Characterising recovery from renal transplantation and live-related donation using cardiopulmonary exercise testing

Post-operative recovery of live-related kidney donors and recipients

Original article

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Abstract

Background

An association between end-stage renal failure and exercise intolerance exists. Whether live kidney donation impacts on exercise tolerance is unknown. Here recovery post renal transplant and donation using cardiopulmonary exercise testing is investigated.

Methods

Renal donors (n=28) and recipients (n=24) undertook a cardiopulmonary exercise test, Duke activity score index and patient reported health score questionnaires pre-operatively and in the 7th and 14th week post-operatively. Anaerobic threshold, peak oxygen uptake and ventilatory equivalents were measured in relation to activity and reported health scores. Haemoglobin and renal function was recorded.

Results

Recipients showed impaired cardiopulmonary function compared to donors with lower anaerobic threshold (10.5 vs. 14.4 ml/kg/min) and peak oxygen uptake (18.5 vs 23.0 ml/kg/min). Post-operatively the anaerobic threshold of recipients improved and normalised by the 14th week, whereas that in donors fell by ~20% by the 7th (mean 11.4 ml/kg/min), recovering by the 14th (mean 15.6 ml/kg/min). Reported health but not activity scores showed similar changes.

Conclusions

Recovery following renal transplantation and donation differ. Transplantation improves renal function resulting in an increase in anaerobic threshold and peak oxygen uptake which essentially normalise by the 14th week post-operatively. Donors suffer a 20% reduction in cardiopulmonary reserve post-operatively, which recovers by the 14th week, suggesting no associated chronic exercise intolerance.

Key words: Kidney donors; Post-operative; Fitness; Kidney failure; Physiological burden

Introduction

Many studies have highlighted the association between exercise intolerance and chronic kidney disease (CKD)[1-6]. This is thought to be a result of the interplay of nutritional, metabolic and pathological factors which also contribute to the higher incidence of cardiovascular morbidity and mortality associated with end-stage renal failure (ESRF). In this group of patients exercise capacity may be an important factor in morbidity and mortality post-transplant [7-10]. ESRF patients have impaired peak oxygen uptake (VO_2 peak) and impaired exercise endurance which may reflect the high prevalence of heart failure and ischaemic heart disease [3-5,11-14]. Patients with ESRF, and a low anaerobic threshold (AT), are more likely to have left ventricular hypertrophy, poor left ventricular ejection fraction and have lower 5 year survival post- transplant [14]. Psychological factors are also thought to play a role in ESRF which has a high incidence of depression, anxiety and stress [10,13,15-17]. The combination of psychological morbidity with impaired exercise tolerance and perceived health limitation, results in a reduced quality of life in this group[15-17].

For patients with CKD, live or cadaveric transplantation is transformational in terms of quality of life, cost of treatment and survival, reducing mortality in ESRF by 40-60% compared to those that remain on dialysis [18,19]. Recovery from successful renal transplantation is accompanied by reversal of metabolic sequelae of ESRF and an associated improvement in exercise capacity and perceived health status [7,17]. The success of renal transplantation as a treatment for ESRF has seen a significant increase in the demand for both cadaveric and live kidney donation (LKD) [20].

Live donors are otherwise healthy individuals who altruistically undergo major surgery to donate to a patient with ESRF. Recovery following LKD is less well understood. It is

associated with a low complication rate and small incidence of ESRF, however, data regarding the impact of LKD on otherwise well patients is sparse. Renal transplantation appears to improve exercise capacity and perceived physical activity showing a rise in VO_2 peak compared to pre-transplantation [3-5,12]. However, there exists only limited data on the effects of renal donation on peri-operative exercise capacity [11] and to date there are no studies investigating the effect of LKD on cardiopulmonary exercise parameters.

Cardiopulmonary exercise testing (CPET) provides a dynamic assessment of cardiac and respiratory capacity which clinically has been shown to have powerful diagnostic and prognostic value [21-27]. It is a non-invasive test which objectively determines cardiopulmonary performance under stress; measuring breath-by-breath VO_2 and carbon dioxide production (VCO_2) to a uniform and incremental increase in the work of exercise [27-28]. In addition to its use by exercise physiologists to measure performance and guide training, it produces physiological data which can be used to detect cardiac ischaemia, pulmonary hypertension and chronic respiratory illness [27]. Of note is that it is particularly good in the diagnosis of the presence, degree and progression of heart failure, and the response to treatment [22,27]. Recently it has been used to risk stratify patients prior to major surgery through calculation of the AT; the oxygen uptake above which aerobic energy production is supplemented by anaerobic mechanisms resulting in lactate production. In essence, AT is an objective measure of cardiopulmonary fitness such that those with a low AT (<11 ml/kg/min) are at higher peri-operative risk of complications [21,23-26].

