Assessment of Exercise Intolerance in Patients with Pre-Dialysis CKD with Cardiopulmonary Function Testing: Translation to Everyday Practice

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Keywords

Cardiopulmonary exercise testing · Chronic kidney disease · Exercise intolerance · Cardiovascular reserve · VO₂peak · VO₂max

Abstract

Background: Chronic kidney disease (CKD) is often characterized by increased prevalence of cardiovascular risk factors and increased incidence of cardiovascular events and death. Reduced cardiovascular reserve and exercise intolerance are common in patients with CKD and are associated with adverse outcomes. **Summary:** The gold standard for identifying exercise limitation is cardiopulmonary exercise testing (CPET). CPET provides an integrative evaluation of cardiovascular, pulmonary, hematopoietic, neuropsychological, and metabolic function during maximal or submaximal exercise. It is useful in clinical setting for differentiation of the causes of exercise intolerance, risk stratification, and assessment of response to relevant treatments. A number of recent studies have used CPET in patients with pre-dialysis CKD, aiming to assess the cardiovascular reserve of these individuals, as well as the effect of interventions such as exercise training programs on their functional capacity. This review provides an

in-depth description of CPET methodology and an overview of studies that utilized CPET technology to assess cardiovascular reserve in patients with pre-dialysis CKD. **Key Messages:** CPET can delineate multisystem changes and offer comprehensive phenotyping of factors determining overall cardiovascular risk. Potential clinical applications of CPET in CKD patients range from objective diagnosis of exercise intolerance to preoperative and long-term risk stratification and providing intermediate endpoints for clinical trials. Future studies should delineate the association of CPET indexes, with cardiovascular and respiratory alterations and hard outcomes in CKD patients, to enhance its diagnostic and prognostic utility in this population. © 2021 S. Karger AG, Basel

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem, with increasing incidence and prevalence, high costs, and poor outcomes [1]. It is currently estimated that more than 850 million individuals worldwide have kidney diseases [2], while the prevalence of CKD is estimated at about 9% of the world population,

increasing to 12% in several Western countries [3]. As a result, CKD currently lists among the fastest growing global causes of death and is projected to become the fifth global cause of death by 2040 [4]. Several epidemiological studies have shown that patients with CKD are at increased risk for cardiovascular events and all-cause mortality, while elevated levels of urine albumin excretion (i.e., moderately or severely increased albuminuria) are also associated with an increased risk of cardiovascular events, as well as a faster progression of CKD [5, 6]. Classical cardiovascular risk factors (including age, hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking), as well as nonclassical risk factors relevant to CKD and the uremic environment per se (i.e., anemia, disturbed metabolism of calcium and phosphate, and others) are highly prevalent in patients with CKD and also contribute to the risk of developing cardiovascular disease [7–9]. Therefore, cardiovascular complications are the principal cause of death in patients with CKD [10].

Cardiorespiratory fitness reflects the ability of the cardiovascular and respiratory systems to transport oxygen to the working muscles of the human body during physical activity. Impaired cardiorespiratory fitness is strongly associated with early all-cause and cardiovascular-related mortality [11, 12]. Patients with CKD have lower cardiorespiratory fitness than the general population; this occurs early in the disease process, declines further with renal function drop, and is also associated with increased aortic stiffness, poor left ventricular function, and higher risk of cardiovascular events [12–14]. Thus, exercise intolerance, a prognostic factor of morbidity and mortality, is inherently associated with CKD [15–17]. The ability of these patients to exercise can be related to a number of factors, including cardiac function disturbances, endothelial dysfunction, arterial stiffness, morphological and functional abnormalities of skeletal muscles, dysautonomia of nervous system, anemia, depression, and others. The above-mentioned causes lead these patients to inactivity, diminished functional capacity, feeling of fatigue, social isolation, and finally, low quality of life [18, 19].

Cardiopulmonary exercise testing (CPET) is a dynamic, noninvasive technique that is useful in various clinical settings for diagnosis, risk stratification, and the evaluation of response to cardiopulmonary therapies [20]. It is long considered to be the gold standard for evaluating the degree and differentiating the causes, by unmasking physiological mechanisms of exercise intolerance [21, 22]. A number of observational studies and randomized trials have applied CPET technology to evaluate cardiopulmonary reserve in patients with pre-dialysis CKD and

end-stage kidney disease. In this review, we attempt to provide an in-depth description of CPET methodology and the underlying exercise physiology, its key findings depending on the underlying cause and pathophysiology of exercise limitation, as well as an overview of studies that utilized CPET technology to assess cardiovascular reserve in patients with pre-dialysis CKD, that is, a population of patients that is highly prevalent, but rather poorly characterized in terms of exercise physiology.

Cardiopulmonary Exercise Testing

CPET provides an integrative assessment of the cardiovascular, pulmonary, muscular, and neuropsychological responses during exercise; this allows the assessment of the physiological reserves of these systems that are not adequately reflected through the measurement of individual organ system at rest [22, 23]. CPET should be considered the gold standard for evaluating the causes of exercise intolerance, especially in patients with cardiovascular or respiratory disorders, and is based on the principle that system failure typically occurs while the system (e.g., muscle-energetic, cardiovascular, or pulmonary) is under stress [21]. This noninvasive, dynamic test permits the evaluation of both submaximal and peak exercise responses, providing the physician with relevant information for clinical decision-making [24]. CPET is being used increasingly in a wide spectrum of clinical applications for evaluation of undiagnosed exercise intolerance and for objective determination of functional capacity and impairment [23, 24].

During CPET, a vast number of “routine” exercise testing variables and more sophisticated cardiorespiratory parameters are continuously (breath-by-breath) measured or estimated; this volume of physiological data obtained is necessary in order to assess each organ system response in coupling external respiration (i.e., oxygen uptake (VO_2) and carbon dioxide output at the airways) to cellular respiration (i.e., oxygen consumption and carbon dioxide production), during exercise. Indications of CPET include: (a) evaluation of exercise capacity, (b) evaluation and differential diagnosis of exercise intolerance, (c) evaluation of disability, (d) designing the rehabilitation program and assessing its efficacy, (e) preoperative evaluation, (f) functional and prognostic evaluation of patients with heart diseases, (g) functional and prognostic evaluation of patients with respiratory disorders, and (h) assessing treatment efficacy [25]. Commonly measured variables during CPET are presented in Table 1.

