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Cardiac and Noncardiac Determinants of Exercise Capacity in CKD

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ABSTRACT

Background Impaired exercise capacity is a significant symptom of CKD and is associated with poor survival. Furthermore, there is a growing interest in applying exercise as a diagnostic tool or as therapy in CKD. However, an in-depth understanding of exercise physiology in CKD is still lacking.

Methods To evaluate the role of cardiac (central) and noncardiac (peripheral) determinants of exercise capacity in CKD, we conducted a cross-sectional study of 70 male patients with CKD (stages 2–5) without diabetes or cardiac disease, 35 healthy controls, and 25 patients with heart failure. An integrated cardiopulmonary exercise test using a CO_2 rebreathing technique was used to measure peak O_2 consumption (VO_{2peak}) and peak cardiac output simultaneously, and to calculate peak peripheral O_2 extraction (C[a-v]O_2), the peripheral determinant (the ability of exercising skeletal muscles to extract oxygen). We performed multiple regression analysis and used Bayesian information criteria (BIC) changes to quantitatively assess the individual contribution of central and peripheral factors.

Results Compared with healthy controls, in patients with CKD, the VO_{2peak} was impaired proportionate to its severity. Peak cardiac output was the predominant determinant of VO_{2peak} in healthy controls and patients with heart failure, whereas C(a-v)O_2 played a more significant role in determining VO_{2peak} in CKD (β=0.68, P<0.001) compared with cardiac output (β=0.63, P<0.001). In addition, the magnitude of BIC reduction was greater for C(a-v)O_2 compared with cardiac output (BIC, 298.72 versus 287.68) in CKD.

Conclusions In CKD, both peak cardiac output and peak C(a-v)O_2 are independent predictors of VO_{2peak}, and the more significant roleplayed by peak C(a-v)O_2 highlights the importance of noncardiac factors in determining exercise capacity in CKD.

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Exercise capacity is impaired in CKD and ESKD.[1–3] Furthermore, reduced exercise capacity is associated with poor survival and quality of life in this cohort.[4] Hence, there is growing interest in utilizing objective measures of exercise capacity in evaluating cardiovascular fitness, predicting mortality and morbidity, selecting patients for transplantation, and assessing benefits of exercise training in CKD. The successful application of the parameters of exercise physiology in studying patients with CKD depends on a clear understanding of the factors that determine exercise capacity in these patients. Merely extrapolating information from studies on healthy volunteers or patients with heart failure (HF) may not suffice.

The gold-standard measure of exercise capacity is peak O_2 consumption (VO_{2peak}).[5] VO_{2peak} depends on both the *O_2 delivery* to exercising skeletal muscles and *O_2 utilization* by those skeletal muscles. Fick's equation states that $VO_2 = CO \times C(a\text{-}v)O_2$, where

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CO is the cardiac output, which is the central determinant of exercise capacity, and C(a-v)O_2 is the peripheral O_2 extraction, which is the peripheral (skeletal muscle) determinant. Although previous studies have evaluated the role of demographic, anthropometric, and some biochemical parameters in determining VO_{2peak} in CKD, the crucial information on the differential effects of cardiac (central) and noncardiac (peripheral) factors in determining exercise capacity in CKD remained hitherto unknown. In this study, we used an integrated cardiopulmonary exercise test (CPX) to measure VO_2 and CO simultaneously at peak exercise, for the first time in CKD, to gain deeper insights into the determinants of exercise capacity. We also measured such parameters in healthy volunteers and patients with HF for comparison.

Significance Statement

A detailed understanding of the determinants of exercise capacity in CKD has been lacking. For the first time, the authors demonstrate the differential role of cardiac and noncardiac factors in determining exercise capacity in CKD, finding that the exercising skeletal muscles' ability to extract oxygen is the predominant determinant of exercise capacity in CKD, followed by the heart's ability to generate stroke volume and raise heart rate. Exercise capacity in CKD was impaired even in the absence of any known cardiac diseases or diabetes mellitus, and with a graded decline proportionate to CKD severity. These findings have significant implications in the interpretation of objective measures of exercise capacity in CKD when evaluating cardiovascular fitness, quantifying the benefits of exercise training, and selecting patients for renal transplantation.

METHODS

Subjects and Methods

Study Subjects

Asymptomatic male patients with CKD (n=70) aged >18 years were recruited from the renal outpatient clinic of a tertiary United Kingdom referral center for CPX. Exclusion criteria comprised of an inability or contraindication to exercise on a treadmill; diabetes mellitus; any known cardiac disease (ischemic, arrhythmic, or valvular); limitation of exercise ability due to overt musculoskeletal, cardiovascular, pulmonary, hepatic, neurologic, or other nonrenal medical disorders, and clinical hypervolemia. Venous blood samples were taken at the time of recruitment to assay serum creatinine, urea, hemoglobin, serum calcium, inorganic phosphate, and parathyroid hormone. Urine samples were assayed for urine protein-creatinine ratio. eGFR was calculated using the four-variable modification of diet in kidney disease (MDRD) formula.[6] The participants' height, weight, and body mass index (BMI) were measured. Estimated lean body mass (eLBM) was calculated using Boer's formula (Table 1).[7]

CPX data from healthy male volunteers (n=35) and age-matched male patients with HF in New York Heart Association class II and III (n=25) were obtained for comparison. The study was approved by the South Yorkshire Research Ethics Committee (Ref: 11/H1310/8) and all subjects provided informed written consent before participation. These clinical investigations conformed with the Declaration of Helsinki.