In this prospective study, we aimed to examine the functional status of renal recipients and donors in the pre-operative and recovery phases of transplant and donation surgery. CPET was used to characterise cardiopulmonary reserve (as defined by VO_2 peak and AT) pre- and

post-operatively, to investigate whether transplantation reverses the chronic exercise intolerance associated with CKD and whether renal donation is associated with a sustained reduction in exercise tolerance. Recovery from major surgery can be simply defined as return to pre-operative state or better [5,11,28,29]. Most studies investigating recovery from surgery have focused on questionnaires designed to elucidate the functional, emotional and psychological, nociceptive and satisfactory status of patients at various time points following surgery using composite and dichotomous scoring systems [28]. Few studies have investigated objective functional status in combination with patient reported outcome measures to characterise recovery from renal transplant and donation [5,11]. The present study combines CPET with a patient reported health status (PRHS) & Duke Activity Scale Index (DASI) to characterise recovery.

Methods

Patients and Recruitment

Renal donors (n=28) and recipients (n=24) were recruited in the renal outpatient's clinic during pre-operative assessment for the LKD-recipient program between 2010 and 2015. Informed consent was obtained by a consultant or clinical research fellow trained in Good Medical Practice. All patients received consultant delivered surgical and anaesthetic care. The study received local ethical approval from our local Health Research Authority, Bristol NRES Southwest, with restrictions that limited the study design such that it was not possible to recruit consecutive patients. Patients over the age of 18 years were considered for the study, with the following exclusions; Patients that suffered post-operative complications or were considered inoperable, those patients unable or unwilling to perform a CPET test or participate in the study, and patients from outside the Bristol area for whom participation would represent a significant burden. The study incorporated patient safety pathways to

identify patients with potentially reversible cardiac or pulmonary morbidity; in such cases the surgeon was informed and the patient referred to the appropriate specialty.

Cardiopulmonary exercise testing

Pre-operatively each patient underwent a CPET test between 2 days and 28 days pre-operatively (median 10 days) conducted by a trained Consultant Anaesthetist and technician in accordance with the American Thoracic Society and American College of Chest Physician Guidelines. 80% of patients had a pre-operative CPET within 2 weeks of the operative date. Thereafter, related renal donors and recipients were invited to attend repeat CPET test and routine blood tests in the 5-7th weeks (median 6.4 weeks; during the 7th week) post-operatively, to coincide with surgical follow-up and again 6 weeks later 12-14th weeks (median 13.4 weeks; during the 14th week) post-operatively. Routine blood tests included a full blood count and renal function tests including estimated glomerular filtration rate (eGFR). Prior to each test patients were weighed such that CPET data was weight-adjusted and each patient completed PRHS and DASI questionnaire. The following demographic data was collected; age, sex, height, weight, smoking status, chronic disease status (CKD, dialysis, diabetes, hypertension, heart failure, ischaemic heart disease, peripheral vascular disease, lung disease, cerebrovascular and other endocrine disease). Eight renal donors and six renal recipients did not return to complete the study. These patients were not different from their respective cohort in their demographics, blood tests (Hb, eGFR), CPET parameters (AT, VO_2 peak, VE/VCO_2) or outcome measures (PRHS and DASI, independent t-test, data not shown).

CPET tests were conducted on a cycle ergometer (Ergoline P10) with continuous side stream gas exchange analysis (Nspire Health, UK), as previously described [26]. Each patient was seated on the cycle ergometer connected to a 12 lead ECG, oxygen saturation monitor and

continuous non-invasive blood pressure cuff. Respiratory gas exchanged was measured from a tight-fitting facemask. An initial 2 min period of baseline data was collected at rest prior to a 90 second period of unloaded cycling. A ramp protocol was then applied and the patient was instructed to continue cycling at a constant cadence of 60 rpm as long as they could. Patients were positively encouraged to perform to their best prior to and during all of the exercise tests performed. The test was terminated if the patient indicated that they could not continue, if cadence fell below 55 rpm due to fatigue or dyspnoea, or developed abnormal cardiac signs or symptoms such as ischaemia and arrhythmia. The patients were continually monitored for a recovery period of 2 minutes unloaded cycling before finishing the test. Patients were kept under observation for a further 10 minutes after the test prior to being discharged.

