Cardiorespiratory Fitness Is Related to Physical Inactivity, Metabolic Risk Factors, and Atherosclerotic Burden in Glucose-Intolerant Renal Transplant Recipients

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The mechanisms of reduced cardiorespiratory fitness (CF) in renal transplant recipients (RTR) have not been studied closely. This study evaluated the relationships between CF and specific cardiovascular risk factors (metabolic syndrome [MS], physical inactivity, myocardial ischemia, and atherosclerotic burden) in glucose-intolerant RTR. Data were recorded on 71 glucose-intolerant RTR (mean age 55 yr; 55% male; median transplant duration 5.7 yr). MS was defined using National Cholesterol Education Programme Adult Treatment Panel III criteria. Resting and exercise stress echocardiography were performed, and myocardial ischemia was identified by new or worsening wall motion abnormalities. Cardiorespiratory fitness was determined using peak oxygen uptake (VO_2) by expired gas analysis. Atherosclerotic burden was assessed by carotid intima-media thickness (IMT). Mean peak VO_2 was 19 ± 7 ml/kg per min and was significantly lower than predicted peak VO_2 (29 ± 6 ml/kg per min; $P < 0.001$). Patients with MS (63%) had reduced CF (17 ± 6 *versus* 22 ± 8 ml/kg per min; $P = 0.001$) and were more likely to be physically inactive (76 *versus* 48%; $P = 0.02$). CF was reduced in 14 patients with myocardial ischemia (15 ± 3 *versus* 20 ± 7 ml/kg per min; $P = 0.05$). CF was positively correlated with male gender, height, and physical activity and inversely correlated with number of MS risk factors and IMT (adjusted $R^2 = 0.66$). Carotid IMT added incremental value to clinical variables in determining VO_2 (adjusted $R^2 = 0.65$ *versus* 0.63; $P = 0.04$). Reduced CF is associated with physical inactivity, MS, and atherosclerotic burden in glucose-intolerant RTR. Further studies should address whether increasing exercise and modifying MS risk factors improve CF in RTR.

Clin J Am Soc Nephrol 1: 1275–1283, 2006. doi: 10.2215/CJN.00210106

Cardiorespiratory fitness (CF) is a well-validated predictor of cardiovascular outcome both in individuals with underlying cardiovascular disease (CVD) and in normal individuals (1). Patients with advanced chronic kidney disease have reduced CF, attributable to the uremic state and deconditioning imposed by chronic illness (2,3). Although CF improves after transplantation (4), it remains reduced compared with age- and gender-matched control subjects (5).

In the general population, the correlates of CF may be divided broadly into four categories: (*1*) Demographic variables; (*2*) cardiovascular risk factors such as glucose intolerance, hypertension, obesity, and dyslipidemia (6–8), which commonly coexist as the metabolic syndrome (MS); (*3*) behavioral factors including smoking and physical inactivity (9); and (*4*) myocardial parameters such as left ventricular (LV) hypertrophy and systolic dysfunction (6). Similar variables may limit CF in renal transplant recipients (RTR). MS risk factors, such as glucose intolerance, itself an extremely common complication of renal transplantation (10) that contributes significantly to the cardiovascular risk factor profile of this patient group (11), are particularly important because they occur frequently in RTR (12). However, other factors that are relevant to renal transplantation, such as immunosuppression, renal dysfunction, and subclinical atherosclerosis, also may determine CF in RTR (13,14). To date, no studies have explored specifically the correlates of reduced CF in RTR. In particular, the relationship among MS risk factors, physical activity, and CF in RTR is uncertain. We evaluated the relationships between CF and specific cardiovascular risk factors (MS, physical inactivity, myocardial ischemia, and atherosclerotic burden) in a high-risk (glucose-intolerant) cohort of established (>1 yr) RTR.

Materials and Methods

Study Design and Population

This study was an observational analysis of glucose-intolerant RTR from the Princess Alexandra Hospital (Brisbane, Australia). Inclusion criteria were patients who were >1 yr after transplant and had impaired glucose tolerance or diabetes defined according to 1999 World Health Organization specifications (15) and an estimated GFR (eGFR) >25 ml/min using the Nankivell formula (16). All eligible patients gave informed consent to participate in the study, which was approved by the Human Ethics Committee of the University of Queensland and

Received January 17, 2006. Accepted August 20, 2006.

Published online ahead of print. Publication date available at www.cjasn.org.