Table 1. Commonly measured CPET variables [28]

Parameter measured (units)	Definition
VO ₂ max (in mL/min or L/min)	The product of the highest CO and arterial and venous O ₂ content difference (A – V) O ₂ , VO ₂ max = COmax × (A – V) O ₂ max
VO ₂ peak (in mL/min or L/min)	The highest value obtained at the end of an exercise test to exhaustion
RER	The ratio of CO ₂ production and O ₂ consumption (VCO ₂ /VO ₂)
VE	The product of RR by the volume of air exhaled at every respiratory cycle (tidal volume, Vt)
Ventilatory equivalents for O ₂ (VE/VO ₂) and CO ₂ (VE/VCO ₂)	The ratio of pulmonary ventilation and O ₂ consumption (VE/VO ₂) or the ratio of pulmonary ventilation and CO ₂ production (VE/VCO ₂)
VE-VCO ₂ slope	The relationship between VE (plotted in the y-axis), and VCO ₂ (plotted in the x-axis)
PETCO ₂ (in mmHg)	The carbon dioxide partial pressure at the end of expiration
AT or VT	It is defined as the point at which minute ventilation increases disproportionately relative to VO ₂
Oxygen pulse (VO ₂ /HR) (in mL of O ₂ /min/bpm)	It is the ratio between VO ₂ and the heart rate
ΔVO ₂ /ΔWR relationship (VO ₂ in mL/min and workload in watts)	It is the relationship between VO ₂ and workload. It is measured during exercise on a cycle ergometer with a ramp protocol
Respiratory reserve (VE/MVV) (both VE, MVV in L/min)	It is the ratio between maximum VE and MVV assessed at rest
IC (L or mL)	It is the maximum amount of air that can be expired after a normal exhalation

CO, cardiac output; CPET, cardiopulmonary exercise testing; VO₂max, maximum oxygen uptake; VO₂peak, peak oxygen uptake; RER, respiratory exchange ratio; IC, inspiratory capacity; AT, anaerobic threshold; VT, ventilatory threshold; PETCO₂, end-tidal CO₂ partial pressure; VE, pulmonary ventilation; VE, ventilation during exercise; MVV, maximum voluntary ventilation; RR, respiratory rate.

Most Commonly Used CPET Indexes

In the following paragraphs, we briefly analyze the most important variables obtained during CPET.

VO₂ and Peak Oxygen Uptake

VO₂ is the volume of O₂ extracted from the air inhaled during pulmonary ventilation in a period of time. It is usually expressed in mL/min or L/min. Historically, the VO₂ plateau demonstrated by a series of high intensity constant work-rate tests was used to define maximum VO₂ (VO₂max), in healthy individuals. However, the flat-tening of the VO₂-work rate relationship is often not seen during incremental exercise tests; thus, VO₂max is defined as the highest VO₂ attainable for a given form of exercise, as evidenced by a failure for VO₂ to further increase, despite a progressive increase in work rate. In practice peak VO₂ (VO₂peak), that is the highest value reached at the end of an exhausting exercise test, is used alternatively to VO₂max, both in healthy individuals and diseased populations [26]. Mean values at intervals of 10–

60 s should be measured depending on the protocol (short-interval means for protocols with short stages and longer interval means for protocols with longer stages) [27, 28]. VO₂peak is considered abnormal when below 85% of the predicted value [29]. VO₂peak has become the “gold standard” laboratory measure of cardiorespiratory fitness and the most important measurement during the functional exercise testing. It has been used as a universal marker, which can reflect disease severity in patients with heart failure, pulmonary hypertension, hypertrophic cardiomyopathy, chronic obstructive pulmonary disease, and restrictive pulmonary disease, in addition to physical fitness level [30].

Anaerobic Threshold

The anaerobic threshold (AT) (Fig. 1), also known as the lactate threshold, lactic acid threshold, or gas exchange threshold, is considered an estimator of the onset of metabolic acidosis caused predominantly by the increased rate of arterial lactate concentration during exercise. The

Fig. 1. Lactic acid levels during exercise testing showcasing the AT. The AT is the level of exercise VO_2 , above which aerobic energy production is supplemented by anaerobic mechanisms, which is reflected by an abrupt increase in the arterial lactic acid concentration. AT, anaerobic threshold.

AT is referenced to the VO_2 at which this change occurs and is expressed as a percentage of the predicted value of $\text{VO}_{2\text{peak}}$ ($\%\text{VO}_{2\text{peak}}$ predicted). From the physiological viewpoint, AT represents the upper limit of workloads during exercise, which can be sustained over a prolonged period of time without progressively increasing arterial blood lactate or as the level of exercise VO_2 above which aerobic energy production is supplemented by anaerobic mechanisms. The normal mean AT values expected for adults are around 40–65% of peak VO_2 [29]. The AT is calculated with the V-slope method; when VCO_2 is plotted against VO_2 , their relationship is composed of 2 linear components, the lower of which has a slope of less than 1 and the upper has a slope steeper than 1. The intercept of these 2 slopes is the AT [26]. The ability to achieve the AT can assist in differentiating cardiac and noncardiac causes of exercise limitation; fatigue before reaching AT is likely related to noncardiac causes [28].

Respiratory Exchange Ratio

It expresses the ratio between CO_2 output and O_2 uptake (VCO_2/VO_2). It is currently the best noninvasive indicator of maximal exercise intensity. Values above 1.0 can reflect intense exercise, but those ≥ 1.10 are those searched on CPET, and have been accepted as a parameter of maximal effort/exhaustion [28, 30].

Methodology

Two modes of exercise are commonly employed in CPET: treadmill and cycle ergometer, with the latter being the preferable one. Although there are many computerized systems for data collection and analysis available for the clinical laboratory, it is important that the methods used be validated, that appropriate calibration be performed, and that quality assurance be undertaken and maintained [24]. To evaluate the metabolic responses to exercise, breath-by-breath analysis techniques are used. Expired gas can be collected and analyzed via a non-rebreathing valve which allows inspired from expired gas flows to be separated and is connected to a mouthpiece or face mask. Moreover, gas analyzers are incorporated to the exercise testing system, allowing the measurement of the fraction of oxygen or carbon dioxide in the total gas [25]. The respired gas volume and flow rates are also computed during exercise, and several methods have been applied. Whereas, expired flow is usually measured and integrated into volume, physiological variables may be also calculated, with the appropriate adjustments, from inspired flow or volume [25]. Continuous 12-lead electrocardiogram (ECG) monitoring, pulse oximetry, and frequent noninvasive blood pressure measurements are required as well, during CPET. Since verbal communication is usually not possible with the mouthpiece apparatus, hand signals are usually used by the patient during exercise [23, 31]. CPET can be performed using incremental or constant work rate protocols, according to the purpose of the test and the functional status of the patient. Importantly, the day of the test the patients are advised to adhere to their regular medication. In CKD patients, hemoglobin (Hgb) level is an issue that should be taken under consideration. Since the oxygen-carrying capacity of the blood depends directly on the level of Hgb, a 3 g/dL decrease in Hgb concentration would result in a reduction of the total oxygen-carrying capacity by 4 mL per 100 mL blood [32]; thus, it is important when serial CPET measurements are evaluated, Hgb levels to be within recommended range.