AT was determined following each test using the V-plot technique and confirmed by ventilatory equivalents [27]. VO_2 peak was measured as the highest VO_2 attained over a 30 second period at peak exercise. V-plots and ventilatory equivalents at AT were calculated using the Zan 600 software (NSpire Health, UK). All CPET variables were determined on the day of the test and then independently verified by two researchers with CPET expertise and who were blinded to the donor/recipient status, PRHS and DASI analysis. The researchers performing the tests were not blinded to the groups as it was considered that blinding might present patient safety issues.

Duke activity scale index and patient reported health status

The DASI is a self-reported questionnaire which scores daily activities and estimates peak VO_2 [30], whereas the PRHS is a visual analog scale from 0 to 100% health status; here

patients were asked to mark on the scale how well they felt on the day of CPET testing, 100% being in the best health state and 0% being the worst health they could imagine.

Operative technique

Live donors underwent a left laparoscopic donor nephrectomy as previously described [11]. Post-operatively, pain was managed using a fentanyl patient controlled analgesia and switched to oral analgesia (paracetamol and tramadol) 24 hours' post-operative. Non-steroidal anti-inflammatories were avoided in both groups. Patients could eat and drink and were supplemented with intravenous maintenance fluid. Patients were considered for discharge once they were voiding consistently (>0.5ml/kg/min) and their urea and electrolytes were stable, tolerating food and fluids, and their pain was well controlled. They were routinely followed up at 5-7 weeks post-operatively.

Statistical Analyses

Statistical analysis was performed independently by the Applied Statistics Group of the University of the West of England. For an effect size of 0.67, or larger, (i.e. mid-point medium effect size), a sample size of n=20 would have in excess of 80% power to detect changes in AT (two sided, alpha = 0.05). Group comparisons were analysed using the independent t-test. Paired analyses were made using the paired sample t-test. Data is presented as mean ± standard deviation (± SD) or median (range). Two sided tests of statistical significance were used throughout and significance was taken as less than 5%.

Results

The demographic data for each group is shown in Table 1. There were no differences in the age or weight/BMI of patients and each group had similar proportions of male and female participants. Chronic disease status was markedly different as might be expected in comparison of renal recipients and those with live donors (see Table 1) with a relatively high incidence of hypertension and diabetes in the renal recipients, however the converse related to smoking status, with 20% of donors smoking tobacco at the time of pre-operative assessment. There was a difference in renal function and haemoglobin concentration between recipients and donors, again reflecting the CKD of the recipients (Table 1). In relation to CPET parameters, pre-operative AT, max heart rate and VO_2 peak were significantly lower in the recipient group compared to the donors, whereas ventilatory equivalents, VE/VCO_2 and VE/VO_2, were significantly higher in the recipient group (independent t-test; Table 1, Figure 1). Similarly, the recipient group scored significantly lower in the DASI and PRHS compared to renal donors (Table 1).

Further subdivision of recipients into those planned for pre-emptive transplantation and those who were treated with dialysis (Table 2), were comparable in all but baseline AT. The mean AT being significantly higher in patients with planned pre-emptive transplantation compared to patients undergoing dialysis ($P<0.01$, Independent t-test).

Renal transplantation was associated with a marked improvement in renal function with an increase in eGFR by the 7th week which was sustained in the 14^{th} week post-operatively ($p<0.001$, paired samples t-test; Table 3). This increase was accompanied by an improved cardiopulmonary reserve with a 25% increase in AT from 10.5 ± 2.8 ml/kg/min to 14.0 ± 3.6 ml/kg/min ($p<0.005$, paired samples t-test) and an increase in maximum heart rate (MHR) from 125 ± 24 bpm to 143 ± 21 bpm ($p<0.005$, paired samples t-test) in 14^{th} week post-operatively (Table 3, Figure 1a). Thus, by the 14^{th} week post-transplantation these parameters had essentially normalised being no different when compared to the mean AT and MHR of

donors pre-operatively (NS, independent t-test; cf. Tables 3 & 4). The effect of renal transplantation on AT was independent of changes in blood haemoglobin concentration (Hb), which did not change post-transplantation (Table 3). Renal transplantation had no effect on VO_2 peak or VE/VCO_2 at 7^{th} and 14^{th} weeks post-operatively (paired samples t-test; Table 3). However, O_2 pulse fell significantly post-transplantation ($p<0.005$, paired samples t-test; Table 3). Additionally, renal transplantation was associated with an increase in PHRS in the recipient group of 20% in the 7^{th} week post-operative and a further 8% by the 14^{th} week ($p<0.005$, paired samples t-test; Table 3), however in this group there was no change in the DASI over this period (Table 3).