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ISSN: 1555-9041/106-1275

Princess Alexandra Hospital. A group ($n = 25$) of individuals who had normal glucose tolerance and were age, gender, and transplant duration matched were used as a control cohort.

Clinical Data

Demographic data were recorded, including age, gender, race, cause of renal disease, and duration of current transplant. Assessment of cardiovascular risk factors included a history of any of the following either before or after transplantation: (*1*) A previous cardiac event (nonfatal myocardial infarction, acute coronary syndrome requiring hospitalization, coronary artery bypass graft, or percutaneous coronary intervention), (*2*) peripheral vascular disease (angioplasty, bypass, or amputation), (*3*) cerebrovascular disease (transient ischemic attack or stroke with neurologic deficit), (*4*) hypertension (previous or current use of antihypertensive agents or self-reported), (*5*) dyslipidemia (previous or current use of lipid-lowering therapy or self-reported), (*6*) diabetes (defied as previous or current use of oral hypoglycemic agents or insulin or self-reported), and (*7*) smoking status (current, former, or never). MS was defined according to the National Cholesterol Education Panel Adult Treatment Panel III (NCEP) criteria (17).

Physical Activity Assessment

Physical activity data were recorded using a core set of questions, adapted from the Physical Activity Statewide Questionnaire (18) (Table 1). The number of sessions and the total time spent on each category of activity in the preceding week were noted, as well as the patients' perceptions of how active they considered themselves to have been (activity status). From the patients' responses, it was determined whether they were achieving recommended targets of physical activity (activity target) (19).

Clinical Measurements

BP, weight, height, and waist and hip circumference were measured using standardized equipment, and body mass index (BMI) and waist-to-hip ratio were determined. Central obesity was defined as waist circumference ≥102 cm in men or ≥88 cm in women (20).

Biochemical Analyses

After an 8-h overnight fast, serum concentrations of creatinine, hemoglobin, glucose, HbA1c%, calcium, phosphate, C-reactive protein, homocysteine, and lipids (total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, and triglycerides) were analyzed using standard techniques.

CF

CF was assessed by measuring oxygen consumption (VO_2) by breath-by-breath analysis of expired gas (V29C Sensorimedics, Yorba Linda, CA), during standard treadmill exercise testing. The VO_2 at the time of termination of the test was recorded as peak VO_2. Age-predicted peak VO_2 and ventilatory limitation (%) were determined using standardized formulas (21,22). The respiratory quotient, defined as the ratio of CO_2 production to VO_2, was calculated and a value >1 at peak exercise was taken as a physiologic indicator of maximal effort. Mean peak VO_2 in the study cohort was compared with mean peak VO_2 in the control cohort.

Two-Dimensional and Exercise Echocardiography

Before and immediately after exercise, patients had resting two-dimensional echocardiography. Images were obtained in five standard views of the left ventricle and were saved onto magneto-optical disc for off-line analysis.

Atherosclerotic Burden

Acquisition of carotid intima-media thickness (IMT) data was performed before exercise testing using high-resolution B-mode ultrasonography (ATL HDI5000, Philips/ATL, Bothell, WA) with a 12-MHz imaging probe and automated off-line analysis. Our method for IMT measurement was described previously (23).

Echocardiographic Analysis

A physician who was blinded to the clinical data interpreted the echocardiographic data. Left atrial and LV volumes were measured from standard views. Ejection fraction was computed by Simpson's method of discs. LV mass index (indexed to height to the power of 2.7) and LV hypertrophy (defined as septal or posterior wall thickness >1.2 cm) were assessed. Early diastolic tissue velocity (E prime) was used as a marker of diastolic dysfunction. An abnormal exercise echo was defined as the presence of scar (resting wall-motion abnormality that did not change with stress) or ischemia (new or worsening wall-motion abnormality).

Statistical Analyses

Statistical analyses were performed using standard statistical software (SPSS Version 11.5, North Sydney, Australia). Results are expressed as mean ± SD, median (interquartile range [IQR]), or frequencies (%) depending on the distribution of the data. Comparisons of means were made using unpaired *t* test, the Mann-Whitney test, or

Table 1. Assessment of physical activity levels in the preceding week[a]

Category	Core Questions
1	How many times have you walked continuously, for at least 10 min, for recreation, exercise, or to get from place to place?
2	How many times did you do household chores that made you breathe harder or puff and pant?
3	How many times did you do gardening or heavy work around the yard that made you breathe harder or puff and pant?
4	How many times did you do vigorous exercise that made you breathe harder or puff and pant (*e.g.*, tennis, jogging, cycling)?

