Clinical Kidney Journal, 2021, vol. 14, no. 2, 720–722

doi: 10.1093/ckj/sfaa010
Advance Access Publication Date: 24 March 2020
Letter to the Editor

LETTER TO THE EDITOR

Reversal of asymptomatic cardiac dysfunction following renal transplantation

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Renal transplantation (RTx) has been shown to have a favourable effect on cardiac morbidity and mortality in advanced chronic kidney disease (CKD) [1]. RTx has also been shown to cause regression of left ventricular hypertrophy (LVH) [2], raising the possibility of cardiac 'reverse remodelling' with RTx. However, although these structural changes have been identified, the changes in cardiac function with RTx, especially in asymptomatic patients, have not yet been studied. Our recent work showed the presence of subclinical cardiac dysfunction, the precursor of overt heart failure, in CKD even in asymptomatic patients with no known cardiac disease or diabetes mellitus [3]. We measured peak cardiac power (CPO_{max}) non-invasively to reveal the subclinical cardiac dysfunction. In the present study, we measured CPO_{max} and central haemodynamics before and after RTx to test the hypothesis that successful RTx, with improved renal function, improves subclinical cardiac dysfunction. In addition, we also evaluated the relationship between the changes in aerobic exercise capacity [maximal oxygen consumption (VO_{2max})] and central haemodynamic parameters following RTx.

In this prospective study, six asymptomatic male patients (>18 years of age) with CKD [Stages 4 and 5 (predialysis)] listed for RTx were recruited from the outpatient renal clinic of a tertiary UK centre. Patients with any primary cardiac diseases, diabetes mellitus, clinical hypervolaemia, uncontrolled hypertension and inability to exercise fully secondary to musculoskeletal or any other non-renal medical disorders were excluded. A specialized cardiopulmonary exercise (CPX) test employing the carbon dioxiderebreathing method was utilized to measure CPO_{max}, VO_{2max} and central haemodynamics before and after RTx as described in previous methodological articles [3, 4]. The full methodology is also presented in the Supplementary data. Comparisons between study parameters before and after RTx were performed using a paired sample t-test. A P-value <0.05 was considered significant. The results are presented as mean ± standard deviation. SPSS 17.0 (IBM, Armonk, NY, USA) software was used in the analysis. These clinical investigations conformed to the Declaration of Helsinki.

The patients had a mean age of 48.4 years. Their underlying aetiologies were immunoglobulin A nephropathy (two patients), polycystic kidney disease (two patients), interstitial nephritis (one patient) and reflux nephropathy (one patient). Their estimated glomerular filtration rate improved from 12.5 ± 4.0 mL/min before to 64.9 ± 6.5 mL/min after transplantation (P = 0.004). The median time to CPX testing post-transplantation was 5 months. All six patients showed an increase in CPO_{max} following RTx (Figure 1), with the mean CPO_{max} rising from 3.82 ± 1.03 to 4.55 ± 0.80 W (P = 0.003), which is a mean increment in CPO_{max} of 21.6 ± 12.7%. The percentage increment in CPO_{max} ranged between 6.3% and 35.5%. The patient with the greatest impairment in CPO_{max} pre-RTx showed the greatest gain in CPO_{max} post-RTx. Indeed, the percentage increment in CPO_{max} showed a strong negative correlation with baseline CPO_{max} ($r = -0.89$, P = 0.02). The improvement in CPO_{max} resulted from increases in peak mean arterial pressure (MAP; 98.5 ± 15.9 versus 110.8 ± 12.3 mmHg; P = 0.001) and peak cardiac output (CO; 17.29 ± 2.37 versus 18.47 ± 2.05 L/min; P = 0.04) (Figure 1). Peak exercise heart rate also improved (134.8 ± 26.1 versus 156.8 ± 29.1/min, P = 0.04) (Figure 1). Multiple regression analysis showed that improvement in peak carbon monoxide was the strongest predictor of improvement in CPO_{max} ($\beta = 0.74$, P = 0.005) versus ther change in MAP (ΔMAP; $\beta = 0.39$, P = 0.028).

