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The Interpretation of Standard Cardiopulmonary Exercise Test Indices of Cardiac Function in Chronic Kidney Disease

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Abstract: Background and Aims: As there is growing interest in the application of cardiopulmonary exercise test (CPX) in chronic kidney disease (CKD), it is important to understand the utility of conventional exercise test parameters in quantifying the cardiopulmonary fitness of patients with CKD. Merely extrapolating information from heart failure (HF) patients would not suffice. In the present study, we evaluated the utility of CPX parameters such as the peak O_2-pulse and the estimated stroke volume (SV) in assessing the peak SV by comparing with the actual measured values. Furthermore, we compared the anaerobic threshold (AT), peak circulatory power, and ventilatory power with that of the measured values of the peak cardiac power (CPO_{peak}) in representing the cardiac functional reserve in CKD. We also performed such analyses in patients with HF for comparison. Method: A cross sectional study of 70 asymptomatic male CKD patients [CKD stages 2–5 (pre-dialysis)] without primary cardiac disease or diabetes mellitus and 25 HF patients. A specialized CPX with a CO_2 rebreathing technique was utilized to measure the peak cardiac output and peak cardiac power output. The peak O_2 consumption (VO_{2peak}) and AT were also measured during the test. Parameters such as the O_2-pulse, stroke volume, arteriovenous difference in O_2 concentration [$C(a\text{-}v)O_2$], peak circulatory power, and peak ventilatory power were all calculated. Pearson's correlation, univariate, and multivariate analyses were applied. Results: Whereas there was a strong correlation between the peak O_2-pulse and measured peak SV in HF, the correlation was less robust in CKD. Similarly, the correlation between the estimated SV and the measured SV was less robust in CKD compared to HF. The AT only showed a modest correlation with the CPO_{peak} in HF and only a weak correlation in CKD. A stronger correlation was demonstrated between the peak circulatory power and CPO_{peak}, and the ventilatory power and CPO_{peak}. In HF, the central cardiac factor was the predominant determinant of the standard CPX-derived surrogate indices of cardiac performance. By contrast, in CKD both central and peripheral factors played an equally important role, making such indices less reliable markers of cardiac performance per se in CKD. Conclusion: The results highlight that the standard CPX-derived surrogate markers of cardiac performance may be less reliable in CKD, and that further prospective studies comparing such surrogate markers with directly measured cardiac hemodynamics are required before adopting such markers into clinical practice or research in CKD.

Keywords: chronic kidney disease; cardiopulmonary exercise test; heart failure; oxygen pulse; anaerobic threshold

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1. Introduction

There has been a significant revival in the application of physical exercise as a diagnostic tool and as therapy per se in chronic kidney disease (CKD) and end stage renal disease. The diagnostic application includes assessment of cardiovascular fitness and risk

stratification before renal transplant surgery, and the therapeutic application takes the form of exercise training [1,2]. All these applications require objective measures of exercise capacity and a clear understanding of the scope and limitations of these measures. The gold standard technique to measure exercise capacity is a cardiopulmonary exercise test (CPX). However, there are very few studies evaluating the utility of CPX-derived indices of cardiovascular fitness in CKD.

The crux of CPX testing is the Fick's equation [$VO_2 = SV \times HR \times C(a\text{-}v)O_2$], where VO_2 is the O_2 consumption, SV is stroke volume, HR is heart rate, and $C(a\text{-}v)O_2$ is arteriovenous difference in the O_2 concentration. Of the variables in the Fick's equation, in a standard CPX only VO_2 and HR are measured at peak exercise. Stroke volume and $C(a\text{-}v)O_2$ are not measured. Peak O_2 consumption (VO_{2peak}) or maximal aerobic capacity is widely used as a marker of cardiovascular fitness in the general population and in patients with heart failure (HF). Along with VO_{2peak}, the indices O_2-pulse (VO_2/HR), a surrogate of SV, and VO_2 at the anaerobic threshold (AT), are also widely used as surrogate markers of cardiovascular fitness. An important assumption in these applications is that impaired cardiac function is the predominant determinant of impaired exercise capacity. In the above applications, $C(a\text{-}v)O_2$ is assumed to be a constant.

