A clinical evaluation of VO₂ kinetics in kidney transplant recipients

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Abstract

Purpose Aerobic exercise capacity is reduced in patients with chronic kidney disease, partly due to alterations at the muscular and microvascular level. This study evaluated oxygen uptake (VO₂) kinetics as indicator of muscular oxidative metabolism in a population of Kidney Transplant Recipients (KTRs).

Methods Two groups of KTRs enrolled 3 (n = 21) and 12 months (n = 14) after transplantation and a control group of healthy young adults (n = 16) underwent cardiopulmonary exercise testing on cycle-ergometer. The protocol consisted in two subsequent constant, moderate-load exercise phases with a final incremental test until exhaustion.

Results The time constant of VO₂ kinetics was slower in KTRs at 3 and 12 months after transplantation compared to controls (50.4 ± 13.1 s and 43.8 ± 11.6 s vs 28.9 ± 8.4 s, respectively; P < 0.01). Peak VO₂ was lower in KTRs evaluated 3 months after transplantation compared to patients evaluated after 1 year (21.3 ± 4.3 and 26.4 ± 8.0 mL/kg/min; P = 0.04). Blood haemoglobin (Hb) concentration was higher in KTRs evaluated at 12 months (12.8 ± 1.7 vs 14.6 ± 1.7 g/dL; P < 0.01). Among KTRs, τ showed a moderate negative correlation with Peak VO₂ (ρ = −0.52) and Oxygen uptake efficiency slope (OUES) (r = −0.57) while no significant correlation with Hb and peak heart rate.

Conclusions KTRs show slower VO₂ kinetics compared to healthy controls. Hb and peak VO₂ seem to improve during the first year after transplantation. VO₂ kinetics were significantly associated with indices of cardiorespiratory fitness, but less with central determinants of aerobic capacity, thus suggesting a potential usefulness of adding this index of muscular oxidative metabolism to functional evaluation in KTRs.

Keywords Kidney transplantation · Oxygen uptake kinetics · Cardiopulmonary exercise testing · Haemoglobin · Muscle

Abbreviations

ANOVA Analysis of variance
CKD Chronic kidney disease
Hb Haemoglobin
HR Heart rate
KTRs Kidney transplant recipients
OUES Oxygen uptake efficiency slope

VO₂ kinetics Kinetics of oxygen uptake
VT1 First ventilatory threshold

Introduction

Scientific evidence clearly shows that cardiorespiratory fitness is a strong predictor of all-cause and cardiovascular mortality independent of age, sex, ethnicity, and comorbidities (Myers et al. 2002; Kodama et al. 2009; Mandisager et al. 2018). Patients with chronic kidney disease (CKD) have generally reduced maximal aerobic exercise capacity compared to healthy subjects, which appears to slowly improve in Kidney Transplant Recipients (KTRs), even though often not reaching normal values (Kempe-neers et al. 1990; Painter et al. 2002, 2011; Habedank et al. 2009). There are multiple reasons for this impairment in patients with CKD, since this population may present both central and peripheral limitations to exercise. As a
matter of fact, anaemia, autonomic, vascular and cardiac dysfunction are common in patients with end-stage renal disease, frequently associated with skeletal muscle and/or metabolic abnormalities (Painter et al. 2011). In particular, muscular alterations have been reported in this population such as reduced capillary density, increased diffusion distance and reduced mitochondrial density and/or function (Kempeneers et al. 1990; Moore et al. 1993; Painter et al. 2011). These characteristics may explain the difficulty in restoring these patients’ aerobic capacity to normal values after transplantation, despite an increase in haematocrit and cardiac output, obtained with erythropoietin-stimulating agents and exercise training (Stray-Gundersen et al. 2016), should have a positive impact on maximal oxygen uptake (Johansen et al. 2010). Moreover, also kidney transplantation itself has been shown to facilitate the recovery of some central limitations to exercise. Indeed, with the normalization of renal function after transplantation the reduced blood haemoglobin (Hb) concentration and maximal heart rate may improve (Painter et al. 2011). Furthermore, deteriorations at the muscular level in KTRs might in part also be due to immunosuppressive therapy (Painter et al. 2003; Topp et al. 2003). Nevertheless, an improvement in muscle quality has been hypothesized (Habedank et al. 2009), and muscle alterations have been shown to improve after transplant with withdrawal from immunosuppressive therapy (Topp et al. 2003). The extent of muscle recovery has, however, not yet been elucidated and patients often maintain a condition of frailty and increased risk of falling (McAdams-DeMarco et al. 2017; Zanotto et al. 2017, 2020).