Table 1. List of formulae used in the study

Parameter	Formula
VO_2 (L/min)	CO × C(a-v)O_2
C(a-v)O_2 (ml/dl)	VO_2/CO
MAP (mm Hg)	MAP = DBP+0.412(SBP–DBP)
SVR dyn.sec.cm^{-5}	SVR = (MAP/CO) ×80
eLBM	(0.407× Weight) + (0.267× Height)−19.2

MAP, mean arterial pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

CPX

Peak O_2 consumption and peak CO were determined noninvasively during maximal CPX. Full methodological details have been described in previous reports.[8–10] A summary of the methodology is presented here.

- Resting measures: the O_2 consumption, CO_2 production, respiratory rate, and CO at rest were measured using a Medgraphics CardiO_2 Analytic System (Medgraphics Corp., St. Paul, MN). Resting CO was measured using the Collier CO_2 rebreathing method.[11,12]
- Determination of exercise capacity (VO_{2peak}): subjects then underwent an incremental exercise test on a treadmill according to a standard Bruce protocol (or modified Bruce protocol for patients with HF). The speed and incline of the treadmill were increased every 3 minutes, 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.[13] A 12-lead electrocardiogram was monitored throughout, and the subject's heart rate (HR) was obtained from this. BP was measured at every stage of the CPX.
- Determination of peak CO: a second treadmill test was performed after a rest period of ≥40 minutes. The first treadmill test also served as a familiarization step. The speed and incline of the treadmill were adjusted manually. The subjects exercised on the treadmill to 95% of their VO_{2peak} as established in the incremental exercise test. Two or three CO measurements were made using the Defare's CO_2 rebreathing method.[14] The formulae used in the study are listed in Table 1.

Statistical Analyses

The data were analyzed in three steps:

- First, the study participants were grouped into healthy control (HC), early CKD (CKD 2–3), late CKD (CKD 4–5), and

HF for comparing CPX and hemodynamic parameters in health and disease states. As the control group was older, comparison of VO_{2peak} and hemodynamic variables between study groups was performed using analysis of covariance controlling for age. The difference between any two groups was tested using Bonferroni *post-hoc* test. In addition to analyzing absolute peak values, comparison between groups was also made for reserve values (Δpeak-rest) and number of fold increase from rest to peak.

- Second, to assess the determinants of exercise capacity, the patients with CKD were analyzed as a single group and compared with HF and HC groups. To evaluate the contribution of peak CO (central factor) and peak $C(a\text{-}v)O_2$ (peripheral factor) in determining VO_{2peak}, a multiple regression analysis was performed, and the individual contribution of central and peripheral factors was quantitatively assessed using Bayesian information criteria (BIC) changes.
- Finally, to evaluate the effect of beta blockers on VO_{2peak}, the patients with CKD were divided into two groups on the basis of whether they were on beta blockers. A linear regression analysis, controlling for eGFR, was used to test the difference between the groups. Similar analysis was performedfor anigiotensin converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs).

Normality of data were verified using normal Q–Q plots and numerical methods (Shapiro-Wilk test). Results are presented as mean±SD. $P<0.05$ was considered statistically significant unless specified otherwise. SPSS 25.0 (IBM) statistics software was used in the analysis.

RESULTS

Subject Characteristics

Anthropometric and biochemical characteristics of the patients with CKD ($n=70$), healthy volunteers ($n=35$), and patients with New York Heart Association class II and III HF ($n=25$) are listed in Table 2. The patients with CKD covered the spectrum of CKD from stages 2–5 (predialysis). The etiologies of CKD and antihypertensive usage are shown in Table 3. The participants continued on their routine medications before CPX. None of the patients had a history of primary cardiac disease (ischemic, arrhythmic, or valvular) or diabetes mellitus. No patient had electrocardiographic evidence or symptoms of angina pectoris, myocardial ischemia, or arrhythmia during exercise testing.