In general, since the subject is exercising in the laboratory under close monitoring and with resuscitation measures readily available, there are only a few absolute contraindications for the conduction of CPET, even in patients with multiple comorbidities. The most important refer to acute or uncontrolled cardiovascular conditions (e.g., syncope, unstable angina, uncontrolled heart failure, acute myocardial infarction, and acute pulmonary embolism), serious cardiac dysrhythmias on resting ECG or severe respiratory failure (rest oxygen saturation, $\text{sPO}_2 \leq 85\%$). Severe electrolyte abnormalities and uncontrolled

Fig. 2. The oxygen transport chain. The 3 gears represent the functional interdependence between the lungs, circulation, and muscle (modified from Wasserman, 1997 [80]). The determinants of each stage are also displayed.

hypertension at rest (>200 mm Hg systolic, >120 mm Hg diastolic), which may be established among CKD patients are relative contraindications, along with severe pulmonary hypertension and serious valvular disorders. Finally, subjects with orthopedic or neurologic disorders, are also not ideal candidates for CPET [24].

CPET can be combined with invasive hemodynamic assessment, for example, radial or pulmonary arterial catheters in place, but the noninvasive (conventional) one, is the appropriate initial test to evaluate exercise intolerance [33].

Physiology of Exercise and Fick Equation

At rest, the metabolic processes of the human body are met primarily through aerobic metabolism. During activity, an increase in $\dot{V}O_2$ is required to meet the metabolic demand of the working muscle. Initially, increasing $\dot{V}O_2$ is largely dependent on the rate and amount of oxygen delivered to exercising muscle, a function of the cardiac output, oxygen carrying capacity of the blood, and vascu-

lar convective transport [34]. Once oxygen is delivered to the working muscle, $\dot{V}O_2$ is dependent on oxygen utilization properties of the skeletal muscle [35] (Fig. 2). As long as the activity intensity levels remain light to moderate, aerobic metabolism effectively matches the energy demand [36]. High intensity exercise, though, is limited by the capacity of aerobic metabolism and often results in $\dot{V}O_2$ rising to its most tolerable limit, due to symptom-related fatigue that causes the individual to stop the activity [37].

According to the Fick equation, $\dot{V}O_2$ equals cardiac output times the arterial-mixed venous oxygen content difference: $\dot{V}O_2 = (SV \times HR) \times (CaO_2 - CvO_2)$, where $\dot{V}O_2$ is the oxygen uptake, SV is the stroke volume, HR is heart rate, CaO_2 is arterial oxygen content, and CvO_2 is the mixed venous oxygen content [23]. In most cases, $\dot{V}O_2$ is normalized for body weight and expressed in mL O₂/kg/min. One metabolic equivalent is the resting $\dot{V}O_2$ in a sitting position and equals 3.5 mL/kg per min. At maximal exercise, the Fick equation is expressed as follows: $\dot{V}O_{2max} = [(SV_{max}) \times$

(HRmax)] $\times$ [(CaO₂max) – (CvO₂min)]. VO₂max reflects the maximal ability of a person to take in, transport, and use oxygen; it therefore equals the functional aerobic capacity of that individual. In practice, however, VO₂peak, that is, the highest value obtained at the end of an exercise test to exhaustion, is used as VO₂max [23, 38].

Exercise Intolerance

Exercise intolerance (or decreased exercise capacity) is defined by the presence of abnormally low VO₂peak, of any cause. Based on the Fick equation, any factor that may impair maximum cardiac output (e.g., heart failure) or affect arterial or mixed venous oxygen content (e.g., diseases of the lungs, skeletal muscle dysfunction, or anemia) may result to decreased VO₂peak [23]. Furthermore, in patients with chronic respiratory disorders, mechanical constraints of ventilation is another important cause of exercise limitation, since produced respiratory discomfort may limit exercise capacity before actual physiological limitation occurs [39]. Exercise intolerance is highly prevalent in CKD and is associated with increased frailty, worsened quality of life, and high risk of hospitalization and mortality [37]. The mechanisms of exercise intolerance in CKD appear to be a complex interaction between central and peripheral factors, including kidney disease-related metabolic derangements, cardiac and pulmonary dysfunction, altered physiologic responses to oxygen consumption, vascular derangement, abnormal neuro-circulatory control, and sarcopenia. These central and peripheral factors may result in exercise limitation, principally of circulatory etiology, via several mechanisms, such as deconditioning, anemia, uncontrolled hypertension, sarcopenia, and heart failure, creating one or more distinct CPET patterns, which permit prioritization of contributing factors. However, these abnormalities remain to be fully elucidated, particularly in the non-dialysis CKD population [37].

CPET Studies in Patients with Pre-Dialysis CKD

In previous years, various studies aimed to quantify the cardiovascular reserve of CKD patients who were not on renal replacement therapy or kidney transplanted using the CPET technology. In the following lines, existing studies using CPET in patients with non-dialysis CKD are described, categorized by type of design; observational studies, and randomized trials.

Observational Studies Using CPET in Non-Dialysis CKD Patients

A few early studies used CPET in small samples of pre-dialysis CKD patients to evaluate exercise tolerance in association with other cardiovascular factors [40, 41]. Observational studies with better defined design are summarized in Table 2.

Studies Comparing CPET Parameters in CKD Patients of Various Stages with Controls

In a cross-sectional analysis, Nelson et al. [42] used CPET in 93 CKD stage 3 patients, in comparison to 840 individuals with renal function >60 mL/min/1.73 m². Patients with CKD had lower predicted VO₂peak, lower peak heart rate, lower AT, and impaired heart rate recovery. Kirkman et al. [14] evaluated 31 patients with stage 3–5 pre-dialysis CKD and 21 age-matched healthy controls with CPET observing again that VO₂peak and VO₂ at the AT (VO₂AT) were lower in CKD patients compared to healthy controls. In addition, 2 studies have examined CKD patients categorized by CKD stage, showing deterioration of exercise tolerance with advancing CKD. In particular, Faria Rde et al. [43], evaluated 29 CKD patients (stages 3, 4, and 5 before dialysis) and 18 healthy controls with CPET and 6-min walking test (6MWT), observing significant deterioration of VO₂peak (controls: 28.9 $\pm$ 7.8, CKD stage 3: 23.3 $\pm$ 5.6, CKD stage 4: 21.4 $\pm$ 5.2, CKD stage 5: 20.2 $\pm$ 6.9 mL/min/kg; p = 0.03) and 6MWT distance with advancing CKD. Similarly, Chinnappa et al. [44] evaluated with CPET 70 asymptomatic CKD patients, 35 age-matched healthy controls and 25 age-matched heart failure patients. VO₂max was lower in CKD patients than in controls but higher when compared to heart failure patients (Table 2).