However, our recently published work demonstrated that peripheral non-cardiac factors are the major determinants of exercise capacity in CKD [3]. This contrasts with heart failure where, not surprisingly, central cardiac factors are the predominant determinants of exercise capacity. Exploration of the determinants of exercise capacity was made possible by the novel techniques of measuring non-invasive cardiac output (NICO) during CPX in addition to measuring VO_2 [4–6]. This simultaneous measurement of cardiac output and VO_2 enables computation of $C(a\text{-}v)O_2$ using the Fick's equation. This in turn enables a thorough evaluation of the various determinants of exercise capacity.

In the present study, we evaluated the utility of standard CPX-derived surrogate indices of cardiac performance by comparing with the actual measured values. In addition to testing patients with CKD, we also performed such analyses in patients with heart failure to bear out the distinction between the performance of these surrogate indices in two different settings: one where the cardiac factors are the predominant determinants of exercise capacity (i.e., HF), and the other where the peripheral factors play a major role (i.e., CKD). The surrogate indices evaluated in the study includes the peak O_2-pulse, estimated peak SV and AT. In addition, we also evaluated surrogate indices of the peak cardiac performance and cardiac functional reserve such as the peak circulatory power and the peak ventilatory power with that of the measured parameter, the peak cardiac power (CPO_{peak}) [6].

2. Methods

2.1. Study Subjects

In this cross-sectional study of adult patients, 70 asymptomatic male CKD patients [stages 2–5 (pre-dialysis)] and 25 age-matched male HF patients (NYHA Class II and III) were recruited from a tertiary UK center. Exclusion criteria for the CKD patients comprised 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, neurological, or other non-renal medical disorders.

2.2. Study Investigations

Blood test: Venous blood samples were taken at the time of recruitment to assay serum creatinine, urea, and hemoglobin. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable modification of diet in renal disease MDRD formula [7].

Cardiopulmonary exercise test (CPX): The patients underwent a specialized CPX on a treadmill to measure the VO_{2peak} and peak cardiac output (CO) simultaneously, and compute $C(a\text{-}v)O_2$ using the Fick's equation. The peak cardiac output was measured

non-invasively using CO_2 rebreathing method (Medgraphics Corp., St. Paul, MN, USA) according to previously described methodology [3]. The peak O_2 consumption and peak cardiac output were determined non-invasively during maximal cardiopulmonary exercise (CPX) testing.

- Resting measures: The O_2 consumption, CO_2 production, respiratory rate, and cardiac output at rest were measured 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 [8,9]. The Collier's equilibration method has been shown to have good correlation with thermodilution techniques at rest [10] and is easy to use, and therefore it was utilized for resting measurements.
- 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 HF patients). The speed and incline of the treadmill were increased every three 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 [11]. A 12-lead ECG was monitored throughout, and the subject's heart rate (HR) was obtained from this. Blood pressure was measured at every stage of the CPX test.
- Determination of peak cardiac output: A second treadmill test was performed after a rest period of at least 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 cardiac output measurements were made using the Defare's CO_2 rebreathing method [12]. The Defare's method was chosen because this method has been shown to correlate well with cardiac output obtained with thermodilution techniques during exercise [13]. The formulae used in the study are listed in Table 1. The blood pressure was measured using a sphygmomanometer after each determination of cardiac output.

Table 1. List of formulae used in the study.

Parameter	Formula
VO_2 (L/min)	$CO \times C(a\text{-}v)O_2$
$C(a\text{-}v)O_2$ (mL/dL)	VO_2/CO
O_2 pulse (mL/beat)	VO_2/HR
Estimated SV [14] (mL/beat)	$\frac{O_2 Pulse}{Hb \times 1.34 \times O_2 extraction(\%)}$
MAP (mmHg)	MAP = DBP + 0.412 (SBP − DBP)
CPO (W)	$CO \times MAP \times 2.22 \times 10^{-3}$
Peak Circulatory Power (mmHg L min^{-1})	$MAP \times VO_{2peak}$
Peak Ventilatory Power (mmHg)	$\frac{Peak\ SBP}{Ventilatory\ efficiency\ slope}$
Ventilatory efficiency slope	V_E/VCO_2
eLBM	(0.407 × Weight) + (0.267 × Height) − 19.2

VO_2: O_2 consumption, $C(a\text{-}v)O_2$: arteriovenous O_2 difference, HR: heart rate, Hb: hemoglobin, MAP: mean arterial pressure, DBP: diastolic blood pressure, SBP: systolic blood pressure, CO: cardiac output, CPO: cardiac power output, V_E: minute ventilation, VCO_2: CO_2 production, LBM: estimated lean body mass (Boer's formula).