Table 3. Etiologies of CKD and antihypertensive usage

Etiologies	No. of patients
IgA nephropathy	19
Polycystic kidney disease	15
Reflux nephropathy and chronic pyelonephritis	15
Membranoproliferative GN	3
FSGS	3
Alport's nephropathy	2
Interstitial nephritis	1
Hypertensive nephropathy	1
Minimal change disease	1
Uncertain etiology	10
Antihypertensive medications	
Angiotensin converting enzyme inhibitors	43
Angiotensin receptor antagonists	24
β-adrenoceptor antagonists	14

Cardiopulmonary Exercise Test Parameters

Resting CPX Parameters

The resting CPX parameters of the study groups such as resting VO_2, HR, mean BP, CO, stroke volume (SV), and systemic vascular resistance (SVR) are presented in Table 4. The resting VO_2 was not significantly different between the study groups. There was a nonsignificant trend toward higher resting $C(a\text{-}v)O_2$ in CKD 4–5 and HF compared with HCs.

Peak CPX Parameters

All patients with CKD successfully performed a *high intensity* cardiopulmonary exercise test to volitional exhaustion as

Table 2. Participant characteristics

Characteristic	HC ($n=35$)	Early CKD Stages 2–3 ($n=29$)	Late CKD Stages 4–5 ($n=41$)	HF ($n=25$)	*P*
Age (yr)	59.1±7.0	45.4±11.4	50.5±13.1	49.4±14.6	<0.05
BMI (kg/m^2)	27.2±3.6	27.6±3.9	28.0±4.0	25.1±3.2	NS
BSA (m^2)	1.98±0.15	2.03±0.18	2.02±0.16	1.93±0.18	NS
eGFR (ml/min)	–	57.8±17.2	16.9±5.9	69.3±16.9	<0.05
Creatinine (μmol/L)	–	132.3±35.5	403.9±171.1	110.4±22.8	<0.05
Urea (mmol/L)	–	9.4±3.0	23.3±6.5	7.9±2.0	<0.05
Hemoglobin (g/dl)	–	14.5±1.4	12.5±1.6	14.4±1.13	<0.05
Calcium (mmol/L)	–	2.35±0.07	2.31±0.15	–	NS
Phosphate (mmol/L)	–	1.10±0.17	1.22±0.15	–	<0.05
Bicarbonate (mmol/L)	–	26.9±2.7	22.0±3.2	–	<0.05
PTH (pmol/L)	–	12.9±21.1	34.8±26.3	–	<0.05
Urine PCR (mg/mmol)	–	26.6±31.1	128.3±130.7	–	<0.05

P value is for ANOVA across the study groups. BSA, body surface area; PTH, parathyroid hormone; PCR, protein creatinine ratio.

Table 4. Resting cardiopulmonary exercise parameters of study subjects

Variables	HC (n=35)	Early CKD Stages 2–3 (n=29)	Late CKD Stages 4–5 (n=41)	HF (n=25)
HR_{rest} (beats/min)	69.9±9.5	76.5±13.9	76.4±13.0	78.5±16.4
SBP_{rest} (mm Hg)	119.6±8.4	111.7±13.1	115.4±11.9	100.8±19.4[a]
DBP_{rest} (mm Hg)	75.2±7.3	72.4±7.9	72.3±8.3	66.8±11.6
MAP_{rest} (mm Hg)	93.5±6.9	88.6±8.5	90.1±8.5	80.8±14.1[a]
VO_{2rest} (ml/min)	277.3±85.6	312.5±92.1	336.5±123.9	302.4±92.5
CO_{rest} (L/min)	4.6±0.9	5.2±1.1	4.4±0.9	4.05±1.17
SV_{rest} (ml/min)	66.3±18.4	68.6±13.7	62.2±13.9	56.3±21.1[a]
SVR_{rest} dyn.sec.cm^{-5}	1706.1±508.7	1455.6±355.1	1700.8±402.2	1694.3±435.3
Resting C(a-v)O_2 ml/dl	6.1±1.6	6.5±1.3	7.7±2.7	7.8±2.4

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.
[a]P<0.05 versus control.

Table 5. Peak cardiopulmonary exercise parameters of study subjects

Variables	HC (n=35)	Early CKD Stages 2–3 (n=29)	Late CKD Stages 4–5 (n=41)	HF (n=25)
Exercise duration (min)	11.5±3.7	11.5±3.1	9.7±3.9	5.5±2.8 min[a,b]
RER	1.21±0.13	1.16±0.10	1.15±0.09	1.1±0.29
Peak ETpCO_2 (mm Hg)	38.2±4.9	40.1±5.6	35.2±5.3	29.9±8.7[b]
Peak HR (beats/min)	173.6±13.4	160.5±17.8[b]	148.5±20.0[c]	128.9±40.1[c]
Peak VE/VCO_2	29.9±4.0	29.0±4.0	33.9±4.9[c]	38.8±7.5[c]
AT (L/min)	2.23±0.49	2.00±0.49[b]	1.67±0.40[c]	1.11±0.35[c]
VO_{2peak} (L/min)	3.10±0.62	2.91±0.56[c]	2.50±0.52[c]	1.54±0.38[c]
VO_{2peak} (ml/min per kg)	37.7±7.8	32.5±6.8[c]	27.3±4.8[c]	19.9±3.9[c]
Peak SBP (mm Hg)	161.1±21.7	154.1±13.3	149.1±20.0[b]	112.8±29.6[c]
Peak DBP (mm Hg)	77.4±11.6	73.8±7.1	69.9±9.1[c]	65.8±13.8[c]
Peak MAP (mm Hg)	111.9±13.1	107.0±8.4	102.5±10.8[c]	82.7±18.0[c]
Peak CO (L/min)	24.75±3.59	21.04±2.28[c]	18.73±2.44[c]	12.52±2.37[c]
Peak SV (ml/min)	149.2±22.9	132.1±15.7	128.4±23.7[b]	105.1±37.0[c]
Peak SVR dyn.sec.cm^{-5}	369.7±75.6	435.5±60.2	468.1±74.2[c]	593.2±237.6[c]
Peak C(a-v)O_2 (ml/dl)	13.4±1.5	13.8±2.0	13.3±1.8	12.9±2.2