Studies Examining CPET Parameters in Relation to Vascular Function Measures

Two studies [45, 46] investigated whether endothelial dysfunction or arterial stiffness are associated with exercise capacity in CKD patients. Van Craenenbroeck et al. [45] evaluated 63 patients with CKD divided in 2 eGFR groups, both of which displayed significantly lower VO₂peak and VO₂AT (Table 2). Arterial stiffness measured with pulse wave velocity (β = –0.301, p = 0.01) and eGFR (β = 0.363, p = 0.002) were independently associated with VO₂peak in multiple regression analysis. In the second study, Downey et al. [46] examined exercise capacity in 38 CKD patients divided into 2 groups according to flow-mediated dilation (FMD) levels. Compared

Table 2. Observational studies in pre-dialysis CKD patients using CPET

Study ID	Population characteristics	Study assessments	Follow-up/ time of evaluation	Results
<i>Studies comparing CPET parameters in CKD patients of various stages with controls</i>				
Faria Rde et al. [43]	29 pre-dialytic CKD patients stage 3–5, 9 healthy controls	CPET 6-min walk test Laboratory tests	No follow-up	CKD versus controls: Maximal exercise tolerance (CPET) (VO ₂ peak [mL/kg/min]: stage 3: 23.3±5.6, stage 4: 21.4±5.2, and stage 5: 20.2±6.9, controls: 28.9±7.8, $p = 0.03$) Submaximal exercise tolerance (6-min walk test): (Distance [m]: stage 3: 577.4±66.1, stage 4: 542.7±57.3, stage 5: 531.5±84.2, controls: 627.6±37.8, $p = 0.01$)
Nelson et al. [42]	93 CKD patients stage 3, 840 patients (eGFR >60 mL/min/1.73 m ²)	CPET Echocardiography	No follow-up	CKD stage 3 versus controls (eGFR >60 mL/min/1.73 m ²) Lower VO ₂ peak (mean difference: 6% [95% CI 1–11%]; $p = 0.02$), Lower peak heart rate (mean difference: 9 bpm [95% CI 3–14]; $p = 0.03$), Lower AT (mean difference: 1.1 mL/min/kg [95% CI 0.4–1.7]; $p < 0.001$) Lower heart rate recovery (mean difference: 4 bpm [95% CI 1–7]; $p < 0.001$)
Kirkman et al. [14]	31 CKD pre-dialysis patients stage 3–5, 21 age matched healthy controls	CPET	No follow-up	CKD versus controls: VO ₂ peak: 17.43±1.03 versus 28±2.05 mL/kg/min; $p < 0.01$ VO ₂ at the ventilatory threshold: 9.44±0.53 versus 15.55±1.34 mL/kg/min; $p < 0.01$ Minute ventilation rate/carbon dioxide production slope: 32±0.8 versus 28±1; $p < 0.01$ Expired carbon dioxide pressure: 27±0.6 versus 31±0.9 versus 0.9; $p < 0.01$ Ventilatory cost of VO ₂ : 37±0.8 versus 33±1; $p < 0.01$ Maximum heart rate: 134±5 versus 159±3 bpm, $p < 0.01$ One-minute heart rate recovery: 15±1 versus 20±2 bpm, $p < 0.01$
Chinnappa et al. [44]	70 patients with CKD (male, nondiabetic) 21 CKD 2–3a, 27 CKD 3b–4 and 22 CKD 5, pre-dialysis 35 age-matched healthy controls 25 age-matched patients with heart failure	CPET	No follow-up	CKD versus healthy controls: VO ₂ max (mL/min/kg) (CKD 2–3a: 33.5±6.5, CKD 3b–4: 29.9±5.5, CKD 5: 24.9±3.5, controls: 37.7±7.8, $p < 0.005$) Peak cardiac power (watt) (CKD 2–3a: 5.02±0.78, CKD 3b–4: 4.59±0.53, CKD 5: 4.02±0.73, controls: 6.13±1.11, $p < 0.005$) CKD versus heart failure patients: VO ₂ max (mL/min/kg) (CKD 2–3a: 33.5±6.5, CKD 3b–4: 29.9±5.5, CKD 5: 24.9±3.5, heart failure: 19.9±3.9, $p < 0.005$) Peak cardiac power (Watt) (CKD 2–3a: 5.02±0.78, CKD 3b–4: 4.59±0.53, CKD 5: 4.02±0.73, heart failure: 2.34±0.63, $p < 0.005$)
<i>Studies examining CPET parameters in relation to vascular function measures</i>				
Van Craenenbroeck et al. [45]	63 patients with CKD stage 1–5 eGFR >45 mL/min/1.73 m ² : 32 eGFR <45 mL/min/1.73 m ² : 31 18 healthy controls	CPET Vascular assessment (Endothelial-dependent vasodilation, Arterial stiffness, Targeted quantification of miRNA)	No follow-up	CKD (eGFR >45 vs. eGFR <45 [mL/min/1.73 m ²]) versus controls: VO ₂ peak (mL/min/kg) (eGFR >45: 28.13±8.34, eGFR <45: 24.05±5.44, controls: 35.99±6.43, $p < 0.001$) VO ₂ at the AT (mL/min/kg) (eGFR >45: 25.08±7.47, eGFR <45: 21.31±3.53, controls: 30.83±7.33, $p < 0.001$) VO ₂ peak was independently associated (multiple regression analysis) with: Arterial stiffness (via pulse wave velocity, [$\beta = -0.301$, $p = 0.01$]) eGFR ($\beta = 0.363$, $p = 0.002$)
Downey et al. [46]	38 patients with CKD stage 2–3, 21 healthy controls	CPET FMD	No follow-up	CKD versus healthy controls: VO ₂ peak (mL/min/kg) (CKD: 22±1, controls: 30±2, $p < 0.001$) Maximum diastolic BP during CPET (mm Hg) (CKD: 88±2, controls: 82±2, $p = 0.015$) Among CKD patients ([low FMD group] versus [high FMD group]) VO ₂ peak (mL/min/kg): low: 19.47±1.47, high: 24.57±1.51, $p < 0.001$)
<i>Studies examining the efficacy of exercise programs</i>				
Hama et al. [47]	86 patients with CKD stage 3–4	CPET	Follow-up: 3 months	Before versus after rehabilitation: VO ₂ peak (mL/min/kg): before: 15.0±3, after: 15.8±3, $p = 0.002$ Peak work rate (Watt): before: 65.5±21, after: 70.2±25, $p = 0.001$.