2.3. Statistical Analysis

Independent sample *t*-test was utilized to compare anthropometrics, biochemistry, and CPX parameters between CKD and HF patients. Pearson's correlation was used to

evaluate the association between the surrogate indices and the measured values of peak cardiac performance. Univariate and multivariate regression was used to evaluate the determinants of surrogate indices of cardiac performance. Bland–Altman analysis was utilized to evaluate the agreement between the estimated and measured stroke volume. Normality of data was verified using normal Q-Q plots and numerical methods (Shapiro—Wilk test). All data were normally distributed. SPSS 25 (IBM, Armonk, NY, USA) statistics software was used in the analysis. A p-value of <0.05 was considered significant. Results are presented as mean ± SD.

3. Results

3.1. Patient Characteristics

The mean age of CKD and HF patients were 48.4 ± 12.6 and 49.4 ± 14.6 years respectively. The CKD patients included the spectrum of CKD from stages 2 to 5 (pre-dialysis). There were 21 patients with CKD stages 2–3a, 27 patients with CKD stages 3b–4, and 22 patients with CKD stage 5. The CKD cohort had a wide range of eGFR (6 mL/min to 88.5 mL/min) and hemoglobin (9.3 g/dL to 16.7 g/dL) ensuring that correlation and linear regression analyses were not limited by range restriction. All participants performed exercise to volitional exhaustion. The CKD and HF patients had a mean respiratory exchange ratio of 1.16 ± 0.09 and 1.10 ± 0.29, a peak VO_2 of 2.66 ± 0.57 and 1.61 ± 0.37 L/min, and an AT of 1.81 ± 0.47 and 1.11 ± 0.35 L/min, respectively. Patient characteristics are presented in Table 2.

Table 2. Patient Characteristics.

	CKD (n = 70)	HF (n = 25)	p-Value
Age (year)	48.4 ± 12.6	49.4 ± 14.6	NS
BMI (kg/m^2)	27.8 ± 3.9	25.1 ± 3.2	<0.05
Hb (g/dL)	13.3 ± 1.8	14.4 ± 1.1	<0.05
eGFR (mL/min)	33.9 ± 23.5	69.3 ± 16.9	<0.05
Peak RER	1.16 ± 0.09	1.10 ± 0.29	NS
VO_{2peak} (L/min)	2.66 ± 0.57	1.61 ± 0.37	<0.05
AT (L/min)	1.81 ± 0.47	1.11 ± 0.35	<0.05
AT (mL/min/kg)	21.23 ± 5.18	14.61 ± 4.37	<0.05
Peak CO (L/min)	19.7 ± 2.6	12.5 ± 2.4	<0.05
Peak C(a-v)O_2 (mL/dL)	13.4 ± 1.9	12.9 ± 2.2	NS
Peak HR (beats/min)	153.4 ± 19.9	126.9 ± 30.8	<0.05
Peak SV (mL/beat)	129.9 ± 20.7	105.1 ± 37.0	<0.05
Peak O_2 pulse (mL/beat)	17.48 ± 3.62	13.35 ± 4.54	<0.05
Peak Circ pwr (mmHg L min^{-1})	277.9 ± 68.4	135.9 ± 47.9	<0.05
Ventilatory Power	5.36 ± 1.13	3.20 ± 1.21	<0.05
Peak CPO (W)	4.54 ± 0.77	2.34 ± 0.63	<0.05

BMI: body mass index, Hb: hemoglobin, eGFR: estimated glomerular filtration rate, RER: respiratory exchange ratio, VO_2: oxygen consumption, AT: anaerobic threshold, CO: cardiac output, C(a-v)O_2: peripheral O_2 extraction, HR: heart rate, SV: stroke volume, Circ pwr: circulatory power, CPO: cardiac power output. P-value is for independent sample t-test.

3.2. Association between the Peak SV and Peak O_2-Pulse

The association between the measured peak SV and the peak O_2-pulse in CKD compared to HF is shown in Figure 1.