RER, respiratory exchange ratio; ETpCO_2, end tidal PCO_2; AT, anaerobic threshold; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.
[a]Bruce protocol equivalent.
[b]P<0.05 versus control.
[c]P<0.01 versus control.

verified by exercise duration, peak respiratory exchange ratio, and peak end tidal pCO_2 (Table 5).

VO_{2peak} Across Study Groups

The VO_{2peak} showed a graded decline across the study groups with significant impairment in VO_{2peak} in CKD 2–3, CKD 4–5, and HF compared with HCs (all P<0.001 versus control) (Table 5).

Peak CO, Peak SV, Peak HR, and C(a-v)O_2 Extraction Across Study Groups

There was a graded decline in peak CO across the study groups. Of the components of CO, peak HR showed graded decline across the study groups and peak SV was impaired in CKD 4–5 and HF compared with healthy volunteers. Peak SVR was significantly higher in CKD 4–5 and HF. There was no demonstrable difference in the mean peak C(a-v)O_2 across the study groups (Table 5).

Number of Fold Increase in CPX Parameters from Rest to Peak Exercise

Figure 1 shows the number of fold increase in VO_2, CO, SV, HR, and C(a-v)O_2 from rest to peak across the study groups. In HCs, the VO_2 increased 12.9-fold, contributed by a 5.6-fold increase in CO and 2.35-fold increase in O_2 extraction. In CKD and HF, the number of fold increase in VO_2 and its components are smaller compared with HCs. ANOVA (on log-transformed ratios) showed the difference in number of fold increments in VO_2, CO, SV, HR, and C(a-v)O_2 across the study groups are statistically significant (all P<0.001). The parameters with a statistically significant difference on pairwise comparison with the control group are shown in Figure 1.

Reserve Values (Δpeak–Rest) of CPX Parameters Across the Study Groups

Figure 2 shows the resting, peak, and reserve values of VO_2, CO, HR, SV, and C(a-v)O_2 across the study groups. The resting values are not significantly different between the groups.

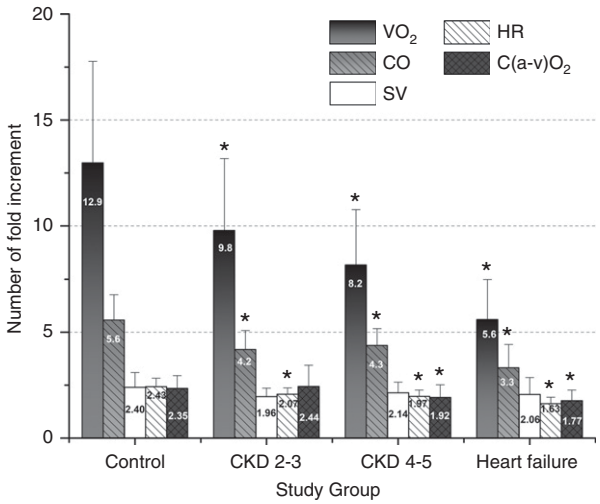

Figure 1. Number of fold increment in VO_2 and its determinants from rest to peak exercise. The number of fold increases from rest to peak exercise in oxygen consumption (VO_2) and its determinants such as CO, SV, HR, and C(a-v)O_2 are smaller in disease states such as CKD and HF compared with HC. Error bars show ±1 SD, *$P<0.05$ versus control on Bonferroni *post-hoc* analysis.

However, $VO_{2reserve}$, $CO_{reserve}$, and $HR_{reserve}$ showed a graded decline across the study groups. Compared with HCs, there was significant impairment in these reserve values in early CKD, late CKD, and HF ($P<0.001$).

Hemodynamic, Biochemical, and Demographic Correlates of VO_{2peak} in CKD

Table 6 shows the correlates of VO_{2peak} in CKD. In addition to the hemodynamic variables, hemoglobin, eGFR, age, eLBM, and BMI also showed a strong positive correlation with VO_{2peak}. Peak SVR showed a significant negative correlation with VO_{2peak}.

