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Effects of Modality Change and Transplant on Peak Oxygen Uptake in Patients With Kidney Failure

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Abstract

Background—Exercise capacity as measured by VO_{2peak} (peak oxygen uptake) is low in hemodialysis patients. The current study assesses the determinants of VO_{2peak} in patients with chronic kidney failure who changed kidney replacement modality to either frequent hemodialysis or received a kidney transplant.

Study design—Cohort study with assessment at baseline and 6-months following modality change.

Setting & Participants—Participants included non-diabetic individuals receiving conventional hemodialysis who a) remained on conventional hemodialysis (n=13), b) changed to short daily hemodialysis (n=10), or c) received a transplant (n=5), and d) individuals who received pre-emptive transplant (n=15). Additionally, 34 healthy controls were assessed at baseline only.

Predictor—Modality change

Measurement & Outcomes—Exercise capacity, assessed from the physiologic components of the Fick equation ($VO_2 = \text{cardiac output} \times a-vO_{2dif}$, where $a-vO_{2dif}$ is arterial to venous oxygen difference) was determined by measurement of VO_{2peak} and cardiac output during symptom-limited exercise testing. Analysis of covariance was used to compare the differences in changes in VO_{2peak} , cardiac output, heart rate, stroke volume, and $a-vO_{2dif}$, at peak exercise between those who remained on hemodialysis and those who underwent transplant.

Results—Transplant was the only modality change that was associated with a significant change in VO_{2peak} , occurring as a result of increased peak cardiac output and reflecting increased heart rate without change in peak $a-vO_{2dif}$, despite increased hemoglobin levels. There were no differences in those who changed to daily hemodialysis compared to those who remained on conventional hemodialysis.

Limitations—Small, non-randomized study.

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Conclusions— $\text{VO}_{2\text{peak}}$ increases significantly following kidney transplant but not with daily hemodialysis; this improvement reflects increased peak cardiac output via increased peak heart rate. Despite statistical significance, the increase in $\text{VO}_{2\text{peak}}$ was not clinically significant, suggesting the need for interventions such as exercise training to increase $\text{VO}_{2\text{peak}}$ in all patients, regardless of treatment modality.

Index Words

Exercise Capacity; oxygen uptake; Fick Equation; cardiac output; ESRD; frequent hemodialysis; kidney transplantation

It is well documented that exercise capacity as measured by peak oxygen uptake ($\text{VO}_{2\text{peak}}$) is low in patients with end stage renal disease (ESRD) treated with dialysis^{1–5}. There are many factors prevalent in dialysis patients that may contribute to low $\text{VO}_{2\text{peak}}$ in this patient group, including anemia, cardiac dysfunction (reduced contractility, increased preload and afterload), vascular dysfunction (limiting ability to divert cardiac output to skeletal muscle), skeletal muscle abnormalities (reduced fiber size, capillary density, mitochondrial density/function, increased diffusion distance) and/or metabolic abnormalities and autonomic dysfunction^{6–8,9, 10,11,12, 13}. A 2002 study by Sietsema et al¹⁰ had sufficient power to perform regression analysis to identify clinical and demographic predictors of $\text{VO}_{2\text{peak}}$; in 193 hemodialysis patients, older age, lower hemoglobin and diabetes were the only significant clinical or demographic predictors of lower $\text{VO}_{2\text{peak}}$. There has been only one published study that measured the determinants of $\text{VO}_{2\text{peak}}$ in hemodialysis patients during peak exercise (e.g. cardiac output and arterial to venous oxygen difference (a- $\text{vO}_{2\text{dif}}$)). This study by Moore, et al¹ found that both cardiac output and a- $\text{vO}_{2\text{dif}}$ were similar to normal reported values at rest; however, at peak exercise, both the cardiac output (primarily reflecting a blunted heart rate response in the setting of a normal stroke volume) and a- $\text{vO}_{2\text{dif}}$ (reflecting reduced arterial oxygen content) were reduced, resulting in reduced oxygen supply to the working muscles.

The suggestion that factors associated with uremia contribute to systemic limitations in $\text{VO}_{2\text{peak}}$ is supported by data published on the effects of kidney transplants on $\text{VO}_{2\text{peak}}$. Painter et al¹⁵ reported that shortly following successful transplant, $\text{VO}_{2\text{peak}}$ increased 27% without exercise training (from 1.68 ± 0.35 to 2.13 ± 0.42 L/min). Peak heart rate increased from 81% of age-predicted levels to 93% of age-predicted levels after transplant, suggesting that this blunted heart rate could contribute to impaired cardiac output at peak exercise. In addition, Chan et al¹⁶ reported increases in $\text{VO}_{2\text{peak}}$ following increases in frequency of hemodialysis from 4 hours thrice weekly to 8–10 hours 5–6 nights/week, although peak heart rates remained below expected normal levels. In these studies, normal age-predicted levels of $\text{VO}_{2\text{peak}}$ were not achieved after either of these modality changes.