Table 2 (continued)

Study ID	Population characteristics	Study assessments	Follow-up/ time of evaluation	Results
Wilkinson et al. [12]	32 patients with pre-dialysis CKD stage 3b–5 (not-dialysis)	CPET	Follow-up: 12 weeks	Before versus after exercise training program: No meaningful changes in any other cardiorespiratory value obtained (VO ₂ peak; $p = 0.602$, Peak minute ventilation [VE]/VO ₂ ; $p = 0.853$, Peak VE; $p = 0.095$, Peak respiratory exchange ratio [RER]; $p = 0.864$) OUES calculated at 100%, 90%, 75%, and 50% of exercise duration did not change after 12 weeks of exercise training ($p = 0.642$, $p = 0.250$, $p = 0.196$ and $p = 0.869$, respectively)
<i>Studies examining the reproducibility</i>				
Wilkinson et al. [48]	41 patients with pre-dialysis CKD stage 3b–5	CPET ISWT STS e1RM	Follow-up: 6 weeks	ISWT, STS-60, e1RM, and CPET: intraclass correlation coefficient [®] values of 0.973, 0.927, 0.927, and 0.86, respectively ISWT and VO ₂ peak: strong correlation ($r = 0.73$ and 0.74)

CPET, cardiopulmonary exercise testing; CKD, chronic kidney disease; VO₂, oxygen uptake; VO₂peak, peak oxygen uptake; AT, anaerobic threshold; bpm, beats per minute; CI, confidence interval; miRNA, microRNA; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilation; ISWT, incremental shuttle walk test; STS, “sit-to-stand” test; e1RM, estimated 1 repetition maximum for quadriceps strength; OUES, oxygen uptake efficiency slope; VE, ventilation.

with patients at the high group (equal to or higher than the common median FMD value of 2.95%), these at the low FMD (lower than the common median FMD value) had significantly poorer exercise capacity.

Studies Examining the Efficacy of Exercise Programs

Among studies evaluating the efficacy of rehabilitation programs, a retrospective post hoc analysis of a clinical trial [47] in which CPET was performed at the beginning and end of a 3-month cardiac rehabilitation program evaluated 86 patients with CKD stage 3–4, who were hospitalized for cardiovascular disease-related events. Both VO₂peak and the work rate improved significantly after cardiac rehabilitation. Another study [12] included 32 patients with CKD 3b–5 (not requiring dialysis), in which CPET was performed at baseline, following a 12-week exercise training program and after a 6-week non-exercise period. The study evaluated the VO₂ efficiency slope that represents the relationship between VO₂ and total ventilation, providing an indication of cardiorespiratory reserve. The VO₂ efficiency slope calculated at 100%, 90%, 75%, and 50% of exercise duration did not change significantly after 12 weeks of exercise training; similarly, no meaningful changes were observed following the exercise program in all other cardiorespiratory parameters examined (Table 2).

Studies Examining the Reproducibility of CPET Testing

Wilkinson et al. [48] tried to determine the reliability and the estimated minimal detectable change of CPET and other physical function tests in 41 patients with pre-dialysis CKD. Assessments were performed at 2 time points (test 1 and 2) separated by a 6-week period in which patients were instructed to maintain their habitual lifestyle. There was minimal difference between the 2 CPET tests (intraclass correlation coefficient [r] 0.866) and all the other tests examined, with the exception of sit-to-stand test-5.

Randomized Trials Using CPET in Non-Dialysis CKD Patients

All randomized trials using CPET in patients with pre-dialysis CKD have studied the effects of programs of exercise training. Among these trials, summarized in Table 3, several suggest significant improvement of physical performance of CKD patients following exercise interventions. The earliest of positive studies which showed significantly improved VO₂peak and endurance time in the exercise group, randomized 20 pre-dialysis CKD patients in a 12-month exercise program or standard care [49]. Several studies in pre-dialysis CKD patients of various stages with populations ranging from 11 to 142 patients and study duration up to 12 months have shown beneficial effects of various exercise programs on VO₂peak and other CPET parameters [49–62]. In some cases, more than one type of exercise training were examined; for example,