Determinants of Exercise Capacity in CKD

Independent Contribution of Central and Peripheral Factors in Determining VO_{2peak}

In CKD, the β coefficients for peak C(a-v)O_2 and peak CO were 0.68 ($P<0.001$) and 0.63 ($P<0.001$), respectively, with a larger BIC reduction for peak C(a-v)O_2, making it a predominant determinant of VO_{2peak} in CKD. On the contrary, peak CO is the predominant determinant of VO_{2peak} in control and HF (Table 7). Figure 3 summarizes the differential role of central and peripheral factors in determining VO_{2peak} across the study groups (control, CKD, and HF). The *P* value for interaction analysis of slope difference is <0.001.

Independent Contribution of Peak HR and Peak SV in Determining Peak CO

Further analysis was performed to evaluate the role of peak SV and peak HR in determining peak CO (CO = SV × HR). Although peak SV is the predominant determinant of peak CO in all three groups, the role of peak HR appeared to be more pronounced in CKD and HF compared with HC (Table 8).

Independent Predictors of Peak C(a-v)O_2

An analysis of the independent predictors of C(a-v)O_2 in CKD showed that eLBM ($\beta=0.38$, $P=0.002$) and hemoglobin ($\beta=0.35$, $P=0.02$) were independent predictors accounting for 40% of the variation in C(a-v)O_2.

The Effect of Drugs on VO_{2peak} in CKD

There was no significant difference in VO_{2peak} between patients with CKD who were on beta blockers and those who were not (2.54±0.61 L/min versus 2.69±0.56 L/min, $P=0.84$). Although the mean peak HR was lower in the beta blocker group by 26.85 min^{-1} ($P<10^{-3}$), the mean peak SV was greater in the beta blocker group by 26.63 ml ($P<10^{-3}$), offsetting the reduction in peak HR. Hence, there was no net effect on peak CO or VO_{2peak}. There was no significantdifference in VO_{2peak} between patients with CKD who were on ACE-I or ARB, and those who were not (2.68±0.59 L/min versus 2.56±0.49 L/min, $P=0.49$).

DISCUSSION

We set out to develop a greater understanding of the determinants of reduced exercise capacity in patients with CKD. In particular, we sought to evaluate the differential role of cardiac (central) and noncardiac (peripheral) determinants of exercise capacity (VO_{2peak}), and the results demonstrated that C(a-v)O_2 is a stronger predictor of VO_{2peak} in CKD compared with peak CO. This is clearly distinct from HCs and patients with HF in whom peak CO is the predominant determinant of VO_{2peak}.

Further exploration of the components of peak CO showed both peak SV and peak HR are significant determinants of peak CO in CKD, HF, and HC. Although peak SV is the strongest determinant of peak CO in all three study groups, it is interesting to note peak HR plays a bigger role in CKD and HF compared with HC. In summary, the predominant determinant of exercise capacity in CKD is the ability of the exercising skeletal muscles to extract O_2, followed by the heart's ability to generate SV and its ability to raise HR, the cardiac inotropic and chronotropic properties, respectively.

The study showed impaired exercise capacity in CKD even in the absence of any known cardiac diseases or diabetes mellitus, with a graded decline proportionate to the severity of CKD. Figure 1 shows a snapshot of the study findings with impairment in VO_{2peak} and all its components in early CKD, late CKD, and HF compared with HCs. It is widely known in the field of exercise physiology that a 10- to 20-fold increase in VO_2 from rest to peak exercise is seen in healthy adults, depending on their age and activity level.[5]