The aim of the current study was to identify physiologic mechanisms whereby uremia limits exercise capacity and the extent to which they change with a kidney transplant or more frequent dialysis. The hypothesis was that the physiological responses to exercise and determinants of $\text{VO}_{2\text{peak}}$ would improve in patients who changed to short daily hemodialysis (HD) compared to those who remained on conventional hemodialysis and would be similar to those who received a transplant.

METHODS

Study Design

Four groups of patients with ESRD were studied in a pre-post design 6 months apart (baseline and visit 2): group 1 included patients who were treated with conventional

hemodialysis (3–4 hr, 3x/week) and did not change modality; group 2 changed from conventional hemodialysis to short daily hemodialysis (3 hours, 5–6 days/week); group 3 changed from conventional hemodialysis to receipt of a kidney transplant; and group 4 included patients who received a preemptive kidney transplant. Transplant recipients were tested within 2 weeks of living donor transplant and again 6 months after the procedure. Those changing to short daily dialysis were tested within a week of starting training for daily dialysis and again 6 months after beginning daily treatments. A fifth group comprised of sedentary individuals was recruited from a list of kidney donors and served as controls; these individuals were tested only once.

Subjects

The study was designed to evaluate the effects of reduction of uremia. Thus patients with other comorbidities/conditions that would have independent effects on exercise capacity (i.e. diabetes mellitus, pulmonary disease, cardiac disease, etc) were excluded. Inclusion criteria were: SRD requiring kidney replacement therapy; either stable on conventional hemodialysis for at least 3 months or scheduled for transplant; able to provide informed consent; over 18 years of age; and English speaking. Other exclusion criteria were: orthopedic or musculoskeletal factors that limit or could be exacerbated by exercise; hematocrit <33%; recent (within 1 year) cardiovascular event; pulmonary disease; peripheral vascular disease or progressive degenerative muscular disease; diabetes; and contraindications to maximal exercise testing as defined by the American College of Sports Medicine¹⁷. Demographic and clinical information was obtained from the medical record or dialysis chart or from self-report.

Conventional hemodialysis patients were recruited from five centers, CHD-SDD from 3 centers and transplant recipients from the University of California San Francisco (UCSF) and the University of Minnesota.

Dialysis patients responded to posted fliers or were referred by dialysis staff; preemptive transplant recipients gave permission to nurse coordinators or physicians to be referred. Sedentary healthy control subjects were recruited from kidney donors (>1 year post donation with normal kidney function as indicated by estimated GFR) at the University of Minnesota. A letter was sent to 420 kidney donors within a 100-mile radius of the medical center, from which 180 interested individuals responded. Study subjects were selected in an attempt to match the group of control subjects to the patient group by percentage of women, general physical activity levels and age decades. All subjects provided informed consent, and the study was approved by the Committee on Human Subjects at UCSF and the Institutional Review Board at the University of Minnesota.

Testing

All testing was performed in the General Clinical Research Center at UCSF or the University of Minnesota. Testing was performed on a mid-week non-dialysis day, at least 15 hours after completion of the dialysis treatment; most patients were tested between 20 and 24 hours following completion of their dialysis treatment. All blood pressure medications were held after the dialysis session; since most patients did not take antihypertensive medication prior to dialysis, most were off medications for over 24 hours, including beta-blocking agents. As beta-blockers can affect exercise heart rate, it is important to note that the longest half-life of beta blocking agents is up to 24 hours in patients with kidney failure. Thus, patients were tested when the medication was reduced to at least one-half its peak levels. Non-dihydropyridine calcium channel blockers may also lower heart rates and have a half-life of 12 hours. Patients were fasted upon arrival for blood sampling. Exercise testing was performed one hour after a small meal.

Exercise Testing—Exercise testing used a branching treadmill protocol that started at a brisk walking speed with gradual increases in grade every 2 minutes to assure that at least 4 measurements were obtained between rest and peak exercise. Patients were instructed to exert themselves to maximal levels. When the subject was unable to keep pace with the treadmill or requested to stop, cardiac output and blood pressure were measured before stopping. Electrocardiogram (heart rate) was measured continuously, and blood pressure, oxygen uptake (VO_2 in L/min), and cardiac output were measured at each stage. Peak values were those measured at peak exercise.