The kinetics of oxygen uptake (VO₂ kinetics), i.e., the rate of adjustment of the oxygen consumption to a sudden increase in workload during the transition from rest to constant, moderate intensity exercise, is thought to reflect the oxygen utilization at a peripheral muscular level (Grassi 2005; Poole and Jones 2012). Reboredo et al. previously evaluated VO₂ kinetics during a moderate intensity constant load in patients with CKD before and after a symptom-targeted intra-dialytic training program. The results of their study showed an improvement of this parameter with exercise training (Reboredo et al. 2015). To our knowledge, very limited data exist, specifically assessing VO₂ kinetics in KTRs, particularly for different follow-up periods. The aim of the present study was thus to investigate VO₂ kinetics in this population, to evaluate possible peripheral limitations to exercise that may have an impact on the typically lower exercise tolerance and cardiorespiratory fitness of these patients. Since important cardiopulmonary adaptations take place after renal transplant, we decided to evaluate this parameter 3 and 12 months after the surgical intervention. The secondary aim of the study was to evaluate if the VO₂ kinetics were conditioned by other exercise-related variables in this specific population of KTRs.

**Methods**

This study included KTRs who received transplant at the University Hospital of Padova between 2017 and 2018. Ethical approval of the experimental design was obtained from the Ethics Committee of the University of Padova (approval number 43079). All procedures were conducted in accordance with the Declaration of Helsinki and patients provided written informed consent. The evaluation was performed during routine clinical exercise testing, as previously described for other patient population (Neunhaeuserer et al. 2017, 2020).

A first group of KTRs included 21 patients evaluated 3 months after transplant, while the second group included 14 patients evaluated 1 year after transplant. Patients with significant systolic heart failure were excluded from the study. 16 young and apparently healthy subjects were enrolled as control group for analysis of VO₂ kinetics. The baseline characteristics of the three groups are described in Table 1. The underlying CKDs of the included KTRs were of different aetiologies. Table 2 reports the main clinical features of the two groups of KTRs and shows that there was no difference in blood creatinine concentration, while Hb was significantly higher in the group evaluated 12 months after surgery.

**Exercise testing protocol**

For each patient medical history was taken, physical examination was performed and recent blood Hb and creatinine concentration were obtained. Cardiopulmonary exercise testing was subsequently performed on a cycle ergometer.

**Table 1 Characteristics of the study participants**

| Number (n) | 3-month group | 12-month group | Control group |
|-----------|---------------|----------------|---------------|
| Male/Female (n) | 13/8 | 12/2 | 9/7 |
| Age (years) | 53.52 ± 10.24* | 50.29 ± 5.77** | 26.18 ± 3.41 |
| Height (cm) | 168.96 ± 8.01 | 171.25 ± 9.46 | 173.88 ± 8.21 |
| Weight (kg) | 67.97 ± 11.51 | 74.56 ± 11.83 | 68.15 ± 10.48 |
| BMI (kg/m²)* | 23.72 ± 2.79 | 25.35 ± 2.76** | 22.44 ± 2.14 |

The characteristics of the three groups are expressed as mean ± SD unless otherwise noted.

BMI: Body mass Index

*Significantly different (P < .05) from value obtained in control group

*Data are non-normally distributed in at least one of the three groups
### Table 2: Characteristics of the two groups of kidney transplant recipients