Table 3. Randomized trials in pre-dialysis CKD patients using CPET

Study ID	Population characteristics	Study assessments	Follow-up/ time of evaluation	Results
Eidamak et al. [63]	30 CKD patients (GFR: 25 mL/min/1.73 m ²) (randomized to: Physical training: 15 Maintenance of the usual lifestyle: 15)	CPET Blood tests	Follow-up: 18 months for the exercise group 20 months for the control group	After training intervention: (exercise group versus usual lifestyle group): VO ₂ peak (mL/min/kg); exercise: 25 [13–43], usual lifestyle: 21 [14–40], <i>p</i> = not significant GFR, lipid concentration: no significant differences
Leehey et al. [50]	11 patients with CKD stage 2–4 ([eGFR]: 15–90 mL/min/1.73 m ² with persistent proteinuria), type 2 diabetes and obesity (BMI >30 kg/m ²) (randomized to: 24 weeks of exercise group: 7 Control group: 4)	CPET Nutritional and body composition assessment Laboratory assessments	Follow-up: 6, 24 weeks	Baseline versus 24-week intervention (exercise group): Exercise duration (min) (baseline: 6.6±2.2, after intervention: 10.2±2.8) VO ₂ max (mL/min/kg) (baseline: 14.9±1.1, after intervention: 15.6±2.4) Resting systolic blood pressure (mm Hg) (baseline: 130±28, after intervention: 113±16) Urine protein excretion (mg/24 h) (baseline: 1,020±1,081, after intervention: 821±1,010) No significance between-groups effects over time for exercise duration, oxygen consumption at “isotime,” blood pressure, or 24-h proteinuria, probably due to the small sample size
Mustata et al. [49]	20 pre-dialysis CKD patients (randomized to: 12 months of exercise: 10 Standard care: 10)	CPET Arterial stiffness	Follow-up: 12 months	After exercise intervention: (difference between exercise group versus standard care group): VO ₂ peak (mL/min/kg) (+3.59; 95% CI [0.92, 6.26]; <i>p</i> = 0.01) Endurance time (min) (+10.97; 95% CI [4.34, 17.59]; <i>p</i> = 0.003) Augmentation index (–11.7%; 95% CI [–18.79, –4.61]; <i>p</i> = 0.003)
Headley et al. [51]	21 patients with CKD stage 2–4 (randomized to: Training group: 10 The usual care group: 11)	CPET Laboratory assessments	Follow-up: 24, 48 weeks	Baseline versus 48-week intervention (training group): VO ₂ peak (mL/min/kg) (baseline: 18.1±7.8, after intervention: 19.5±4.6, <i>p</i> < 0.05) Reduction in both resting and ambulatory heart rate Increase in LDL cholesterol
Howden et al. [52]	72 patients with CKD stage 3–4 (randomized to: Lifestyle intervention group: 36 Control group: 36)	CPET Biochemical analyses Echocardiography Arterial compliance Dietary assessment	Follow-up: 12 months	Baseline versus 12 months intervention: (intervention group) VO ₂ peak (mL/kg/min) (difference from baseline: +2.8±0.7; <i>p</i> = 0.01) Weight loss (kg) (difference from baseline: –1.8±4.2; <i>p</i> = 0.02) BP or lipid concentration: no change Diastolic function improved (<i>p</i> = 0.001) but systolic function did not change
Headley et al. [53] ^a Headley et al. [54] ^a Miele et al. [55] ^a	46 patients with CKD MDRD-eGFR: 30–59 mL/min/1.73 m ² (diabetes or hypertension as the primary cause of CKD) (randomized to: Treatment group: 25 Control group: 21)	CPET Arterial stiffness Blood tests Health-related quality of life 24-h ambulatory blood pressure monitoring Dietary assessment	Follow-up: 8, 16 weeks	Baseline versus 16-week intervention (exercise group) VO ₂ peak (mL/min/kg) (baseline: 19.6±6.7, after intervention: 21.2±7.7, <i>p</i> = 0.05) (control group) VO ₂ peak (mL/min/kg) (baseline: 18.0±6.0, after intervention: 17.5±5.7) Aortic pulse wave velocity: no changes Post-exercise hypotension occurred at baseline Lower TC (<i>p</i> = 0.051) and LDL-C (<i>p</i> = 0.07) HDL-C, TGs, and HDL particle size and body composition remained unchanged in both groups
Greenwood et al. [56]	20 patients with CKD stage 3–4 (randomized to: Rehabilitation: 10 Usual care: 10)	CPET Arterial stiffness Blood tests	Follow-up: 6, 12 months	After rehabilitation: (Rehabilitation versus usual care group) VO ₂ peak (mL/min/kg) (between group mean difference: + 5.7 [95% CI, 1.34–10.10], <i>p</i> < 0.01) Pulse wave Velocity (m/s) (between group mean difference: –2.30 [95% CI, –3.02 to –1.59], <i>p</i> < 0.001) Waist circumference (cm) (between group mean difference: –7.1±12.8 [95% CI, –12.4 to –3.2], <i>p</i> < 0.003)

Table 3 (continued)

Study ID	Population characteristics	Study assessments	Follow-up/ time of evaluation	Results
Aoike et al. [57]	29 overweight patients with CKD stage 3–4 (randomized to: Home-based exercise group: 14 Non exercise control group: 15)	CPET Functional capacity tests (6-min walk test, 2-min step test, sit-to-stand test, arm curl test, sit and reach test, back scratch test, time up, and go test) Laboratory data Blood pressure measurement PSQI DEXA	Follow-up: 12 weeks	Baseline versus 12-week intervention group (exercise group) (CPET) Maximal ventilation (L/min) (baseline: 77.5±25.6, after intervention: 90.7±28.1, $p = 0.003$) VO ₂ peak (mL/min/kg) (baseline: 24.1±7.1, after intervention: 26.1±7.0, $p < 0.05$ within group, no significant group by time interactions) VO ₂ in VT (mL/kg/min) (baseline: 14.6±2.6, after intervention: 16.6±3.6, $p = 0.154$) Baseline versus 12-week intervention group (exercise group) (other functional capacity tests) Improvement: (6-min walk test [$p < 0.001$], time up and go test [$p < 0.001$], arm curl test [$p < 0.001$], sit and stand test [$p < 0.001$], 2-min step test [$p < 0.001$], and back scratch test [$p = 0.042$])
Van Craenenbroeck et al. [58]	40 patients with CKD stage 3–4 without established cardiovascular disease (randomized to: Exercise training: 19 Usual care: 21)	CPET Endothelial function Arterial stiffness Cellular markers for vascular function Laboratory test Health-related quality of life	Follow-up: 3 months	Baseline versus 3-month intervention (training group) VO ₂ peak (mL/kg/min) (baseline: 26.5±5.4, Intervention: 32.3±6.8, $p < 0.001$) Vascular function (FMD and carotid-femoral pulse wave velocity) and cellular markers for vascular function: no significant changes
Leehey et al. [64]	36 patients with CKD stages 2–4, and persistent proteinuria (>200 mg/g creatinine for >3 months), type 2 diabetes and BMI >30 kg/m ² (randomized to: Exercise & diet management: 18 Diet management: 18)	CPET 6-minute walk test Timed up and go test Peripheral muscle strength test Questionnaires Body composition assessment Laboratory tests	Follow-up: 12, 52 weeks	Baseline versus 12-week versus 52-week intervention (exercise and diet group) Changes in treadmill times: significantly higher at 12 weeks but not at 52 weeks (diet-alone group) Change from baseline in urine protein to creatinine ratio: slightly greater at 12 weeks but not at 52 weeks No differences in VO ₂ peak between the groups at either 12 or 52 weeks
Aoike et al. [59]	40 overweight patients with CKD stage 3–4 (randomized to: Home-based exercise group: 12 Center-based exercise group: 13 Non exercise control group: 15)	CPET Functional capacity tests (6-min walk test, 2-min step test, sit-to-stand test, arm curl test, sit and reach test, time up and go test) Laboratory data Blood pressure measurement PSQI Quality of life assessment	Follow-up: 12, 24 weeks	Home-based versus center-based exercise group: (CPET) VO ₂ peak and all cardiopulmonary parameters evaluated were similarly improved ($p < 0.05$) after 12 and 24 weeks in both exercise groups (Functional capacity tests) Home-based group: all improved during the follow-up in the home-based group ($p < 0.05$) and reached values similar to those obtained in the center-based group. The benefits achieved in both exercise groups were also reflected in improvement of quality of life and sleep ($p < 0.05$)
Ikizler et al. [65]	111 patients with CKD (mean eGFR _{cysC} : 41±18.6 mL/1.73 m ²) (randomized to: Aerobic exercise and calorie restriction: 30 Usual activity and calorie restriction: 28 Aerobic exercise and usual diet: 27 Usual activity and usual diet: 26)	CPET Body composition assessment Laboratory tests	Follow-up: 2, 4 months	Cardiorespiratory fitness No statistically significant changes in VO ₂ peak versus usual care ($p = 0.43$ for overall treatment effect vs. usual care; $p = 0.56$ for caloric restriction vs. usual diet; $p = 0.37$ for exercise vs. usual activity) Body composition Decrease in body weight with intervention versus usual care ($p = 0.02$ vs. usual care) Most pronounced with caloric restriction ($p = 0.004$ vs. usual diet) but was not among patients who received exercise intervention Similar effect on BMI Oxidative stress and Inflammatory markers The combined intervention and each independent intervention led to significant decreases in F2-isoprostane and IL-6 concentrations