Renal donation was associated with a small sustained decrease in eGFR in the donor group, from 79.5±14.6 ml/min/1.73m^2 pre-operatively to 53.0±12.3 ml/min/1.73m^2 in the 14^{th} week post-operatively ($p<0.005$, paired samples t-test). Similarly, there was a small but significant change in Hb in the donor group by the 7^{th} week which partially recovered, however remained significantly lower than pre-operative values (Table 4). In contrast to renal recipients, the AT in renal donors fell by approximately 20% in the 7^{th} week post renal donation (14.4ml/kg/min pre-operatively vs 11.4 ml/kg/min ($P<0.001$, paired samples t-test), and had normalised by the 14^{th} week post-operatively to 15.6±4.8 ml/kg/min (NS, paired samples t-test cf. pre-operative AT; Table 4, Figure 1b). VO_2 peak showed a similar pattern following renal donation, albeit less marked (Table 4). This peri-operative fall in AT was not accompanied by changes in other CPET variables, however the pattern of change in DASI and PRHS indices were very similar showing approximately a 20% decrease at the 7^{th} week and normalising to pre-operative values at 14^{th} week post-operatively (Table 4).

Discussion

This is the first study to examine recovery using determinants of oxygen uptake in renal donors and recipients on a LKD program. The study confirms that in comparison with normal subjects, patients with ESRF have impaired exercise capacity, activity indices and reported health status [3-5,11,13,14]. Renal transplantation is associated with a progressive improvement in these parameters such that by the 14th week post-operatively they have essentially normalised and are not significantly different to the pre-operative values measured in renal donors. By contrast renal donation is accompanied transient by a decline of approximately 20% in exercise tolerance, demonstrated by a significant fall in AT and VO_2 peak, by the 7th week post-operatively which recovers by the 14th week. The changes in exercise tolerance in the renal donors were accompanied by parallel changes in health status and activity indices. Thus, the findings of the present study demonstrate that recovery from renal donation is different to that following renal transplantation. In addition, the findings suggest that the chronic exercise intolerance associated with renal failure is reversible through transplantation and it is not a feature of renal donation, despite a small but persistent decline in renal function post donation.

There is an established relationship between exercise intolerance and renal failure such that patients with ESRF report low functional health status and perform poorly in exercise tests [1-6]. Underlying this relationship is a high burden of associated heart failure, coronary artery disease and chronic metabolic derangement [7-10]. Consequently, ESRF patients have been shown to have an attenuated MHR response to exercise, reduced VO_2 peak, AT and left ventricular ejection fraction [3,14]. Consistent with these studies are the findings of the present study which show that, pre-operatively, ESRF is associated with impaired cardiopulmonary reserve which appears to be more severe in patients undergoing dialysis

treatment who incidentally were found to have a lower pre-operative AT compared to patients undergoing pre-emptive transplantation. It is important to note that the numbers of patients in this study are however very small and this may not be reflected in future larger studies.

In comparison, renal donors, who, physiologically, are essentially normal subjects, have a significantly higher AT in a graded exercise protocol compared with renal recipients. Higher ventilatory equivalents for O_2 and CO_2 were also found pre-operatively in renal recipients, in comparison to the donors on the program. This suggests less efficient lung performance and V-Q matching in renal recipients, and is likely to be a further contributory factor to the overall impaired exercise tolerance seen in this group of patients. In terms of the DASI and PRHS, renal recipients score significantly lower than donors, again consistent with their measured cardiopulmonary reserve and the association of ESRF with lower perceived health status and psychological comorbidity in ERSF [15-17].