| Parameters                                      | 3-month group | 12-month group | P    |
|-------------------------------------------------|---------------|----------------|------|
| Number                                          | 21            | 14             |      |
| Male                                            | 13 (62%)      | 12 (86%)       |      |
| Creatinine (μmol/L)                             | 115.95 ± 22.92| 123.36 ± 23.41 | .360 |
| Hemoglobin (g/dL)                               | 12.77 ± 1.67  | 14.55 ± 1.75   | .005 |
| B-blocker therapy                               | 12 (57%)      | 6 (43%)        | .407 |
| Type and duration of dialytic therapy           |               |                |      |
| Dialytic therapy                                | 18 (86%)      | 12 (86%)       | 1.000|
| Hemodialysis                                    | 8 (38%)       | 8 (57%)        | .268 |
| Peritoneal dialysis                             | 7 (33%)       | 3 (21.5%)      | .704 |
| Hemodialysis + peritoneal dialysis              | 3 (14.5%)     | 1 (7%)         | .653 |
| Mean Dialysis Time (months)*                    | 30.9 ± 33.6   | 24.9 ± 21.0    | .904 |
| Cause of chronic kidney disease                 |               |                |      |
| Chronic glomerulonephritis                      | 3 (14%)       | –              |      |
| Polycystic kidney disease (APKD)                | 4 (19%)       | 5 (36%)        |      |
| Diabetic nephropathy                            | 3 (14%)       | –              |      |
| Lupus nephropathy                               | 1 (5%)        | –              |      |
| Malformation/renal genetic syndrome             | –             | 2 (14%)        |      |
| Other or unknown                                | 8 (38%)       | 5 (36%)        |      |
| Vasculitis                                      | –             | 1 (7%)         |      |
| Hypertension                                    | 2 (10%)       | 1 (7%)         |      |

Parameters are expressed as mean ± SD or n (%)

*One patient has been excluded from the present analysis because the length of his dialytic treatment was not known

![Fig. 1](https://example.com/fig1.png)

**Fig. 1** The exercise test protocol used for this study and the related oxygen consumption (VO₂) of one of the participants. The dots represent breath-by-breath data of the subject’s VO₂ during the test. The dark (red) bars display the exercise intensities in Watts during the different test phases, while the light (orange) bar shows the unloaded pedaling, performed before the constant load exercise test.
(eBike, General Electrics). To overcome the possible dropouts that could have arisen testing patients on two different days, a specific protocol was designed to obtain both constant load and incremental exercise testing data in a single clinical evaluation (Fig. 1). The protocol consisted of two 5-min constant load tests, both preceded by 2 min of unloaded pedalling and separated by 6 min of resting. At the end of the second constant load exercise, an incremental test until exhaustion was carried out. Given the differences in the age and fitness level between KTRs and healthy subjects, the test protocols were slightly different: a constant load of 30 or 40 W was used for patients 3 months after transplant, a constant load of 40 W was used for patients 12 months after surgery and a constant load of 60 (female) or 75 (males) Watts was used for controls. These loads were chosen to be reasonably below the first ventilatory threshold (VT1) of the subject being tested, to avoid the occurrence of a slow component of VO2 kinetics (Poole and Jones 2012). The final incremental test consisted in a 15 W per minute ramp for patients, and a 25 W per minute ramp for controls. Study participants were asked to keep a constant pedal cadence of 60±5 rpm (70±5 rpm for the control group). Breath by breath cardiopulmonary parameters and 12 lead ECG were recorded during the whole test (Jaeger-Masterscreen-CPX, Carefusion, Germany).

Data analysis

The first two constant load bouts were used for the determination of the VO2 kinetics during the transition from unloaded pedalling to moderate intensity exercise. First, the VO2 responses were linearly interpolated using a mathematical software (MATLAB R2017a, Math Works, MA, USA) to provide one value of VO2 per second; thereafter the values of the two bouts were averaged. Iterative nonlinear regression (Levenberg–Marquardt procedure) was used to characterize the primary VO2 response after removing the first 20 s of data (to eliminate the phase 1 component, known as the “cardiodynamic phase”), fitting the resting 5 min in a mono-exponential function according to the following equation:

\[ \text{VO2} = \text{VO2}(bl) + A \cdot (1 - e^{-(t-TD)/\tau}) \]

where \( \text{VO2}(t) \) is the VO2 at time \( t \); \( \text{VO2}(bl) \) is the baseline VO2 measured in the 30 s preceding the transition to exercise; and \( A_p \), \( TD_p \), and \( \tau \) are the amplitude, time delay, and the time constant of the primary (phase 2) response of VO2 kinetics, respectively.