Received: 26.11.2019. Editorial decision: 7.1.2020

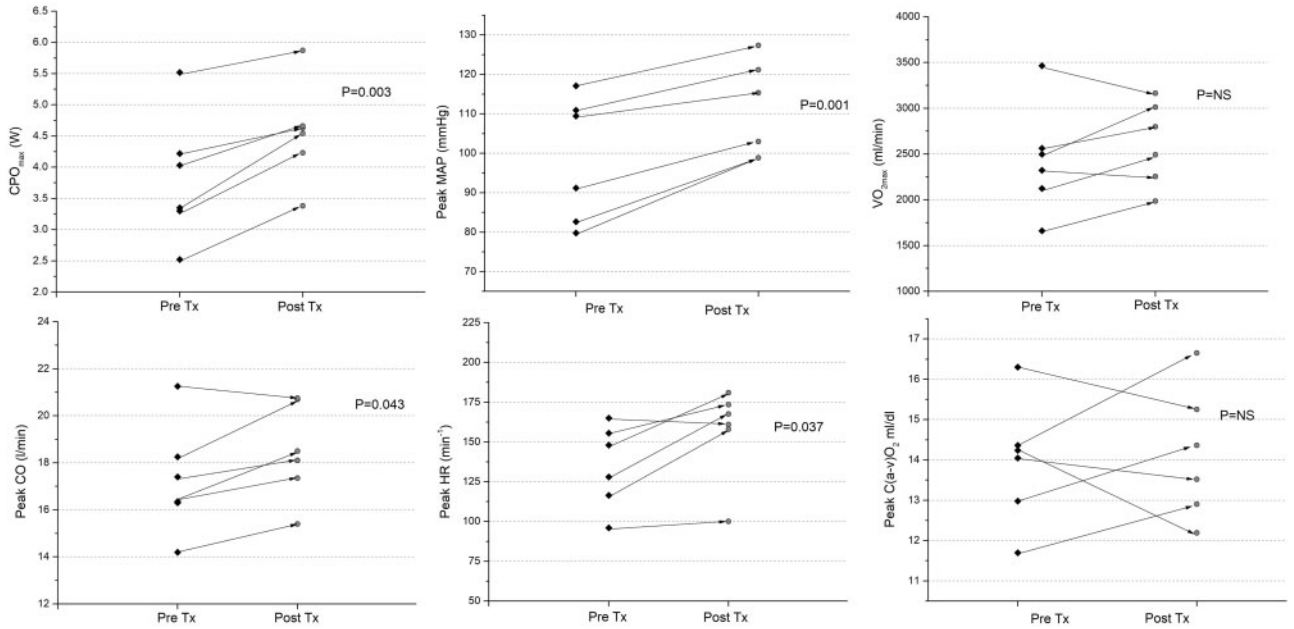

FIGURE 1: CPO_{max}, peak central haemodynamic parameters, VO_{2max} and $C(a-v)O_2$ at peak exercise before and after RTx. HR: heart rate. P-value is for paired sample *t*-test.

Changes in VO_{2max} with RTx (ΔVO_{2max}) were less consistent compared with central haemodynamics (Figure 1), with no statistically significant change in mean VO_{2max} (2.44 ± 0.6 versus 2.62 ± 0.45 L/min; P = NS). Similarly, the change in peak peripheral oxygenextraction [$C(a-v)O_2$] before and after RTx {$\Delta[C(a-v)O_2]$} did not reach statistical significance (Figure 1). ΔVO_{2max} mirrored $\Delta[C(a-v)O_2]$ with a strong positive correlation ($r = 0.86$, P = 0.03) but showed no significant correlation with ΔCO ($r = -0.26$, P = 0.62). Additional CPX and biochemical data are presented in the Supplementary data, Table S1.

The results of the present study demonstrated for the first time that RTx leads to reversal of asymptomatic cardiac dysfunction in CKD. Although improvement in cardiac function post-RTx in patients with clinically apparent left ventricular dysfunction and cardiac comorbidities has been shown in the past [5], the present study is the first instance where cardiac functional improvement has been shown in asymptomatic patients even in the absence of any known cardiac comorbidities. This improvement in CPO_{max} resulted from improvement in both volume and pressure-generating capacities of the heart and its chronotropic reserve. This improvement in the peak cardiac performance and the central haemodynamics demonstrates the potential for 'reverse remodelling' in uraemic cardiomyopathy.

Cardiac remodelling is caused by both mechanical and biochemical stress [6]. CKD has been shown to increase cardiac mechanical stress by increasing both preload and afterload [7, 8]. The biochemical stress in CKD results from sympathetic and renin–angiotensin–aldosterone system activation, uraemic retention solutes and oxidative and inflammatory stress [9–12]. RTx, with the restoration of renal function, has the potential to reverse both the mechanical and biochemical stress, thereby inducing cardiac reverse remodelling.

It can be speculated that the improvement in peak cardiac performance post-RTx is a consequence of the reversal of coronary vasculopathy. However, RTx was not shown to reverse uraemic vasculopathy in the early post-transplant period [13]. Hence the cardiac functional improvement demonstrated in the present study is likely to be a manifestation of myocardial recovery following RTx.

The study also showed changes in $C(a-v)O_2$ appear to be the major determinant of ΔVO_{2max} in CKD, further reinforcing a similar finding from our previously published cross-sectional study [3]. Hence the failure of VO_{2max} to show improvement with RTx [14] no longer means that cardiac dysfunction has not improved with RTx.

Although the small sample size is a potential limitation, the study showed improvement in peak cardiac performance in all patients following RTx and the statistics tell us this is a significant finding to a 1/1000 level. In conclusion, the reversal of cardiac dysfunction demonstrated in the present study complements the existing literature that shows the reversal of LVH, supporting the hypothesis that RTx aids cardiac reverse remodelling in uraemic cardiomyopathy. This finding merits further investigation.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge funding from the Yorkshire Kidney Research Fund and Sheffield Kidney Research Foundation and assistance from Wanda McDonald in CPX testing.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties. No writing assistance was utilized in the production of this manuscript. The study

protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

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