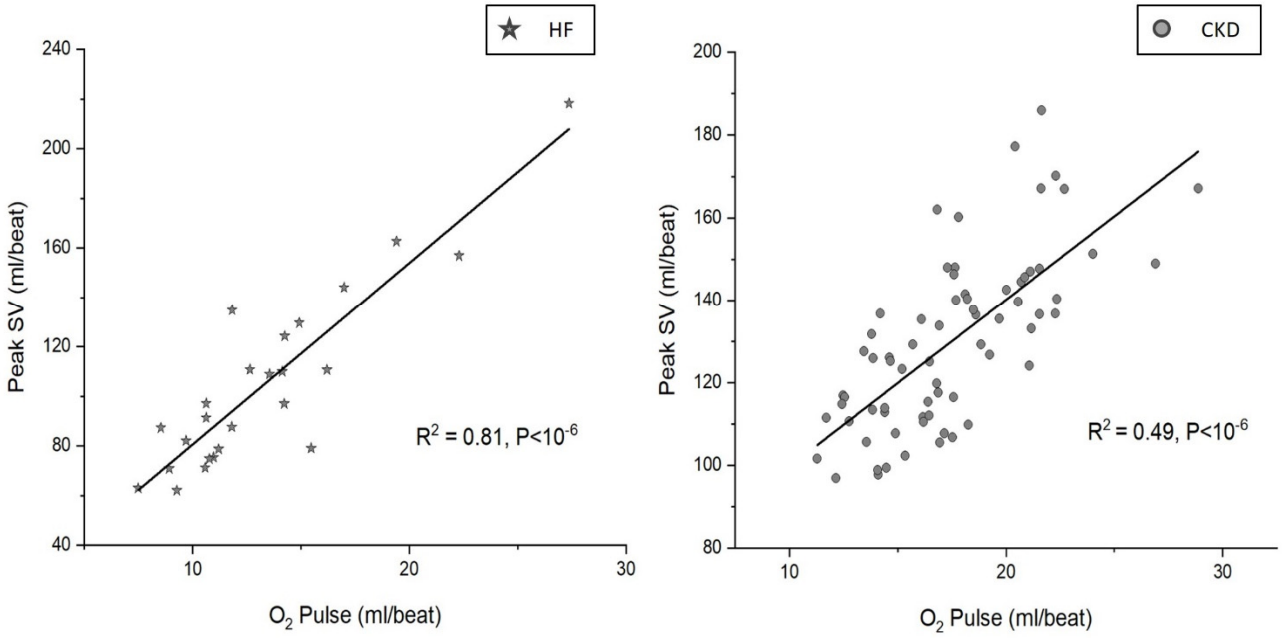

Figure 1. Association between peak O_2 pulse and measured peak stroke volume in heart failure and chronic kidney disease. Peak O_2 pulse shows a stronger association with peak SV in HF compared to CKD. SV: stroke volume, HF: heart failure, CKD: chronic kidney disease.

In HF, there was a stronger association between the measured peak SV and the peak O_2-pulse ($R^2 = 0.81$, $p < 10^{-6}$) compared to CKD ($R^2 = 0.49$, $p < 10^{-6}$). Multiple regression analysis showed that in HF, SV ($\beta = 1.03$, $p < 10^{-3}$) was the predominant determinant of O_2-pulse, and C(a-v)O_2 ($\beta = 0.44$, $p < 10^{-3}$) played a less significant role. However, in CKD both SV ($\beta = 0.78$, $p < 10^{-3}$) and C(a-v)O_2 ($\beta = 0.70$, $p < 10^{-3}$) were significant determinants of O_2-pulse.

3.3. Association between the Estimated and Measured Peak SV

The association between the estimated and measured peak SV in CKD was weaker ($R^2 = 0.34$, $p < 10^{-6}$) compared to that of HF ($R^2 = 0.84$, $p < 10^{-6}$) (Figure 2A). The Bland–Altman plot (Figure 2B) illustrates the agreement between the estimated and measured peak SV. The plot for the CKD group shows that, on average, the SV was overestimated [average bias = 7.64 mL (95% CI 2.50~12.79 units), $p = 0.004$].