VO2 at peak exercise (peak VO2) was determined during a final, incremental ramp testing until patients’ exhaustion, defining peak VO2 as the highest average VO2 recorded during a 30-s period of testing. The first ventilatory threshold (VT1) was estimated using the V-slope method and evaluating the ventilatory equivalent of VO2 (Schneider et al. 1993). The oxygen uptake efficiency slope (OUES) was calculated as the coefficient of the linear relationship between oxygen uptake and the logarithm of total ventilation.

Statistical analysis

Normality of variables was checked using the Shapiro–Wilk test. For comparisons between two groups, a chi-square test was used to assess the differences between categorical variables. In the case expected cell frequencies were greater than five a Fisher’s exact test was used. For continuous variables, a t-test was used for normally distributed variables and a Mann–Whitney U test for non-normally distributed variables. For comparisons between the three groups, one-way analysis of variance (ANOVA) with post hoc analysis (Tukey’s post hoc test) was performed on all normally distributed variables. For parameters that violated the assumption of homogeneity of variances, a Welch test was performed and Games-Howell post hoc tests were used for multiple comparisons. For variables that showed a non-normal distribution in at least one of the three groups, a Kruskal–Wallis H test was performed and pairwise comparisons were conducted using Dunn’s (1964) procedure with a Bonferroni correction for multiple comparisons. A statistical significance level of 0.05 was used for all tests; pairwise comparisons results were expressed as adjusted P values. Controlling data for outliers, the analysis was performed also removing the outliers and their presence was tolerated if they did not alter the significance of the results obtained. To assess correlations between variables, Pearson’s r or Spearman’s rho correlation indexes were used for normally and non-normally distributed variables, respectively. Statistical analysis was performed using SPSS (v 25; IBM Corporation, Armonk, NY).

Results

The parameters of cardiorespiratory fitness obtained during the incremental phase of cardiopulmonary exercise testing were significantly reduced in both groups of KTRs when compared to those of controls, showing lower peak VO2, maximal power output, VO2 at the VT1 and peak heart rate. The VO2/Work Rate slope was, however, comparable between all groups (see Table 3).

When comparing both groups of KTRs, aerobic exercise capacity was higher 12 months after transplant compared to 3 months post-surgery. In particular, peak VO2 (21.30±4.34 vs 26.37±7.96 ml/min/kg; \( P = 0.043 \)), maximal power output (105.48±28.19 vs 148.21±48.22 W; \( P = 0.007 \)) and OUES (1561.14±375.02 vs 1904.05±477.45; \( P = 0.023 \)) were found higher 1 year post-surgery. This was also confirmed by a more efficient ventilation as shown by the
lower VE/VCO₂ slope 12 months after transplantation (29.28 ± 4.25 vs 26.89 ± 2.57, P = 0.048; see Table 3 and Table S1 of the supplementary material).

Finally, the time constant τ of the VO₂ kinetics was slower in KTRs compared to controls (50.40 ± 13.11 s, 95% CI 44.4–56.4 s; 43.8 ± 11.57 s, 95% CI 37.2–50.5 s; 28.91 ± 8.37 s, 95% CI 24.4–33.4 s; both P < 0.01) (Table 3, Fig. 2).

Moreover, the time constant τ of KTRs showed negative correlations with peak VO₂ (ρ = −0.52, P < 0.01), peak power output (ρ = −0.59; P < 0.01), VO₂ at the VT1 (ρ = −0.41; P = 0.01), power output at the VT1 (ρ = −0.71; P < 0.01) and the OUES (r = −0.57; P < 0.01). No significant correlation was found between τ and Hb (r = −0.33, P = 0.06) or percentage-predicted peak heart rate (HR) (r = −0.05, P = 0.80). Conversely, Hb was more strongly correlated with main parameters of cardiorespiratory fitness, similarly to what found for patients’ peak HR (see Fig. 3 and Table S2).