Oxygen uptake was measured by analysis of expired oxygen, carbon dioxide and volume using the Quinton QMC metabolic measurement system (www.cardiacscience.com) at UCSF or the Beck Physiological Measurement System at UMN. The Beck system uses a mass spectrometer for analysis of oxygen and CO_2 , and a pneumotachograph for expired air volumes. Measurement systems were calibrated with known calibration gases prior to each test. Cardiac output (L/min) was measured noninvasively using the Acetylene Open Circuit (OpCirc) inert gas wash-in method, and analyzed by Beck Integrated Physiological System software. The patient breathed into a non-rebreathing valve which is connected to a pneumatic valve that allowed switching the inspired gas from room air to a test gas mixture (0.7% C_2H_2 , 21% O_2 , 9% He, balance N_2). The patient was switched to the test gas during an expiration, so that the following inspiration was test gas. Eight to ten breaths were sampled using a mass spectrometer (Perkin-Elmer 1100; www.matechservices.com). This method of cardiac output measurement was previously tested against direct Fick measurements by Johnson, et al.¹⁸ and was reported to be highly correlated with direct Fick at rest and during exercise ($R^2=0.90$) with coefficient of variation at moderate to high exercise intensities determined to be 3–5%. These investigators concluded that the OpCirc method provides reproducible and reliable measurements of cardiac output during all levels of exercise. The coefficient of variation for this measurement at maximal exercise in our lab is 2.9%, with test-retest correlations during exercise of $r=0.93$.

Calculations/Definitions—The Fick equation was used to calculate arterial-venous oxygen difference ($\text{a-vO}_{2\text{dif}} = \text{cardiac output}/\text{VO}_2$). Also calculated were: stroke volume (which is equal to cardiac output divided by heart rate); arterial oxygen content (equal to $1.36 \times [\text{hemoglobin}] \times 0.97 + 0.3$); mixed venous oxygen content (equal to difference between arterial oxygen content and $\text{a-vO}_{2\text{dif}}$ [assuming 97% saturation and PaO_2 of 95 mmHg with no hemoconcentration with exercise]); and age predicted heart rate (or $220 - \text{age}$). Predicted VO_2 was calculated using the prediction equations referenced by Bruce et al.¹⁹.

Laboratory Measures—Fasting blood samples were used to assess blood chemistries and hematology. The most recent value for Kt/V was obtained from the dialysis chart to assess dialysis adequacy. For the daily dialysis group, the single pool Kt/V value reported in the monthly labs was multiplied by the number of days dialyzed per week.

Statistical Analysis

Basic descriptive data was calculated for all groups. Patient values were compared to sedentary controls at baseline and at visit 2 using analysis of variance. A change score was calculated for each variable (visit 2–baseline). Significance of change from baseline to visit 2 was determined by pooling the data and performing analysis of covariance with baseline values and group as covariates with the change score as the outcome variable. Post hoc analysis compared each of the 3 groups that changed modalities to the reference group that remained on conventional HD.

Because of the small sample sizes in the patient groups and because the two groups that remained on hemodialysis and received a transplant were similar, we combined those who remained on dialysis (those who began on conventional HD and either remained on that modality or changed to short daily HD) and also combined those who received transplants (both those who started on conventional HD and those who had a pre-emptive transplant). Change from baseline to visit 2 was determined for all outcome variables by pooling the data and performing analysis of covariance with baseline values and group (dialysis versus transplant) as covariates. Significance for all tests was set at $p=0.05$. Statistical analysis was performed using SPSS v17 (SPSS, www.spss.com).

RESULTS

Subjects

A total of 61 patients and 36 sedentary controls were recruited into the study and tested. Of the total recruited ($n=97$), 77 subjects are included in the analyses (43 patients and 34 controls). Figure 1 shows the reasons for loss to analysis in all groups.

The patient groups consisted of 18% women (15% in the dialysis group and 22% in the transplant group), and 17% of the controls were women (Table 1). The age within patient groups was similar; however control subjects were significantly older than the patient groups. There was no difference among groups in BMI. Those in the group that changed from conventional HD to transplant were younger than controls, and participants in the combined transplant group were on dialysis less time than those who remained on hemodialysis ($p<.001$). There was no difference in the total number of antihypertensive medications among patient groups. Six patients (all in the preemptive transplant group) were taking non-dihydropyridine calcium channel blockers at baseline. Most patients treated with dialysis were taking erythropoietin stimulating agents at baseline. All but four patients receiving hemodialysis at baseline had arteriovenous fistulas; the four dialyzing with catheters were in the group whose members changed from conventional HD to short daily HD.

Following transplant there were significant improvements in serum BUN (to 21.6 ± 5.1 mg/dL) and creatinine (to 1.7 ± 0.5 mg/dL). Hemoglobin increased slightly (to 13.2 ± 1.9 g/L; $p = 0.05$); however, the hemoglobin remained low in the patient groups compared to the controls. Although serum creatinine and BUN were normalized following transplant, the eGFR was significantly lower than that of the control subjects (49.2 ± 2.4 vs. 69.1 ± 13.1 ml/min/1.73m²; $p=0.01$). Immunosuppression was primarily tacrolimus, sirolimus and mycophenolate mofetil; 12 patients were taking prednisone. Following transplant, 10 were taking beta-blocking agents and 2 remained on non-dihydropyridine calcium channel blockers. Following transplant, 3 of the 5 patients in the conventional HD to transplant group had functioning arteriovenous fistulas.