The estimated boundaries for 95% of the differences between the estimated SV and the measured SV were 49.94 ml (95% CI 41.10–58.78) and −34.66 mL (95% CI −43.49–−25.82). The wide boundaries indicate that the estimated SV can be very imprecise and should be interpreted with caution. The regression slope was positive and statistically significant [slope = 0.26, (95% CI 0.01–0.51), $p = 0.038$], which implied that the positive bias of the estimated SV increased with the true SV. For the HF group, the SV was underestimated on average [average bias = −7.47 units (95% CI −13.61–−1.32 units), $p = 0.017$]. The estimated boundaries for 95% of the differences were 21.70 units (95% CI 11.06–32.34 units) and −36.63 units (95% CI −47.27–−25.99 units). While the boundaries were still wide, the standard deviation in the HF group was significantly smaller than in the CKD group ($p = 0.044$). The regression slope was not statistically significant [slope = 0.011 (95% CI −0.19–0.17), $p = 0.90$].

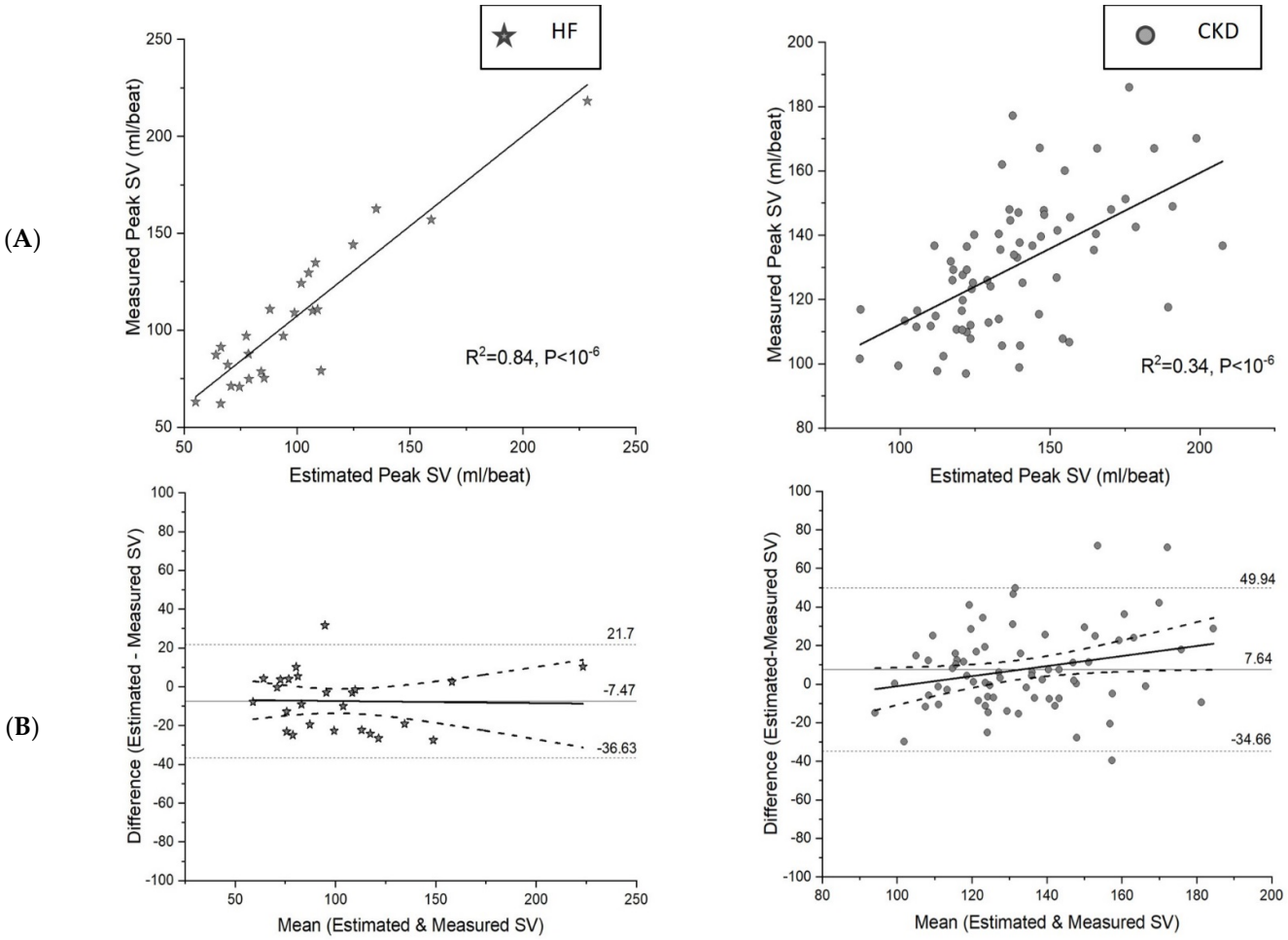

Figure 2. Association between estimated stroke volume and measured peak stroke volume in heart failure and chronic kidney disease. Estimated peak SV shows a stronger association with measured peak stroke volume in HF compared to CKD (**A**). The Bland–Altman plot shows wider limits of agreement in CKD with a statistically significant regression slope implying that estimated SV measurements can be imprecise in CKD (**B**). SV: stroke volume, HF: heart failure, CKD: chronic kidney disease.