### Table 3  Cardiopulmonary exercise test parameters and VO₂ kinetics analysis

| Parameter                                           | 3-month group            | 12-month group            | Control group            |
|-----------------------------------------------------|---------------------------|---------------------------|--------------------------|
| Number                                              | 21 (13 M, 8 F)            | 14 (12 M, 2 F)            | 16 (9 M, 7 F)            |
| Peak VO₂ (mL/min)                                   | 1443.81 ± 374.90* **     | 1951.58 ± 591.74** **     | 2861.49 ± 771.90         |
| Peak VO₂ (mL/kg/min) *                               | 21.30 ± 4.34 **           | 26.37 ± 7.96 **           | 41.70 ± 7.82             |
| Percentage of the predicted VO₂ peak (%)            | 75.7 ± 15.5 **            | 83.7 ± 22.8 **            | 109.9 ± 18.7             |
| Maximal power output (W) *                          | 105.48 ± 28.19 **         | 148.21 ± 48.22 **         | 251.56 ± 58.79           |
| Peak heart rate                                     | 133.43 ± 20.56 **         | 144.07 ± 21.41 **         | 181.25 ± 10.40           |
| Percentage of the maximal predicted heart rate (%)  | 79.67 ± 12.16 **          | 84.29 ± 11.49 **          | 93.38 ± 5.21             |
| Peak Respiratory exchange ratio *                   | 1.18 ± 0.10 **            | 1.18 ± 0.04 **            | 1.27 ± 0.09              |
| Parameters at the first ventilatory threshold       |                           |                           |                          |
| VO₂ (mL/min) *                                      | 910.43 ± 179.27 **        | 1090.86 ± 345.92 **       | 1594.63 ± 514.27         |
| VO₂ (mL/kg/min) *                                   | 13.50 ± 2.30 **           | 14.74 ± 4.50 **           | 23.44 ± 6.42             |
| VO₂ (percentage of peak VO₂)                        | 64.14 ± 7.63              | 56.88 ± 11.21             | 56.3 ± 11.54             |
| Power output (W) *                                  | 50.95 ± 15.70 **          | 70.00 ± 33.29 **          | 123.44 ± 44.22           |
| VO₂ kinetics analysis                               |                           |                           |                          |
| Time constant “tau” (τ) (s)                         | 50.40 ± 13.11 **          | 43.84 ± 11.57 **          | 28.91 ± 8.37             |
| Other parameters                                    |                           |                           |                          |
| VE/VCO₂ slope *                                     | 29.28 ± 4.25 **           | 26.89 ± 2.57              | 24.91 ± 2.93             |
| Oxygen uptake efficiency slope (mL/logL)            | 1561.14 ± 375.02 **       | 1904.05 ± 477.45 **       | 2762.49 ± 654.78         |
| VO₂/Work slope (mL/J/W)                             | 8.77 ± 2.0                | 10.04 ± 1.73              | 9.48 ± 1.42              |

Parameters are expressed as mean ± SD

*Significantly different (P < .05) from value obtained in 12-month group.

**Significantly different (P < .05) from value obtained in control group.

*Data are non-normally distributed in at least one of the three groups.

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**Fig. 2** The average values of VO₂ plotted against time and recorded during the constant load phases in the three study groups. Panel A shows the VO₂ kinetics of kidney transplant recipients evaluated 3 months after surgery, panel B shows VO₂ kinetics of patients evaluated 1 year after surgery and panel C shows VO₂ kinetics of the control group. The respective average time constant (τ) values of VO₂ kinetics are reported.
Discussion

To the authors’ knowledge, this is the first study to evaluate specifically VO₂ kinetics in KTRs with different follow-up periods after transplantation. The aim underlying this study was thus to investigate non-invasively the peripheral limitations to physical exercise in a group of patients with alterations at the muscular and microvascular level.