Patients in the conventional to short daily HD group changed to the NxStage[®] dialysis machine (www.nxstage.com), increasing the frequency of treatments from 3 days/week (3.4 ± 0.3 hours/session) to an average of 5.6 ± 0.5 days/week (2.8 ± 0.2 hours/session), which resulted in a change in a weekly Kt/V from 1.39 ± 0.34 to 2.77 ± 0.48 . Those who remained on conventional hemodialysis dialyzed 3 days/week for 3.4 ± 0.5 hours/session and Kt/V averaged 1.44 ± 0.21 ; this did not change at visit 2. At visit 2, only on dialysis patient in the group that changed to short daily HD had a catheter and three patients in this group had discontinued beta-blocking agents. There were no changes in blood pressure medications in the group that remained on conventional HD.

Exercise capacity

Physiologic variables at baseline and visit 2 for all groups are found in table 2. At baseline the patients that remained on dialysis had significantly lower $\text{VO}_{2\text{peak}}$ than controls, while patients who were scheduled for transplant were similar in $\text{VO}_{2\text{peak}}$ to controls. All patients at baseline had similar peak cardiac output as controls; however patients achieved peak cardiac output through significantly higher peak stroke volumes because peak heart rates were lower in all the patients at baseline compared to controls. The $\text{a-vO}_{2\text{dif}}$ was also lower in all patients at baseline compared to controls (table 2).

$\text{VO}_{2\text{peak}}$ did not change from baseline to visit 2 in those who remained on dialysis but increased significantly among the patients who received a transplant ($p=0.01$) (table 2; figure 2). Significant differences were found between those who remained on dialysis and those who received a transplant in the change in the physiological determinants of $\text{VO}_{2\text{peak}}$: the transplant group increased peak cardiac output compared to hemodialysis ($p=0.002$) as a result of increased peak heart rate ($p=0.04$). The change in $\text{a-vO}_{2\text{dif}}$ was not different in those who remained on dialysis versus those who were transplanted (Table 2 and Figure 2). There were no differences in any of these physiological measures between those who stayed on conventional hemodialysis and those who changed to daily hemodialysis ($p=0.9$) (Table 2).

Despite changes following transplant, patient groups achieved only 68% (hemodialysis) and 79% (transplant) of age-predicted $\text{VO}_{2\text{peak}}$. All patient groups remained significantly lower than the controls in peak heart rate with the dialysis patients achieving only 82% of age-predicted heart rate, and transplant patients achieving an average of 90% of age-predicted heart rate at visit 2. Patients also remained lower than controls in $\text{a-vO}_{2\text{dif}}$ ($p=0.03$).

Discussion

This is the first study to measure the determinants of $\text{VO}_{2\text{peak}}$ in ESRD patients treated with different kidney replacement therapies. Patients who remained on dialysis did not change in $\text{VO}_{2\text{peak}}$ whereas those who were transplanted significantly improved their $\text{VO}_{2\text{peak}}$. This change following transplant was the result of increases in peak cardiac output through increases in peak heart rate with no change in stroke volume. There were no changes in $\text{a-vO}_{2\text{dif}}$, despite a slight but significant increase in hemoglobin in the transplant group. The change in $\text{VO}_{2\text{peak}}$ in transplant recipients in this study was less than has been reported previously¹⁵, perhaps because the current group had higher $\text{VO}_{2\text{peak}}$ prior to transplant than in the earlier study (1.68 L/min vs 2.29 L/min). The increase in $\text{VO}_{2\text{peak}}$ in this study (adjusted mean change of 0.28 L/min), though statistically significant, was minimal in terms of clinical significance. However, given that those remaining on dialysis did not change, increased exercise capacity can be identified as a physiologic benefit of transplants.

Transplant recipients achieved a $\text{VO}_{2\text{peak}}$ similar to that of the control subjects, however, it should be noted that the control subjects in this study performed worse than expected (84% of age predicted $\text{VO}_{2\text{peak}}$). Thus, although $\text{VO}_{2\text{peak}}$ values improved significantly following transplant, they remained low (79% of their age-predicted $\text{VO}_{2\text{peak}}$ levels). Kempeneers et al²⁰ reported that $\text{VO}_{2\text{peak}}$ in kidney transplant recipients remained low compared to normal subjects. It is possible that exercise training may improve $\text{VO}_{2\text{peak}}$ above that observed with TX alone through improvement in muscle function, which might increase the ability to widen the $\text{a-vO}_{2\text{dif}}$. Since we did not observe any change in $\text{a-vO}_{2\text{dif}}$ with transplant alone, exercise training may be warranted to further improve $\text{VO}_{2\text{peak}}$.