3.4. Association between the AT and Peak Cardiac Power (CPO_{peak})

The AT had only a modest association with the CPO_{peak} ($R^2 = 0.19$, $p < 0.05$) in CKD compared to HF ($R^2 = 0.40$, $p < 0.05$) (Figure 3).

The AT indexed to body weight had only a weak association with the CPO_{peak} ($R^2 = 0.098$, $p = 0.01$) compared to HF ($R^2 = 0.31$, $p = 0.007$). The AT expressed as a % of the VO_{2peak} did not have any correlation with the CPO_{peak} in CKD or HF. The independent predictors of the AT in CKD were hemoglobin concentration ($\beta = 0.45$, $p < 10^{-3}$), estimated lean body mass ($\beta = 0.33$, $p < 10^{-3}$), and age ($\beta = -0.33$, $p < 10^{-3}$) together accounting for >50% variability in the AT ($R^2 = 0.53$, $p < 10^{-6}$).

3.5. Association between the Peak Circulatory Power, Peak Ventilatory Power, and Peak Cardiac Power in CKD

The peak circulatory power showed a strong association with the CPO_{peak} in both CKD ($R^2 = 0.54$, $p < 0.01$) and HF patients ($R^2 = 0.59$, $p < 0.01$) (Figure 4).

The peak ventilatory power also showed good association with the CPO_{peak} in CKD ($R^2 = 0.41$, $p < 0.01$) and HF ($R^2 = 0.30$, $p < 0.01$).

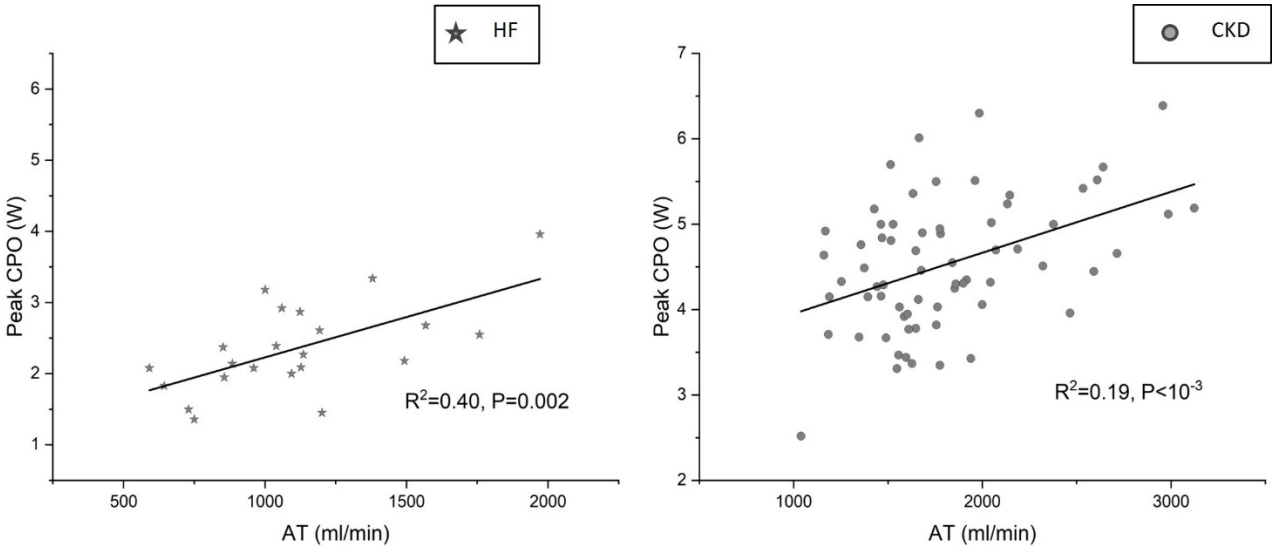

Figure 3. Association between anaerobic threshold and peak cardiac power in heart failure and chronic kidney disease. AT shows only a modest association with CPO_{peak} in CKD compared to HF. HF: heart failure, CKD: chronic kidney disease, AT: anaerobic threshold, CPO: cardiac power output.