KTRs are known to have reduced aerobic exercise capacity in terms of peak VO₂, which tends to show a partial recovery during time after transplant (Kempenwiers et al. 1990; Habedank et al. 2009; Painter et al. 2011). The present study supports this evidence, in fact patients evaluated early after transplant showed an abnormally low peak VO₂ (75.7 ± 15.5% of predicted). This value seems to improve 1 year after transplant (83.7 ± 22.8% of predicted; Table S1). These results confirm existing data on VO₂ improvement after kidney transplant (Habedank et al. 2009; Painter et al. 2011) and, given the cross-sectional design of this study, warrant further longitudinal evaluations on larger numbers of patients. It seems reasonable that the main contributors to exercise intolerance in these patients have to be individually evaluated, considering central and peripheral limitations of the oxygen transport system. CKD patients often carry several complications of end-stage renal disease, such as anaemia, autonomic dysfunction, peripheral vascular disease and muscular abnormalities (Painter et al. 2011). The improvement in exercise capacity seen after kidney transplant has been associated with an increased cardiac output secondary to an increased peak heart rate (Painter et al. 2011), while the contribution of haemoglobin is likely to play a minor role (Marrades et al. 1996; Painter et al. 2011). Peripheral limitations typical of these patients seem to contribute to the impairment of aerobic capacity. Indeed, Painter et al. found no improvement in peripheral oxygen extraction of KTRs during a maximal exercise test compared to the pre-transplant evaluation, suggesting that no changes occur in muscle oxidative capacity with the normalization of renal function.

![Fig. 3](https://example.com/figure3.png)

The time constant τ of KTRs is negatively correlated with parameters of aerobic fitness, such as VO₂/kg (panel A) and the oxygen uptake efficiency slope (panel B). However, the time constant τ seems less associated with patients’ blood Hb concentration and peak heart rate (panel C and D, respectively).
(Painter et al. 2011). Similar results have been found also in patients with CKD, where the improvement in haemato-
crit and cardiac output obtained with erythropoietin-stimulating
agents and exercise training was not sufficient to normal-
ize the patients’ oxygen consumption, likely due to abnor-
malities found at the muscular level (Stray-Gundersen et al.
2016). Thus, the evaluation of muscular oxidative capacity
in patients with CKD or KTRs appears of primary impor-
tance for the assessment of physical function.

Our results showed that the two groups of KTRs had
slower VO₂ kinetics compared to a control group of young
and healthy adults, and that these higher time constants were
correlated with worse cardiorespiratory fitness, suggesting
a contribution of peripheral limitations to these patients’
exercise capacity. Even though few data on KTRs are avail-
able for comparisons, the time constants of our population
and the control group appear to be in line with previous evi-
dence on VO₂ kinetics, indicating feasibility and reproduc-
ability in clinical settings (Tomczak et al. 2008). Moreover,
George et al. analysed the VO₂ time constants in a group
of healthy individuals aged 18–45 year old that performed
physical activity 2–4 times per week and values determined
in the control group of the present study are similar to the
ones they found (τ = 28.91 ± 8.37 s vs 26.8 ± 7.5 s, respec-
tively) (George et al. 2018). Compared to the control group,
the time constants of KTRs were significantly slower at
3 and 12 months after transplantation (50.4 ± 13.11 s and
43.84 ± 11.57 s, respectively). Although methodological dif-
fferences between studies must be considered, VO₂ kinetics
of KTRs 3 months after surgery seemed generally slower
than those of older inactive individuals (44.8 ± 10.9 s),
which were comparable for KTRs of the 12-month group
(George et al. 2018). However, despite the age heterogene-
ity between groups, it was shown that physical fitness and
not aging per se, seems to determine the response of VO₂
kinetics (George et al. 2018). Moreover, even though data
about VO₂ kinetics in KTRs are limited, the values of time
constants previously found in patients with CKD undergo-
ing dialysis (62.5 ± 19.6 s) (Reboredo et al. 2015), let us
to hypothesize a partial recovery of submaximal periph-
eral aerobic metabolism after transplant, associated with
the shown improved cardiorespiratory fitness after kidney
transplantation. However, further longitudinal studies are
needed to ultimately assess the changes in VO₂ kinetics from
end-stage renal disease to a long-term follow-up after renal
transplantation.