It has been suggested that $\text{VO}_{2\text{peak}}$ in hemodialysis patients could be limited by both central oxygen delivery mechanisms and/or peripheral (skeletal muscle) oxygen utilization factors²,

21, 22. The current study is the first to measure the determinants of $\text{VO}_{2\text{peak}}$ using the Fick Equation to evaluate physiologic responses to exercise after a change in uremic state. We found that $\text{VO}_{2\text{peak}}$ is limited by central factors primarily due to a blunted heart rate response to maximal exercise. In hemodialysis patients, treatment of uremia with successful transplant improves but does not normalize these central responses to exercise and does not change peripheral factors (i.e. ability to widen the $\text{a-vO}_{2\text{dif}}$).

Peak heart rates were lower than the controls in the patient groups at both baseline and at visit 2. Beta-blocking agents could have affected the heart rate response to exercise; however, peak heart rate in the transplant group increased at visit 2 despite beta-blocking agents being added to one patient and remained low in the hemodialysis group despite 3 patients discontinuing this class of medication. We attempted to minimize the effects of beta-blocking agents by holding them for at least 15 hours prior to the exercise testing, with most being held from 20–24 hours prior to testing. Painter et al¹⁵ analyzed changes in peak heart rate after transplant in only those not on beta-blockers and reported similar changes. The abnormal chronotropic response to exercise in HD patients has been reported elsewhere and could reflect a manifestation of autonomic dysfunction commonly reported in dialysis patients^{23–28}.

Changes in hemoglobin levels in the transplant group could contribute to changes in $\text{VO}_{2\text{peak}}$; however this would have resulted in a widening (or increase) of the $\text{a-vO}_{2\text{dif}}$, which was not observed. The earlier study by Painter, et al¹⁵ reported that the correlation between change in $\text{VO}_{2\text{peak}}$ following transplant and change in hematocrit was $r^2 = 0.13$. Also, normalization of hemoglobin with epoetin (from 10.7 g/L to 13.6 g/L) in HD patients did not change $\text{VO}_{2\text{peak}}$ ⁴. In a recent systematic review and meta-analysis of exercise capacity and ESA treatment in hemodialysis patients, Johansen et al⁹ concluded that there is no real increase in $\text{VO}_{2\text{peak}}$ with increasing hematocrit beyond partial correction to 30–33%. Likewise, as reported by Stray-Gundersen et al¹⁴ when hemoglobin was increased in hemodialysis patients, the $\text{a-vO}_{2\text{dif}}$ stayed relatively constant (i.e., with the increase in arterial oxygen content, there was a parallel increase in mixed venous oxygen content²⁹, suggesting a set limitation in oxygen extraction (that is represented by $\text{a-vO}_{2\text{dif}}$). In our transplant recipients, the venous oxygen content did not change, suggesting no change in muscle oxygen extraction/utilization after transplant.

The low $\text{a-vO}_{2\text{dif}}$ at both testing times in all patient groups suggests a peripheral limitation in these patients. A limitation in $\text{a-vO}_{2\text{dif}}$ could be due to lower arterial oxygen content, as well as any number of peripheral factors that would affect oxygen extraction by the skeletal muscle (and thus mixed venous oxygen content), including abnormal blood flow to the working muscle^{30, 31}, abnormalities in the skeletal muscle such as reduced capillary density^{2, 32}, increased diffusion distances which reduce oxygen conductance from the capillary to the myofibril³⁰, and abnormal oxidative enzyme levels or activities. Kempeneers et al²⁰ suggested that myopathic abnormalities were responsible for the limitation in $\text{VO}_{2\text{peak}}$ in kidney transplant recipients.

In patients treated with hemodialysis, the only known way to improve $\text{VO}_{2\text{peak}}$ is with exercise training. Moore et al² reported improvements in $\text{VO}_{2\text{peak}}$ following exercise training in hemodialysis patients that were the result of increases in both cardiac output and $\text{a-vO}_{2\text{dif}}$. Their study was performed prior to the availability of epoetin, so arterial oxygen content did not change; thus the change in $\text{a-vO}_{2\text{dif}}$ resulted from changes in oxygen extraction by the skeletal muscle. Although transplants improve $\text{VO}_{2\text{peak}}$ in ESRD patients, the magnitude of the change observed with a transplant alone is similar to that achieved with exercise training in hemodialysis. Exercise training following transplant improves $\text{VO}_{2\text{peak}}$ above what is achieved with a transplant alone³³. Because transplant recipients may still be

limited in cardiac output by a subnormal peak heart rate, optimizing VO_{2peak} following transplant may require exercise training to enhance the skeletal muscle functioning (thus improving the ability to widen the $a-vO_{2dif}$).