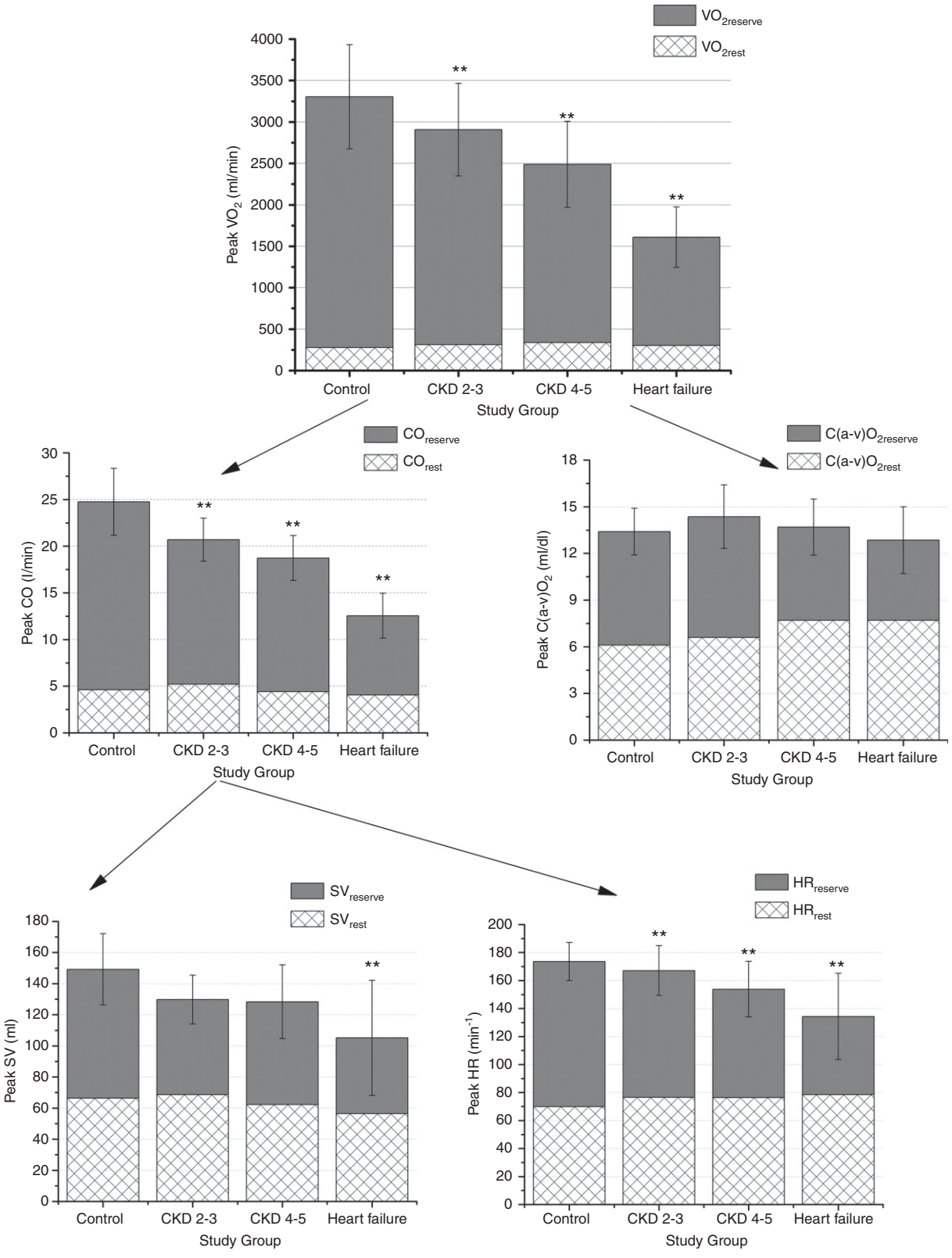

Figure 2. Peak, resting, and reserve values of VO_2 and its components across study groups. There is graded decline in VO_{2peak} and $VO_{2reserve}$ (Δpeak-rest) across the study groups. The graph also shows the corresponding variations in the components of VO_2 such as CO and $C(a\text{-}v)O_2$ as stated in the Fick's equation, $VO_2 = CO \times C(a\text{-}v)O_2$. *$P<0.05$ and **$P<0.01$ versus control for reserve values on Bonferroni *post-hoc* analysis.

Table 6. Hemodynamic, biochemical, and demographic correlates of VO_{2peak} in CKD

Variables	Correlation Coefficient (95% CI)	*P* Value
Hemodynamic variables		
Peak CO	0.74 (0.61 to 0.83)	$<10^{-3}$
Peak SV	0.28 (0.05 to 0.48)	0.02
Peak HR	0.35 (0.13 to 0.54)	0.003
Peak C(a-v)O_2	0.78 (0.67 to 0.86)	$<10^{-3}$
Peak SVR	−0.46 (−0.25 to −0.63)	$<10^{-3}$
Peak MAP	0.22 (−0.02 to 0.43)	NS
Anthropometric variables		
Age	−0.42 (−0.21 to −0.60)	$<10^{-3}$
BMI	0.32 (0.09 to 0.52)	0.007
eLBM	0.54 (0.35 to 0.69)	$<10^{-3}$
Biochemical variables		
Hemoglobin	0.59 (0.41 to 0.72)	$<10^{-3}$
eGFR	0.49 (0.29 to 0.65)	$<10^{-3}$
Calcium	0.11 (−0.13 to 0.34)	NS
Inorganic phosphate	−0.20 (−0.40 to 0.04)	NS
PTH	−0.22 (−0.43 to 0.02)	NS
Bicarbonate	0.25 (0.02 to 0.46)	0.03
Urine PCR	−0.21 (−0.42 to 0.03)	NS

Correlation coefficient on Pearson's correlation. 95% CI, 95% confidence interval; MAP, mean arterial pressure; PTH, parathyroid hormone; PCR, protein-creatinine ratio.

The mean increment in VO_{2peak} in HCs in our study was nearly 13-fold. This compared with a 9.8-fold increase in early CKD, 8.2-fold increase in late CKD, and a mere 5.6-fold increment in patients with HF.