Table 3 (continued)

Study ID	Population characteristics	Study assessments	Follow-up/ time of evaluation	Results
Kirkman et al. [60]	36 non-dialysis CKD patients (eGFR: 44 ± 2 mL/min/ 1.73 m ²) (randomized to: Exercise group: 19 Control group: 17)	CPET Microvascular function Conduit artery endothelial function Central hemodynamics and arterial stiffness Laboratory tests	Follow-up: 12 weeks	Baseline versus exercise training Cardiorespiratory fitness VO_2peak (mL/min/kg): Exercise group (baseline: 17.89 ± 1.21 , after 12 weeks: 19.98 ± 1.59 , $p = 0.04$) Control group (baseline: 18.29 ± 1.73 , after 12 weeks: 17.36 ± 1.60 , $p = 0.10$) Microvascular function: Exercise group: (baseline: $87 \pm 2\%$, after 12 weeks: $91 \pm 2\%$, $p = 0.03$) Control group: (baseline: $86 \pm 2\%$, after 12 weeks: $84 \pm 3\%$, $p = 0.03$) Brachial artery FMD: Exercise group: (baseline: $2.6 \pm 0.4\%$, after 12 weeks: $3.8 \pm 0.8\%$, $p = 0.02$) Control group: (baseline: $3.5 \pm 0.6\%$, after 12 weeks: $2.3 \pm 0.4\%$, $p = 0.02$)
Beetham et al. [61]	142 patients with CKD stage 3–4 (randomized to: Exercise group: 74 Control group: 68)	CPET 6-minute walking test eGFR measurements (MDRDcr, CKD-EPIcr, CKD-EPIcys, and CKD- EPIcr-cys) Questionnaires DEXA	Follow-up: 12 months	Fitness measures VO_2peak (mL/min/kg) Exercise group: difference (after 12 months-baseline): $+1.7 \pm 3.7$, $p < 0.01$ Control group: difference (after 12 months-baseline): -0.9 ± 4.2 , $p < 0.01$ Peak MET tasks Exercise group: the lifestyle intervention resulted in improvement in exercise capacity ($+1.9 \pm 1.8$ METs, $p < 0.001$) No changes in lean mass in both control and exercise groups during the 12 months eGFR measurements (mL/ min/ 1.73 m ²): CKD-EPIcys was lower in both groups at both baseline and 12 months than in CKD-EPIcr, CKD- EPIcr-cys, and MDRDcr
Beetham et al. [62]	14 patients with CKD stage 3–4 (randomized to: High-intensity interval training: 9 Moderate-intensity continuous training: 5)	CPET Muscle biopsy Body composition assessment Blood tests Hemodynamics assessment	Follow-up: 12 weeks	High-intensity interval versus moderate-intensity continuous training group Number of training sessions (high-: 33 ± 7 , moderate- intensity: 33.5 ± 3.3) Change in exercise capacity (MET) (high-: $+0.8 \pm 1.2$, moderate-intensity: $+1.3 \pm 1.6$, $p = 0.01$) Change in muscle protein synthesis (high-: $+0.6 \pm 1.1$, moderate-intensity: $+1.4 \pm 1.7$, $p = 0.04$) No change in VO_2peak in high-intensity interval training group

CPET, cardiopulmonary exercise testing; CKD, chronic kidney disease; VO_2peak , peak oxygen uptake; GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; AT, anaerobic threshold; VO_2max , maximum oxygen uptake; "isotime", defined as a time when workload was the same in all subjects; PSQI, Pittsburgh sleep quality index; eGFRcysC, estimated glomerular filtration rate from cystatin C measurements; BMI, Body mass index; DEXA, Dual energy x-ray absorptiometry; MDRDcr, modification of diet in renal disease-creatinine; CKD-EPIcr, CKD-epidemiology collaboration using creatinine; CKD-EPIcys, CKD-epidemiology collaboration formula using cystatin C; CKD-EPIcr-cys, CKD-epidemiology collaboration formula using creatinine and cystatin C; MET, metabolic equivalent; FMD, flow-mediated dilation; TC, total cholesterol. ^a These 3 reports present the same CPET results of a single trial with different secondary outcomes.

Aoike et al. [59] randomized 40 overweight patients with CKD stage 3–4 to a home-based- ($n = 12$), a center-based- ($n = 13$), and a non-exercise group ($n = 15$), showing that VO_2peak and other CPET parameters were similarly improved after 12 and 24 weeks in both exercise groups. Furthermore, in some of these studies, simultaneous improvements in examined vascular parameters, such as ar-

terial stiffness [49, 53, 56] or peripheral endothelial function [58] were evident.

In contrast to the above findings, there are studies in pre-dialysis CKD patients not suggesting a benefit of exercise training (Table 3) [63–65]. The first study in this field [63], randomizing 30 CKD patients with a median GFR 25 mL/min/ 1.73 m² to a physical training group and

a usual lifestyle group, showed numerically but nonsignificantly higher VO_2peak in the exercise group after 18 months of follow-up. Leehey et al. [64], randomly assigned 36 CKD patients with obesity and type 2 diabetes to “exercise and diet” versus “diet” intervention, reporting no differences in VO_2peak between the groups at either 12 or 52 week of follow-up. Finally, in the largest trial of the field, Ikizler et al. [65] randomized 111 obese patients with CKD into 4 groups: exercise & calorie restriction; usual activity & calorie restriction; exercise & usual diet; and usual activity & usual diet. After 4 months of follow-up, no significant difference in VO_2peak in the exercise compared to the non-exercise groups were noted, regardless of the diet intervention.