Moreover, among patients of the present study, VO₂
kinetics were strongly correlated with indicators of physi-
cal fitness, and showed no significant correlations with cen-
tral determinants of the cardiopulmonary response to exer-
cise such as Hb and peak HR. On the contrary, indicators
of physical fitness showed better correlations with Hb and
peak HR (Table S2). Although these data cannot provide
information regarding the underpinning pathophysiological
mechanisms affecting VO₂ kinetics, study outcomes may
suggest that also peripheral adaptations occur after kidney
transplantation. As previously mentioned, current evidence
supports the hypothesis that slowed VO₂ kinetics during
moderate intensity cycling mainly reflect an impaired oxida-
tive capacity of the muscle. Even if this assumption is
still debated, particularly for patients with chronic diseases
(Poole and Jones 2012), the results of the present study
are in agreement with previous study outcomes, suggest-
ning that VO₂ kinetics could provide additional information
about these patients’ peripheral response to exercise (Tom-
czak et al. 2008). Furthermore, the found correlations and
reproducible absolute τ values when compared with previ-
ous studies show that an evaluation of VO₂ kinetics inside a
clinical setting, with a pre-defined constant load, can provide
reliable values of time constants. Moreover, these outcomes
seem to accurately reflect experimental evaluations of VO₂
kinetics at a defined percentage of the previously assessed
VT1. As previously stated also by Reboredo et al. in rela-
tion to patients with CKD, the assessment of VO₂ kinetics
provides additional information about an exercise intensity
domain that is close to that of most physical activities of
daily living (ADLs) (Reboredo et al. 2015). On these bases,
the analysis of VO₂ kinetics could thus result as a useful
integration to the comprehensive functional evaluation of
KTRs’ physical fitness, being relatively effort-independent.
Indeed, the time constant during submaximal exercise could
be used as marker for peripheral dysfunction in patients
whose exercise tolerance is limited by muscular abnormali-
ties (Stray-Gundersen et al. 2016).

Finally, although the absolute values of the time constants
of KTRs got closer to those of the control group during
12 months of follow-up, a statistically significant difference
was not reached between both groups of patients. Taking
also into account that peak VO₂ was higher 12 months
after transplantation, this might suggest a slower recovery
of peripheral muscle metabolism revealed at submaximal
exercise. Considering the good responsiveness of VO₂ kinet-
ics to exercise training programs, such type of intervention
should be recommended to KTRs to improve their periph-
eral exercise tolerance, especially at the clinically significant
workloads of common ADLs (Reboredo et al. 2015).

Limitations and perspectives

The limitations of the current study are mainly due to the
cross-sectional design, which does not allow exhaustive
considerations on the time course of VO₂ kinetics in KTRs.
Furthermore, this study has not been designed to specifi-
cally investigate underlying pathophysiological mechanisms
but study outcomes should motivate future basic research
to address this issue. Moreover, future studies should
investigate how ageing and exercise test intensity may affect VO₂ kinetics in this population. A prospective randomized controlled study, with a healthy and sedentary age-matched control group, investigating the impact of a specific exercise training intervention on VO₂ kinetics, would provide interesting information on the clinical impact and reversibility of peripheral exercise limitations.

Conclusions

In conclusion, it can be stated that our study is the first to evaluate peripheral oxidative muscle metabolism by VO₂ kinetics with specific standardized exercise testing in KTRs. It has been shown that KTRs have impaired exercise tolerance and physical fitness, with a partial although incomplete recovery 1 year after transplant. Also, the time constant τ of VO₂ kinetics is slower in KTRs at 3 and 12 months after transplantation compared to young and healthy subjects. The reduced aerobic exercise capacity of KTRs strongly correlated with slower VO₂ kinetics, which seem less associated with central determinants. A clinical evaluation of VO₂ kinetics could add useful information to routine cardiopulmonary exercise testing of KTRs, likely reflecting peripheral pathophysiological aspects of the integrated response to physical exercise, also investigating the workload intensities crucial for activities of daily living in this population.

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Authors’ contributions All authors contributed to the study conception. DN, FR, CDB, LF and AE designed the study. All authors were involved in the acquisition and/or interpretation of data. AP, SG and MB analysed the data. AP made the tables and figures, drafted and revised the paper; DN, SO, AG, FB and AE revised the paper. All authors approved the version to be published.

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Availability of data and materials The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of interest The authors have no conflicts of interest to declare that are relevant to the content of this article. LF reports personal fees from Chiesi Pharmacuetics, personal fees from Novartis, personal fees from Astellas, outside the submitted work.

Consent for publication No identifying information about participants is available in the article, details that might disclose the identity of the subjects under study have been omitted.

Ethics approval (include appropriate approvals or waivers) This study was approved by the Ethics Committee of the “Azienda Ospedaliera–Università” of Padova (approval number 43079). All procedures performed were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments.

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