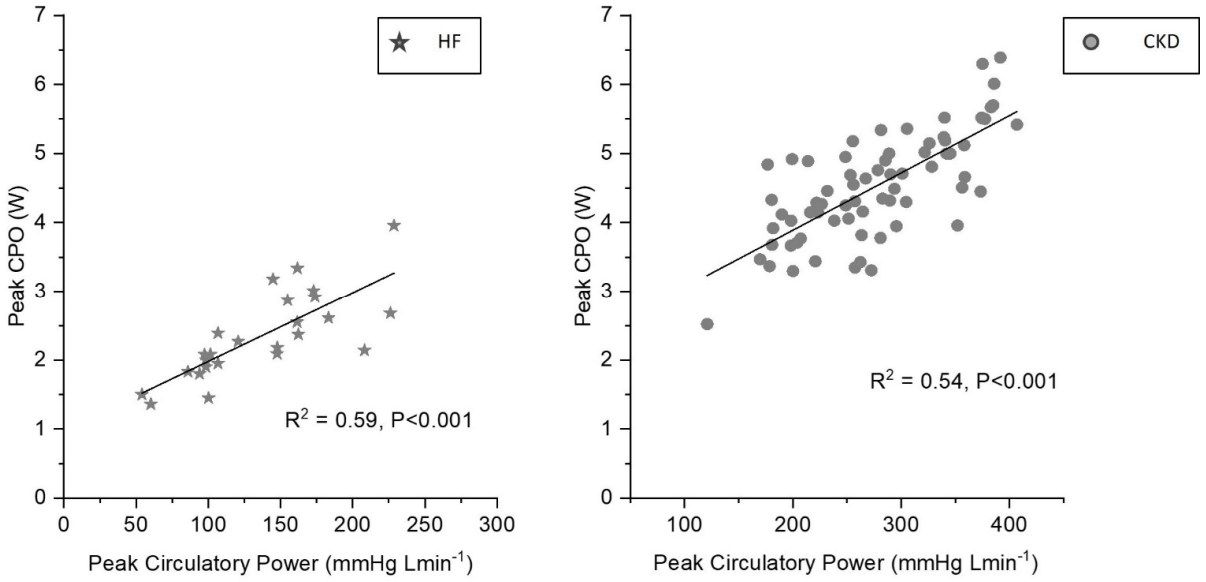

Figure 4. Association between peak circulatory power and peak cardiac power in heart failure and chronic kidney disease. Peak circulatory power shows a strong association with peak cardiac power in both HF and CKD. HF: heart failure, CKD: chronic kidney disease, CPO: cardiac power output.

4. Discussion

The study for the first time compared the utility of the CPX-derived surrogate markers of peak cardiac performance with the actual measured values in CKD and showed that such surrogate markers may be less reliable in CKD. There was a clear distinction between the performance of these surrogate markers in HF and in CKD.

The peak O_2-pulse is a widely used surrogate marker of the peak SV in HF [15–17]. As the central cardiac factor is the predominant determinant of the VO_{2peak} in HF, the peak O_2-pulse performs as a reliable indicator of the peak SV. This has in turn led to the formulation of the estimation equation of the peak SV using the peak O_2-pulse in HF [18]. Our study results support such application in HF too. In our study, more than an 80% variation in the measured peak SV could be predicted by the peak O_2-pulse and the estimated peak SV in

HF. On the contrary, in CKD, as peripheral factors also play a significant role in determining exercise capacity, only 50% of the variation in the measured SV was predicted by the peak O_2-pulse. Furthermore, only 34% of the variation in the measured SV was predicted by the estimated SV, making the parameters less reliable in CKD. The Bland–Altman plot reinforces this finding by demonstrating that the agreement between the estimated SV (derived from O_2 pulse) and the measured SV is weaker in CKD compared to HF.