The effect of exercise training on CPET parameters in patients with CKD has been also examined in recent meta-analyses, which show pooled estimates of improved $\text{VO}_2\text{peak}/\text{VO}_2\text{max}$ with physical rehabilitation programs [66, 67]. It is not yet clear, why exercise training did not improve cardiorespiratory fitness of CKD patients in all relevant studies. One should first note that careful interpretation is needed before considering a study as positive or negative, since results are reported in different ways in individual studies, i.e., as within-group comparisons (baseline vs. post-intervention), between-group comparisons (of change from baseline or post-intervention values), or as group-by-time interactions. Small study samples, or inadequate duration of training programs may apply to some cases [63], although these were also features of some positive pilot studies [50, 62]. Characteristics of the included populations may also affect each study results, as meta-regression analyses suggest that older age, obesity, and diabetes may be factors leading to poor exercise response [67, 68].

Potential Clinical Applications of CPET in Patients with CKD

CPET is a highly useful clinical tool that evaluates organ-specific maladaptive physiological responses which may limit physical performance. It provides breath-by-breath gas exchange measures while progressively increasing exercise intensity in a linear function over time to maximally stress the oxygen delivery and utilization system [24]. CPET may have a wide range of clinical applications that can help to better characterize the cardiopulmonary phenotype of patients with CKD. As discussed above, exercise limitation in patients with CKD can be attributed to a wide variety of coexisting disorders

of the cardiac, respiratory, nervous, and muscular systems that can be directly or indirectly linked with reduced renal function [18, 19]. As CPET is the optimal tool in the differential diagnosis of conditions associated with reduced cardiovascular reserve, it may help towards the identification of previously “hidden” causes of poor exercise capacity in patients with pre-dialysis CKD, such as respiratory functional disturbances and neuromuscular disorders [69]. Moreover, CPET use, through discrimination of the underlying causes of physical impairment and exertional fatigue in CKD patients, who suffer from multiple comorbidities, may facilitate treatment optimization towards symptom relief and functional capacity improvement. Furthermore, as exercise training has shown to improve physical function and walking capacity among subjects with CKD [68], CPET could be used to identify individuals with impaired exercise tolerance that would benefit from intervention. In addition, it can provide valuable information before the initiation of training, i.e., determine the optimal training intensity level and exercise safety, and after program completion, i.e., evaluate the efficacy of the intervention [28].

CPET is also used for several years in preoperative evaluation of different patient groups, including patients before heart surgery or organ transplantation (including heart, lung, and liver) [70]. CPET information can be used to inform the decision-making and consent processes, to direct preoperative interventions, intraoperative anesthetic practice, prehabilitation, and rehabilitation, as well as to estimate the likelihood of perioperative morbidity and mortality. To this end, VO_2peak and VO_2AT are the CPET variables with the higher prognostic value in subjects before major surgeries, as well as in patients with end-stage CKD waitlisted for kidney transplantation [15, 70, 71]. However, there is very little, if any, use of CPET evaluation in CKD patients in preoperative clinical practice. Further, CPET is currently used for long-term risk stratification in a wide range of populations, such as patients with lung diseases and heart failure. For example, in patients with chronic obstructive pulmonary disease, CPET has been used to predict the risk of all-cause mortality, independently of lung function indices [72], while in patients with heart failure, CPET offers incremental value beyond clinical characteristics and ejection fraction in predicting the risks of hospitalization and mortality [73]. However, to our knowledge, there is no risk stratification tool including CPET parameters for CKD patients. As individuals with CKD share several comorbidities with the aforementioned disease populations [74, 75], it would be interesting for future research to examine whether

CPET parameters are associated with relevant outcomes and, as such, they can be used for risk stratification with regards to perioperative complications or long-term cardiovascular and all-cause mortality in patients with CKD.

Finally, as randomized trials in nephrology with hard endpoints (i.e., death or cardiovascular events) are difficult to perform and scarce, several studies, including elegant randomized research efforts in patients with CKD include intermediate cardiac end points, such as left-ventricular mass index and left-ventricular ejection fraction [76, 77]. As of this writing, trials in other patient populations (i.e., individuals with heart failure) have used CPET parameters as intermediate cardiovascular endpoints [78, 79]. On this basis, using comprehensive CPET end points could be a valid option also for cardiorenal outcome trials [69]; for this to happen, long-term and optimally designed studies should first evaluate the association of key CPET parameters, such as $\text{VO}_{2\text{peak}}$, with key outcomes such as cardiovascular and all-cause mortality specifically in patients with CKD.

Conclusions

CKD has a prevalence of 9–12% in Western societies and is per se associated with increased risk for cardiovascular events and all-cause mortality. Among patients with CKD, cardiovascular disease is the leading cause of death. Existing studies suggest that exercise intolerance is an inherent disturbance of CKD patients resulting in inactivity, deconditioning, diminished functional capacity, feeling of tiredness, social isolation, and impaired quality of life. As of this writing, CPET has been used in pilot observational studies that, in most cases, examine exercise capacity in patients with CKD versus non-CKD controls and, in some cases evaluate simple associations with other vascular parameters, such as endothelial function and arterial stiffness. In addition, CPET has been used in randomized trials examining the effect of exercise training

interventions on cardiovascular reserve in patients with CKD, in order to obtain an objective measure of exercise tolerance. However, CPET may have an array of additional applications in patients with CKD, ranging from objective differential diagnosis of exercise intolerance to preoperative and long-term risk stratification and providing comprehensive intermediate endpoints for clinical trials. Overall, future studies using CPET in patients with pre-dialysis CKD in order to examine its diagnostic accuracy for underlying diseases, to delineate the associations of CPET indexes with cardiac and vascular parameters that represent well-known cardiovascular risk factors, as well as to directly assess the prognostic significance of CPET derived indexes for hard outcomes, can be particularly useful in order to establish CPET as a valid diagnostic and prognostic tool for the benefit of our patients.

Statement of Ethics

This is a literature review manuscript and therefore ethics approval was not applicable.

Conflict of Interest Statement

All authors disclose that they do not have any financial or other relationships, which might lead to a conflict of interest regarding this paper.

Funding Sources

This paper was not supported by any source and represents an original effort of the authors.

Author Contributions

A.B. and P.S.: conception of the manuscript; E.P. and M.T.: literature search; E.P. and A.B.: manuscript drafting; P.S.: critical revision of the manuscript for intellectual content.

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