There are limitations to this study, including the fact that patients were not randomized to the various treatments. Although the Frequent Hemodialysis Study is a randomized trial (c comparing remaining on conventional hemodialysis vs. switching to frequent hemodialysis), it is probably not ethical to randomize patients to transplant vs. continued dialysis, especially those who have a living donor readily available. The baseline demographics of the patient groups were similar, and all of the patients who remained on dialysis qualified for transplants (and all except one were on the transplant waiting list). Thus, we believe that the potential bias due to the non-randomized nature of the study was minimized by the strict inclusion criteria. On the other hand, because of our vigorous efforts to include only healthy dialysis patients in order to assure comparable patient groups and isolate the influence of uremia (no diabetes, or cardiovascular disease), this study is not representative of the general ESRD population. We also required significant physical effort over the course of 8 hours, and patients had to be the highest functioning of those on dialysis in order to complete all testing. Thus, we expect that our results overestimate the level of fitness of dialysis patients, but inclusion of sicker dialysis patients would have jeopardized the quality of the exercise tests and run the risk of overestimating the effects of uremia on VO_{2peak} . Additionally, using noninvasive measures often requires assumptions that may not provide a complete picture of what is happening physiologically. The indirect calculation of $a-vO_{2dif}$ with no direct measure of arterial oxygen may not be a true indicator of muscle oxygen use.

The small sample size of our study is also a limitation. We were fully dependent on referrals from the transplant and home hemodialysis programs, and referral was much lower than expected despite weekly reminders and a recruitment system that minimized the time required on the part of the referral programs. Among patients who were referred, several could not be included because of late referral or because of time constraints related to employment. The low numbers required us to collapse the groups into two groups for some analyses.

Despite the disappointing referral numbers, patients who were recruited into the study were highly motivated, allowing us to obtain excellent effort on the exercise test as evidenced by average respiratory exchange ratio >1.1 and average subjective ratings of perceived exertion of >17 (out of 20). Our control subjects were without known disease but were very sedentary and had low levels of fitness (85% of age predicted values). We selected sedentary controls because we felt it was inappropriate to compare the patients to physically active controls, since these patients were basically inactive, and no exercise intervention was prescribed.

In summary, patients with CKD requiring renal replacement therapy have low exercise capacity as measured by VO_{2peak} . Kidney transplant improves VO_{2peak} but daily dialysis does not. The changes in VO_{2peak} following transplant are due to increases in central (oxygen delivery) mechanisms, and the improved oxygen delivery is the result of an increase in peak cardiac output that is due to an increase in peak heart rates rather than changes in peak stroke volume. Thus, a transplant appears to exert its beneficial effects on cardiorespiratory fitness through mitigation of the limitation of peak heart rate observed in hemodialysis patients.

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Figure 1.

Recruitment and loss to analysis. Abbreviations: CHD->CHD, **remained on** conventional hemodialysis; CHD->SDD, changed from conventional hemodialysis to short daily hemodialysis; CHD->Tx; changed from conventional hemodialysis to transplant; No HD-TX, received a preemptive transplant

Figure 2. Changes in determine of VO_2 at peak exercise. P value pertains to difference in Change between Dialysis and Transplant. Abbreviations: CHD->CHD, **remained on** conventional hemodialysis; CHD->SDD, changed from conventional hemodialysis to short daily hemodialysis

Table 1

Demographic and Clinical Characteristics at Baseline

Variable	Individual Groups					Composite Groups	
	CHD->CHD (n=13)	CHD->SDD (n=10)	CHD->Tx (n=5)	No HD->Tx (n=15)	Controls (n=34)	Remained on HD* (n=23)	Tx recipient** (n=20)
Sex (M/F)	11/2	9/1	5/0	13/2	28/6	20/3	17/3
Age	45.5 ± 10.4	42.6 ± 12.4	34.1 ± 11.1 *	44.2 ± 10.4	47.7 ± 8.5*	41.0 ± 11.3	43.5 ± 10.9
BMI	27.4 ± 4.0	28.3 ± 4.4	29.2 ± 4.1	28.2 ± 4.6	27.1 ± 4.7	27.1 ± 4.4	28.1 ± 5.0
Time on dialysis (mo)	28.5 ± 21.2	33.8 ± 44.3	16.6 ± 21.1	0	-	38.3 ± 32.5	5.3 ± 13.7
Ethnicity (%)							
White	52.9%	50.0%	83.3%	93.3%	100%	51.6%	93.1%
African American	29.4%	35.7%	-	6.7%		32.3%	3.4%
Hispanic	11.8%	7.1%	16.6%	-		9.7%	3.4%
Asian	-			-		3.2%	-
Native American	5.9%	7.1%		-		3.2%	-
Cause of Kidney Failure							
Hypertension	23.5%	21.4%	-	13.3%	-	22.6%	6.9%
GN/FSGN	17.6%	7.1%	16.6%	20.0%		12.9%	17.2%
IgA Nephropathy	11.8%	-	33.3%	26.7%		6.5%	24.1%
PKD	5.9%	14.3%	16.6%	26.7%		9.7%	24.1%
Other/Unknown	41.4%	58.1%	33.3%	13.3%		48.4%	38.4%
Baseline medication use							
No. of antihypertensive medications	1.8 ± 1.0	1.4 ± 1.3	1.0 ± 1.4	2.3 ± 0.9	2	1.6 ± 1.1	1.8 ± 1.1
# of patients on beta blockers	9	4	3	6	1	13	9
Receiving ESA	82.4%	78.6%	66%	26.6%	-	80.5%	41.4%
SCr (mg/dL)	8.9 ± 1.9 [†]	10.2 ± 2.2 [‡]	8.3 ± 2.4 [†]	6.1 ± 2.2 [‡]	1.2 ± 0.2	9.7 ± 2.2 [‡]	6.8 ± 2.4 [‡]

