biochemical parameters on Pearson's correlation. PTH: parathyroid hormone.

1116x1490mm (96 x 96 DPI)