Perhaps the most encouraging finding is that the restorative effects of renal transplantation are not just restricted to measured renal function but also to cardiopulmonary exercise parameters, activity indices and reported health status. Hence, transplantation was associated with an acute and sustained improvement in eGFR and MHR following transplantation and a progressive increase in AT, normalising by the 14^{th} week post transplantation. However, there was no associated increase in VO_2 peak and a slight fall in O_2 pulse was observed in this group. Previous studies have demonstrated variable effects on VO_2 and O_2 pulse following renal transplantation such that Painter *et al.*, [3] have demonstrated an increase in VO_2 peak 6 months post transplantation, whereas Habedank *et al.*, [12] showed an initial fall in VO_2 peak at 3 months which had recovered 1 year following transplantation. Whilst these differences may reflect differences in the timing of CPET testing and variation in the

patient's volition and effort, it is noteworthy that in haemodialysis patients VO_2 peak will only improve with training [32] and that transplantation in combination with training is much more effective than transplantation alone at increasing VO_2 peak. In terms of cardiac output, the small reduction in O_2 pulse with a 14% increase MHR broadly supports the findings of previous studies, [3,11,14,32,33] suggesting an overall increase in cardiac output which contributes to improved exercise performance following renal transplantation.

Renal transplantation was associated with a sustained improvement in PRHS, however no change in the DASI. This may suggest that renal recipients may feel better but do not necessarily feel capable of increasing their activity by the 14th week following renal transplantation. The present study did not record patient activity following transplant. In renal donors changes PRHS and DASI mirrored those in AT and VO_2 peak; an initial fall in the 7th week post-operatively followed by normalisation to pre-operative values in the 14th week coincident with an increase in CPET parameters.

The difference in recovery profiles are unlikely to have resulted merely from the peri-operative changes in Hb experienced by the two groups which were not of adequate magnitude to explain the observed changes in AT and VO_2 peak; a change of 1g Hb is equivalent to only 0.97 ml/kg/min VO_2 [34]. The different profiles are more likely to result from a complex interplay of different pathological processes occurring in the two groups. Major surgery is associated with a severe stress response characterised by activation of the hypothalamo-pituitary adrenal and immune axes resulting in a deranged hormonal and inflammatory responses which precipitate hypermetabolism and hypercatabolism [35]. This response increases post-operative oxygen demand by 40-50% following major surgery [25], and in individuals unable to meet this demand, this can be catastrophic. Consequently, low

cardiopulmonary reserve, AT < 11ml/kg/min, is associated with higher complication rates and death post-operatively [21,23-26]. Pre-operatively, 14% (4/28) of renal donors in this study had an AT < 11ml/kg/min and would be considered at high risk for major complications peri-operatively which suggests that perhaps more rigorous risk stratification of donors might be a consideration if this is reflected in larger cohorts. The post-operative fall in AT and VO_2 peak in the donors probably reflects the impact of the surgical stress response on the cardiopulmonary reserve of these patients and it is tempting to postulate that measured earlier in the post-operative period these changes might be more profound. In contrast to the renal donors, patients with ESRF have reduced exercise capacity pre-operatively [7-10]. This is thought involve the interplay of nutritional, metabolic and pathological factors giving rise to uremic malnutrition, electrolyte disturbance, dyslipidaemia, anaemia and insulin resistance [36-39] which underlie the higher incidence of heart failure, atherosclerosis and mortality in these patients [40,41]. Renal transplantation is likely to be accompanied by a similar stress response to surgery as that seen in the renal donors, however in transplant patients there is a transformational change in metabolism occurring with the reversal of ESRF which may overpower and mask the effects of the surgical stress response.

Whatever the explanation it is clear from the results presented that the characteristics of recovery from renal transplant and donation are quite different. This has an important practical application in the peri-operative counselling of prospective renal donors and recipients. In our LKD program, the majority (>80%) of donors and recipients are related and as such witness each-others recovery. Greater knowledge of the recovery process is of value in both setting expectations and explaining the marked differences in recovery profiles of donors and recipients. This knowledge also helps patients to discharge plan and provides a more informed indication as to when return to work might be feasible. Previous studies have

shown that the majority of renal donors (79%) are concerned with their return to pre-operative fitness and returning to work, rather than the length of their hospital stay [29]. Interestingly Bergman *et al.,* [11] found that the median time to return to work following donor nephrectomy was 30 days, which, considering the present results, seems to coincide with return of cardiopulmonary fitness post-operatively.

For the renal recipients, the results of the present study are encouraging, they indicate that transplantation is associated with a gradual improvement and near normalisation by the 14th week post-operatively. This is accompanied by a similar increase in perceived health status and overall the results, whilst broadly consistent with previous studies, extend our understanding of recovery post transplantation from live donated kidneys in terms of the AT which represents a more objective and consistent measure of cardiopulmonary function than the changes in VO_2 peak previously reported [3-5].