The putative mechanisms of impaired exercise capacity in CKD are manifold. In Fick's equation, where $VO_2 = CO \times C(a\text{-}v)O_2$, CO represents the convective O_2 transport to the exercising skeletal muscles, and $C(a\text{-}v)O_2$ represents the diffusive O_2 transport across the skeletal muscles. Broadly, the convective O_2 transport could be affected in CKD due to impaired cardiac function secondary to uremic cardiomyopathy[10,15,16] and uremic vasculopathy,[17,18] and due to the impaired O_2 carrying capacity of the blood secondary to anemia.[5,19,20] Furthermore, cardiac autonomic neuropathy of uremia[21] may impair HR response during exercise.

Table 7. Independent contribution of central and peripheral factors in determining VO_{2peak} in CKD, HF, and HC

Parameter	Standardized Coefficient β (95% CI)	*P* Value	BIC Reduction
CKD			
Peak CO	0.63 (0.61 to 0.65)	<0.001	287.68
Peak C(a-v)O_2	0.68 (0.66 to 0.70)	<0.001	298.72
HF			
Peak CO	0.83 (0.79 to 0.87)	<0.001	107.69
Peak C(a-v)O_2	0.69 (0.65 to 0.73)	<0.001	98.28
Control			
Peak CO	0.79 (0.76 to 0.81)	<0.001	166.14
Peak C(a-v)O_2	0.62 (0.60 to 0.65)	<0.001	150.04

P value for interaction analysis of slope difference: <0.001. 95% CI, 95% confidence interval.

Uremic milieu was shown to cause skeletal muscle abnormalities such as reduced capillary density,[22] fiber atrophy,[23] impaired substrate utilization,[24] impaired O_2 conductance between capillary and muscle mitochondria,[25] and impaired muscle mitochondrial energetics.[26] Thus uremic myopathy has the potential to limit aerobic exercise capacity in CKD[27] by limiting diffusive O_2 transport. This study offers an experimental model to test the differential roles of such convective and diffusive transport in CKD.

Previous studies on the determinants of exercise capacity in CKD and ESKD had shown the effects of age, BMI, hemoglobin, and comorbidities.[2,28] Our previous study had shown the association between exercise capacity and novel risk factors, such as uremic toxins.[29] But no study has hitherto explored exercise physiology in CKD in depth and demonstrated the role of central and peripheral determinants of exercise capacity. Studies in patients with HF had achieved this by using cardiac imaging techniques in the immediate post-peak exercise period.[30,31] We used a specialized CPX test with ability to measure both VO_2 and CO simultaneously, right at peak exercise for the first time in CKD, enabling us to gain deeper insights into exercise physiology in CKD.

Implications and Future Directions

The study has shown that, unlike in HF where cardiac dysfunction is the major determinant of exercise capacity, in CKD the peripheral factors play a more significant role. Therefore, the measures of exercise capacity such as VO_{2peak} should not be misinterpreted as measures of cardiac performance or cardiac reserve *per se* in CKD.[32] We therefore recommend direct measurement of cardiac hemodynamics in CKD if evaluation of peak cardiac performance is required in a clinical or a research setting.

There is growing interest in CPX as diagnostic tool in pretransplant cardiac assessment in CKD.[33] But one must be mindfulthat standard CPX-derived measures such as VO_{2peak} or anaerobic threshold (AT) may not be good markers of cardiovascular fitness in CKD. CKD-specific studies may be required in the future to evaluate the application of CPX parameters in preoperative assessment, because anemia and skeletal myopathy would be strong confounders in the assessment of cardiovascular fitness for surgery using CPX.

VO_{2peak} in CKD is a composite measure of physical functional reserve that incorporates elements of cardiovascular function, skeletal muscle size and function, hemoglobin level, and potentially other uremic factors that are not yet identified. Hence, therapeutic strategies to improve exercise capacity in CKD may need a multipronged approach that includes aerobic training, resistance training, anemia correction, and nutritional support.

Strengths and Limitations

Instead of relying on control data and regression equations from studies from a different population, our comparator groups (HC and HF) were drawn from the same population as our patients with CKD. Our unit has extensive experience