The AT marks the point in incremental exercise where O_2 demand exceeds O_2 supply and the skeletal muscle switches to anaerobic respiration to generate ATP. The O_2 supply depends on the O_2 carrying capacity of the blood and the cardiac output. Furthermore, the skeletal muscle properties such as the muscle mass, its vascularization, mitochondrial function, etc., would determine the O_2 utilization and thereby the AT. In CKD, the O_2 carrying capacity is impaired due to impaired cardiac function secondary to uremic cardiomyopathy [19–21] and uremic vasculopathy [22,23], and due to the impaired O_2 carrying capacity of the blood secondary to anemia [24–26]. In addition, the O_2 utilization is impaired due to the reduced capillary density of the skeletal muscles, sarcopenia, and mitochondrial dysfunction, collectively called as uremic skeletal myopathy [27–29]. It is therefore not surprising that, in CKD, the AT showed only a weak correlation with the peak cardiac power output, an objective measure of the peak cardiac performance and the cardiac functional reserve [30,31]. It is also pertinent to note that the hemoglobin level, estimated lean body mass, and age were the independent predictors of the AT in CKD accounting for >50% variability of the AT.

The AT is widely used as a marker of cardiovascular fitness for surgery in the general population. In CKD, there is growing desire to apply the AT in the assessment of cardiovascular fitness prior to renal transplant surgery [32]. Furthermore, the AT is also being considered as a marker of the peak cardiac performance and cardiac functional reserve in CKD. However, our study showed that the AT may not be a reliable indicator of the cardiac functional reserve in CKD. The results of the study highlight that one must be mindful of the fact several non-cardiac factors play a significant role as the determinants of such surrogate markers of cardiac performance in CKD. Therefore, CKD-specific studies may be required in the future to evaluate the application of the AT in the assessment of cardiovascular fitness for renal transplantation or other surgeries in patients with CKD.

The peak circulatory power and peak ventilatory power are relatively novel indices of the cardiac functional reserve calculated from standard CPX parameters such as the peak blood pressure, VO_{2peak} and ventilatory efficiency slope (V_E/VCO_2 slope). Such indices are shown to predict survival in patients with heart failure [33,34]. Our study showed that such surrogate indices demonstrated better correlation with CPO_{peak} than the AT. Further prospective studies are required to evaluate the application of such surrogate indices of the cardiac functional reserve in CKD.

The study has several strengths. A significant strength of the study is the use of HF patients as a positive control to highlight the distinction between the impaired exercise capacity due to predominantly cardiac factors and impairment due to multifactorial etiology as in CKD. Our unit has extensive experience of nearly three decades in the measurement of non-invasive cardiac output using the CO_2 rebreathing technique [6,30], and all our study participants underwent CPX studies using the same standardized protocol. The study protocol with strict exclusion criteria is also a strength that helped minimize confounders that may affect exercise capacity other than CKD such as diabetes mellitus, cardiovascular diseases, respiratory disorders, etc. A limitation of the study is that we did not measure $C(a\text{-}v)O_2$ directly. However, this is unlikely to have any impact on the study results as the calculated $C(a\text{-}v)O_2$ from non-invasive cardiac output measurements and the directly measured $C(a\text{-}v)O_2$ values using blood gas analysis were shown to have good agreement [4]. The assessments were limited to one gender to minimize confounders that arise because of gender and body composition on central hemodynamics and aerobic exercise capacity [5,24]. We employed treadmill exercise instead of bicycle ergometry because treadmill studies are shown to achieve higher VO_{2peak} [35] 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.

In conclusion, the standard CPX-derived surrogate markers of cardiac performance may be less reliable in CKD, and further prospective studies comparing such surrogate markers with the directly measured cardiac hemodynamics are required before adopting such markers into clinical practice or research in CKD.

Author Contributions: S.C. and A.M.'s contribution includes design and conduct of the study, data analysis, manuscript preparation, and revision. Y.-K.T. and M.-C.S. performed the statistical analyses. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was approved by the South Yorkshire Research Ethics Committee ([Ref: 11/H1310/8], Date 1 November 2011). These clinical investigations conformed with the Declaration of Helsinki.

Informed Consent Statement: All subjects provided informed written consent before participation.

Data Availability Statement: Data are contained within the article.

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Conflicts of Interest: The authors do not have any conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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