There are obvious limitations to the present study. The stipulations of the ethics committee limited the recruitment to the local patient population, dictating the study design such that consecutive patients could not be recruited. This slowed the study progression and limited numbers recruited. In this study 27% (14/52) individuals dropped out of the study after the pre-operative evaluations. It is unlikely that this resulted in a cardiopulmonary fitness selection bias as their pre-operative CPET parameters were not different to those patients who went on to complete the study. However, there may have been some psychological differences with these individuals which may have influenced the PRHS and DASI scores. In this regard, the data presented may not be generalisable to the patient populations studied. In retrospect, it would have been informative to have some indices of the activity of patients over the study period to correlate with their reported activity and the CPET parameters measured. However, it is encouraging that within each of the groups, individual recovery

profiles showed similar patterns of change over time and showed internal consistency. Furthermore, the results in the renal recipients concur with previous studies cited. The study also benefits from a blind approach between measured variables and CPET reporting, and the use of an independent statistician.

In conclusion, the results of this study show that recovery from renal transplantation and live kidney donation differ temporally in terms of cardiopulmonary reserve. The chronic exercise intolerance associated with ESRF is reversible on transplantation and live kidney donation does not appear to affect cardiopulmonary reserve which recovers to pre-operative levels by the 14th week post-operative.

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Tables

Table 1: Base Line Demographics, cardiopulmonary parameters and biochemistry for recipients and donors, as measured pre-operatively

Demographics, CPET parameters and biochemistry	**Recipients (n=24)**	**Donors (n=28)**
Mean Height (*cm (±SD)*)	175.2 (9.0)	172.1 (9.0)
Mean Weight *(kg (±SD)*	79.4 (11.1)	71.1 (12.5)
Median Age (range)	46 (18-67)	50 (28-72)
Haemodialysis/ CAPD (n)	10/2	0
Hypertension	71%	10%
Diabetes	19%	0
Smoking status	0	20%
Beta blockers	19%	5%
Insulin	9.5%	0
AT (ml/kg/min)	10.5 (2.7)***	14.4 (3.2)
VE/VCO_2	30.6 (3.8)***	27.1 (2.6)
VE/VO_2	33.5 (4.4)**	30.8 (1.3)
Max Heart Rate (bpm)	123 (23)***	150 (18)
VO_2 Peak ml/kg/min	18.5 (5.3)**	23 (5.8)
eGFR ml/min/1.73m^2	9.5 (3.0)***	79.6 (13.9)
Hb g/l	11.8 (1.4)***	13.9 (1.2)
DASI	28.5 (6.6)***	34.3 (0.9)
PRHS	53.8 (13.8)***	89.8 (8.3)

*Independent t-test comparing means between donor and recipient groups; *** P<0.05, ** P<0.01, ***P<0.005.*

Table 2. Comparison of baseline cardiopulmonary parameters, biochemistry and patient reported outcomes in recipients that received pre-emptive kidney transplantation and those who with dialysis treatment prior to transplantation.

Demographics, CPET parameters and biochemistry	Pre-emptive Transplantation (n=12)	Dialysis (n=12)
AT (ml/kg/min)	11.9 (2.4)**	9.2 (2.6)
VE/VCO_2	30.8 (4.1)	29.0 (2.8)
VE/VO_2	33.6 (5.1)	32.4 (3.6)
Max Heart Rate (bpm)	113 (17)	129 (4)
VO_2 Peak ml/kg/min	15.3 (3.2)	14.3 (5.6)
eGFR ml/min/1.73m^2	9.9 (3.1)	8.3 (3.3)
Hb g/l	11.7 (1.4)	11.9 (1.5)
DASI	32.3 (5.3)	28 (6.6)
PRHS	53.8 (12.0)	49.6 (14.2)
Dialysis vintage (months)		18.5 (1-86)

*Independent t-test, ** P<0.01 between pre-emptive transplantation and dialysis treatment. Dialysis vintage is presented as mean with the range in parentheses.*

Table 3: Changes (mean ± SD) in peri-operative cardiopulmonary parameters, patient reported outcomes and biochemistry for renal recipients (n=18) and 95% Confidence intervals for the mean difference compared to pre-operative values [lower, upper].