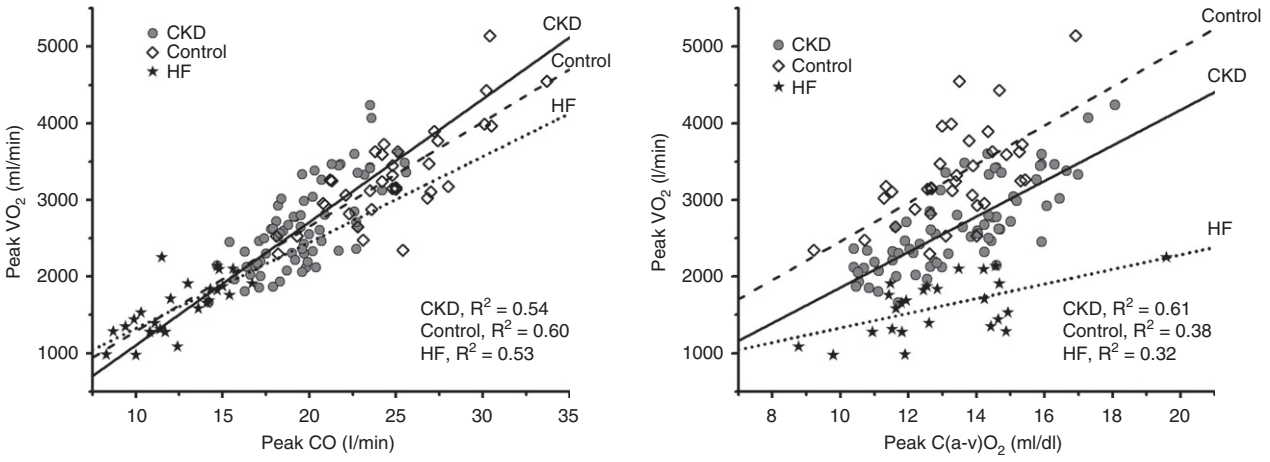

Figure 3. Association between exercise capacity and its central and peripheral determinants in CKD, control, and patients with HF. The graphs show the relationship of peak CO and peak C(a-v)O_2 with VO_{2peak}. The peripheral factor, C(a-v)O_2 shows stronger association with exercise capacity in CKD compared with control and HF.

of over two decades in noninvasive CO measurement using a CO_2 rebreathing technique,[8,9] and all our study participants underwent CPX studies using the same standardized protocol. Another significant strength of the study is comparison of CKD with a positive control group (HF) to bear out the distinction between impaired exercise capacity due to predominantly cardiac factors and impairment due to combination of peripheral and central factors. The study protocolwith strict exclusion criteria is also a strength that helped minimize confounders that may affect exercise capacity other than CKD such as diabetes mellitus , cardiovascular disease , respiratory disorders, etc.

We used treadmill exercise instead of bicycle ergometry because treadmill studies are shown to achieve higher VO_{2peak},[34] enhancing the probability of discrimination between health and disease states. Furthermore, treadmill exercise was a more familiar form of exercise in our cohort, minimizing the number of dropouts. We acknowledge the tradeoff was the absence of data on work rate in a treadmill test, which a bicycle ergometry test automatically generates. We limited the study to one sex because VO_2 and hemodynamic parameters have different peak values in men and women,[5] and the two groups cannot be compared. We acknowledge the limitation of the CO_2 rebreathing method is that it does not allow multiple measurements of CO during the CPX study, and hence CO measurements at submaximal exercise were not performed. Because the focus of this study was peak exercise parameters, this limitation had little effect on our study results. Nevertheless, we acknowledge that future studies with multiple measurements of CO at different stages of CPX may help understand the trends in CO increment during exercise. Finally, we did not measure C(a-v)O_2 directly. Instead, we calculated C(a-v)O_2 from Fick's equation using measured values of VO_2 and CO. This is unlikely to have any effect on the study results because calculated C(a-v)O_2 from noninvasive CO measurements and directly measured C(a-v)O_2 values using blood gas analysis are shown to have good agreement.[35] More importantly, our technique obviated the need for invasive blood tests, and significantly minimized the discomfort for our participants.

Table 8. Independent contribution of peak SV and peak HR in determining peak CO in CKD, HF, and HC

Parameter	Standardized Coefficient β (95% CI)	*P* Value	BIC Reduction
CKD			
Peak SV	1.18 (1.13 to 1.23)	<0.001	234.53
Peak HR	1.07 (1.02 to 1.13)	<0.001	221.98
HF			
Peak SV	1.38 (1.11 to 1.65)	<0.001	42.18
Peak HR	1.11 (0.84 to 1.38)	<0.001	33.26
Control			
Peak SV	1.05 (1.02 to 1.08)	<0.001	180.58
Peak HR	0.57 (0.54 to 0.60)	<0.001	138.05

P value for interaction analysis of slope difference: <0.001. 95% CI, 95% confidence interval.

In conclusion, exercise capacity in CKD is impaired even in the absence of any known cardiac diseases or diabetes. Although both central cardiac factors and peripheral skeletal muscle factors are important determinants of exercise capacity, the latter was shown to be a more significant determinant in CKD. This is in stark contrast to patients with HF and HCs, in whom cardiac factors are the major predictors of exercise capacity. These results have significant implications in the interpretation and application of CPX parameters in diagnostics and therapeutics in CKD.

DISCLOSURES

A. Mooney reports receiving honoraria from AstraZeneca, Napp pharmaceuticals, and Novartis; and has other interests/relationships as Treasurer and Trustee of British Renal Society. All remaining authors have nothing to disclose.

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S. Chinnappa and A. Mooney designed the study and were responsible for data analysis and manuscript preparation; M.-C. Shih and Y.-K. Tu were responsible for statistical analyses; O. Baldo, S. Chinnappa, N. Lewis, and A. Mooney conducted the study and were responsible for the manuscript revision.

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