Variable	Individual Groups					Composite Groups	
	CHD->CHD (n=13)	CHD->SDD (n=10)	CHD->Tx (n=5)	No HD->Tx (n=15)	Controls (n=34)	Remained on HD* (n=23)	Tx recipient** (n=20)
SUN (mg/dL)	36.2 ± 9.2 [†]	45.1 ± 23.8 [†]	38.2 ± 14.8 [†]	68.4 ± 23.2 [†]	17.9 ± 5.1	40.3 ± 17.1 [†]	58.3 ± 25.0 [†]
Hemoglobin (g/dL)	12.6 ± 0.9 [†]	12.2 ± 1.4 [†]	13.7 ± 0.5	11.9 ± 1.4 [†]	13.4 ± 1.4	12.6 ± 0.9 [†]	12.5 ± 1.4 [†]

Note: Continuous variables are given as mean +/- SD; categorical variables are given as percentage.

Abbreviations and definitions: CHD->CHD, remaining on conventional hemodialysis; CHD->SDD, conventional hemodialysis to short daily hemodialysis; CHD->Tx, conventional hemodialysis to transplant; No HD->Tx, received a preemptive transplant; GN/FSGN; Glomerulonephritis/Focal Sclerosing Glomerulonephritis; PKD: polycystic Kidney Disease; IgA; immunoglobulin A; ESA; erythropoiesis-stimulating agents; SUN, serum urea nitrogen; SCr, serum creatinine; BMI, body mass index

* combines CHD->CHD and CHD->SDD

** combines CHD->Tx and no HD->Tx

[†] p<.03 values compared to controls

Conversion factors for units: serum creatinine in mg/dL to µmol/L, x 88.4; urea nitrogen in mg/dL to mmol/L, x 0.357.