	Pre-Op	**7th week post-operative**	**14th week post-operative**
AT ml/kg/min	10.5 (2.8) $^{\Psi\Psi\Psi}$	12.2 (2.6)*** [-2.61, -0.87]	14.0 (3.6)*** [-5.27, -1.71]
VE/VCO_2	30.2 (3.9) $^{\Psi\Psi}$	31.8 (4.4) [-3.76, 0.61]	31.7 (4.2) [-3.64, 0.60]
VE/VO_2	33.9 (4.6)	37.8 (6.2)*** [-6.82, -1.13]	37.7 (6.4)* [-7.10, -0.51]
Max Heart Rate (bpm)	125 (24) $^{\Psi\Psi\Psi}$	145 (25)*** [-33.4, -7.62]	143 (21)*** [-33.6, -8.54]
O_2 Pulse 100ml(beat*kg)	15.7 (4.4)	13.5 (4.4)*** [0.98, 3.40]	13.8 (3.6)** [0.15, 3.58]
VO_2 Peak ml/kg/min	19.2 (5.4) $^{\Psi}$	18.4 (4.9) [-0.96, 2.56]	19.5 (5.1) [-2.58, 1.90]
eGFR ml/min/1.73m^2	9.6 (3.2) $^{\Psi\Psi\Psi}$	52.8 (12.3)*** [-49.62, -36.82]	53.6 (10.6)*** [-49.49, -38.21]
Hb g/l	11.9 (1.4) $^{\Psi\Psi\Psi}$	12.2 (1.6) [-1.16, 0.50]	12.9 (1.7) [-2.08, 0.06]
DASI	29.2 (6.5) $^{\Psi\Psi\Psi}$	27.5 (6.3) [-0.56, 4.90]	29.0 (6.5) [-2.5,2.65]
PRHS	50.4 (11.5) $^{\Psi\Psi\Psi}$	71.4 (12.2)*** [-27.91, -13.04]	79.8(12.6)*** [-35.90, -19.89]

****p<0.005, **p<0.01, and *p<0.05 paired samples t-test mean (±SD) compared to pre-operative value and independent t-test ($^{\Psi\Psi\Psi}$p<0.005,$^{\Psi\Psi}$p,0.01,$^{\Psi}$p<0.05) between recipient and donor pre-operative means (cf Tables 1 & 2).*

Table 4: Changes (mean ± SD) in peri-operative cardiopulmonary parameters, patent reported outcomes and biochemistry for live donors (n=20) 95% Confidence intervals for the mean difference compared to pre-operative values [lower, upper].

	Pre-Op	7th week post-operative	14th week post-operative
AT ml/kg/min	14.4 (3.4)	11.4 (2.9)*** [2.03, 3.86]	15.6 (4.8) [-3.14, 0.74]
VE/VCO_2	27.4 (2.6)	27.9 (2.7) [-5.13, 1.34]	28.4 (3.7) [-5.59, 0.83]
VE/VO_2	31.7 (3.8)	32.4 (3.6) [-2.20, 0.83]	35.3 (6.0)* [-6.59, -0.52]
Max Heart Rate (bpm)	151 (18)	148 (18) [-2.32, 8.82]	154 (16) [-8.94, 3.54]
O_2 Pulse 100ml(beat*kg)	15.3 (3.8)	14.3 (3.9) [-1.56, 2.42]	15.9 (6.3) [-3.84, 1.48]
VO_2 Peak ml/kg/min	23.3 (6.2)	21.0 (6.3) [-1.41, 4.00]	23.5 (6.9) [-3.69, 1.27]
eGFR ml/min/1.73m^2	79.5 (14.6)	53.6 (11.9)*** [21.89, 29.91]	53.0 (12.3)*** [24.02, 30.98]
Hb g/l	13.9 (1.1)	13.0 (1.5)* [0.48, 1.43]	13.4 (1.0)* [0.19, 0.77]
DASI	34.3 (1.0)	27.6 (5.8)*** [4.26, 9.36]	33.1 (3.3) [-0.19, 2.45]
PRHS	89.1 (8.5)	73.1 (11.1)*** [10.73, 21.27]	91.3 (7.1) [-5.80, 1.40]

****p<0.005, **p<0.01, *p<0.05 paired samples t-test of mean (±SD) pre-operative value.*

Figure 1. Individualised changes in AT for renal recipients (1a) (n=18; left panel) and donors (1b) (n=20; right panel) measured pre-operatively (time = 0) and during the 7^{th} and 14^{th} weeks post-operatively.