Table 2

Physiologic Variables at Peak Exercise

Variable	Individual Groups					Composite Groups	
	CHD->CHD (n=13)	CHD->SDD (n=10)	CHD->Tx (n=5)	No HD->Tx(n=15)	Controls (n=34)	Remained on HD ^{**} (n=23)	Tx recipient ^{***} (n=20)
VO₂ (L/min)							
Baseline	2.17 ± 0.43 [†]	1.97 ± 0.55 [†]	2.31 ± 0.62	2.27 ± 0.56	2.40 ± 0.54	2.08 ± 0.48 [†]	2.28 ± 0.57
Visit 2	2.08 ± 0.48 [¶]	1.91 ± 0.48 [¶]	2.53 ± 0.74	2.56 ± 0.52		2.01 ± 0.47 [¶]	2.55 ± 0.57
Adjusted mean change*	-0.08 (-0.32, 0.15)	-0.15 (-0.43, 0.13)	0.11 (-0.25, -0.46)	0.29 [§] (0.06, 0.53)		-0.10 (-0.27, 0.06)	0.28 [@] (0.10, 0.47)
Cardiac Output (L/min)							
Baseline	17.46 ± 3.94	14.12 ± 3.64	18.42 ± 3.91	17.01 ± 3.20 [†]	15.28 ± 3.76	16.01 ± 4.09	17.46 ± 3.41
Visit 2	16.37 ± 3.49	13.68 ± 2.85	20.51 ± 4.08	18.17 ± 3.45 [¶]		15.21 ± 3.36	18.88 ± 3.71 [¶]
Adjusted mean change*	-0.86 (-0.22, 0.48)	-0.15 (-2.91, 0.34)	2.82 (0.83, 4.80)	0.96 [§] (-0.33, 2.25)		-1.03 (-2.05, -0.01)	1.45 [@] (0.39, 2.59)
Stroke Volume (ml/beat)							
Baseline	117.0 ± 29.3 [†]	101.4 ± 28.4 [†]	122.3 ± 37.7	114.9 ± 25.5 [†]	89.2 ± 23.7	110.2 ± 29.4 [†]	117.3 ± 29.2 [†]
Visit 2	115.4 ± 28.8 [¶]	93.7 ± 18.7	135.3 ± 38.1	112.9 ± 21.1 [¶]		105.9 ± 26.8 [¶]	119.7 ± 28.5 [¶]
Adjusted mean change*	-0.71 (-9.62, 8.19)	-11.28 (-21.6, 0.92)	18.19 (5.08, 31.31)	-3.45 (-12.05, 5.13)		-5.21 (-12.56, 2.15)	2.92 (-4.97, 10.80)
Heart Rate (beats/min)							
Baseline	150 ± 18 [†]	141 ± 21 [†]	155 ± 23	151 ± 24 [†]	173 ± 15	147 ± 19 [†]	152 ± 23 [†]
Visit 2	145 ± 21 [¶]	147 ± 23 [¶]	158 ± 21	162 ± 23 [¶]		146 ± 23 [¶]	161 ± 22 [¶]
Adjusted mean change*	-5.06 (-12.91, 2.78)	4.08 (-5.02, 13.2)	-1.11 (-8.80, 10.58)	11.32 [§] (3.75, 18.91)		-1.22 (-7.41, 4.98)	7.75 [@] (1.11, 14.39)
a-vO₂diff (ml/100ml)							
Baseline	12.72 ± 2.75 [†]	14.45 ± 4.97 [†]	12.91 ± 2.83	13.55 ± 3.36 [†]	15.99 ± 3.15	13.47 ± 3.87 [†]	13.35 ± 3.15 [†]
Visit 2	12.95 ± 2.54 [¶]	14.17 ± 3.08 [¶]	11.78 ± 2.53 [¶]	14.22 ± 1.97 [¶]		13.48 ± 2.79 [¶]	13.48 ± 2.38 [¶]
Adjusted mean change*	-0.21 (-1.42, 0.99)	0.33 (-1.02, 1.71)	-1.62 (-3.39, 0.15)	-0.81 (-0.35, 1.96)		0.04 (-0.91, 0.98)	0.79 (-0.93, 1.09)

Variable	Individual Groups					Composite Groups	
	CHD->CHD (n=13)	CHD->SDD (n=10)	CHD->Tx (n=5)	No HD->Tx(n=15)	Controls (n=34)	Remained on HD** (n=23)	Tx recipient*** (n=20)
Arterial O2 content (ml/100ml)							
Baseline	16.9 ± 1.1 [†]	15.9 ± 1.1 [†]	17.8 ± 0.6	15.6 ± 1.7 [†]	18.8 ± 1.1	16.5 ± 1.2 [†]	16.3 ± 1.8 [†]
Visit 2	16.6 ± 1.6 [¶]	15.3 ± 1.7 [¶]	17.3 ± 3.0	17.1 ± 2.3 [¶]		16.0 ± 1.7 [¶]	17.2 ± 2.3 [¶]
Adjusted mean change*	0.01 (-1.27, 1.29)	-1.02 (-2.42, -0.38)	0.69 (-1.11, 2.49)	0.92 (-0.27, 2.11)		-0.46 (-1.38, 0.45)	0.85 [@] (-0.06, 1.76)
Mixed venous O2 content (ml/100ml)							
Baseline	4.3 ± 3.2	1.5 ± 5.4	4.9 ± 2.5	2.0 ± 3.3	2.8 ± 2.6	3.0 ± 4.5	2.0 ± 3.3
Visit 2	3.7 ± 1.9	1.1 ± 2.4	5.9 ± 2.2	2.9 ± 1.5		2.5 ± 2.5	3.8 ± 2.2
Adjusted mean change*	0.52 (-0.32, 1.36)	-1.30 (-2.22, 0.38)	2.49 (1.31, 3.67)	0.39 (-0.37, 1.17)		-0.32 (-1.03, 0.39)	0.58 (-0.32, 1.35)

Note: unless otherwise indicated, values are given as mean +/- SD.

Abbreviations and definitions: CHD->CHD, remaining on conventional hemodialysis; CHD->SDD, conventional hemodialysis to short daily hemodialysis; CHD->Tx; conventional hemodialysis to transplant; No HD->Tx, received a preemptive transplant; VO2, ***, a-VO2diff, arterial to venous oxygen difference

** combines CHD->CHD and CHD->SDD

*** combines CHD->Tx and no HD->Tx

* change scores adjusted for baseline values; 95% confidence intervals are given in parentheses

[†] p<0.03 baseline values compared to controls;

[¶] p<0.05 compared to controls at visit 2.

[§] p<0.02 for change from baseline to visit 2, compared to those who remained on CHD.

[@] p<0.04 for change from baseline to visit 2, compared to remained on dialysis;