[a]Adapted from the Physical Activity Statewide Questionnaire (18). Categories 1, 2, and 3 are classed as moderate-intensity activity; category 4 is classed as vigorous activity.

Table 2. Baseline characteristics of glucose-intolerant renal transplant recipients with and without MS

Variable	With MS ($n = 45$)	Without MS ($n = 26$)	P
Demographics			
age (yr)	55.3 ± 9.8	52.6 ± 9.5	0.27
male gender (%)	25 (56)	15 (58)	0.86
white race (%)	39 (87)	18 (69)	0.08
transplant duration (yr)	6.8 (3.1 to 13.2)	5.4 (2.9 to 10.3)	0.63
BMI (kg/m^2)	29.0 ± 4.4	26.9 ± 6.1	0.09
eGFR (ml/min)	66.9 ± 21.4	66.7 ± 16.1	0.97
Primary cause of renal failure (%)			
glomerulonephritis	16 (36)	7 (27)	0.45
adult polycystic kidney disease	8 (18)	6 (23)	0.59
miscellaneous	11 (24)	5 (19)	0.61
diabetic nephropathy	3 (1)	2 (1)	0.87
uncertain cause	7 (16)	6 (23)	0.43
Cardiovascular risk factors (%)			
previous cardiac event	7 (16)	5 (19)	0.69
hypertension	42 (93)	22 (85)	0.24
dyslipidemia	34 (76)	17 (65)	0.36
diabetes	25 (56)	12 (46)	0.45
smoking (current or former)	16 (36)	11 (42)	0.57
MS risk factors			
hypertension (%)	44 (98)	23 (89)	0.1
central obesity (%)	36 (80)	6 (23)	<0.001
hypertriglyceridemia (%)	34 (76)	4 (15)	<0.001
reduced HDL cholesterol (%)	8 (18)	0 (0)	0.02
FBG ≥6.1 mmol/L or diabetes	37 (82)	13 (50)	0.004
Immunosuppression (%)			
prednisolone	36 (80)	19 (73)	0.50
cyclosporine	31 (69)	17 (65)	0.76
tacrolimus	9 (20)	5 (19)	0.94
mycophenolate mofetil	21 (47)	15 (58)	0.37
azathioprine	13 (29)	9 (35)	0.62
Physical activity (%)			
active	19 (47)	18 (70)	0.03
activity target	22 (48)	20 (76)	0.02
CF and imaging parameters			
peak VO_2 (ml/kg per min)	16.9 ± 5.9	22.4 ± 7.5	0.001
left atrial volume (cm^2)	65 ± 16	61 ± 21	0.42
LV end systolic volume (ml)	38 ± 22	40 ± 21	0.77
LV end diastolic volume (ml)	86 ± 34	88 ± 44	0.86
ejection fraction (%)	59 ± 9	56 ± 10	0.15
LV mass index (g/m$^{2.7}$)	64 ± 22	53 ± 17	0.04
E prime (cm/s)	5.8 ± 1.4	6.1 ± 1.8	0.07
LV hypertrophy (%)	37 (82)	21 (81)	0.88
myocardial ischemia (%)	10 (22)	4 (15)	0.49
carotid IMT (mm)	0.63 ± 0.13	0.60 ± 0.09	0.31

Data are mean ± SD, median (IQR), or frequencies (%). BMI, body mass index; eGFR, estimated GFR; E prime, early diastolic tissue velocity; FBG, fasting blood glucose; IMT, intima-media thickness; LV, left ventricular; MS, metabolic syndrome; VO_2, oxygen consumption.

Pearson χ^2 test. $P < 0.05$ was considered statistically significant. Univariate and multivariate linear regression analyses were performed to determine, first, which demographic, clinical, and imaging variables were associated with peak VO_2 and, second, the incremental value of imaging parameters over demographic and clinical variables in predicting peak VO_2.

All variables first were evaluated by univariate linear regression analysis to identify those that were associated with peak VO_2. The following variables were assessed: (*1*) demographic (age, gender, race, height, weight, and BMI), (*2*) clinical (duration of dialysis before transplantation and duration of current transplant, cardiovascular risk factors [previous cardiac event, hypertension, dyslipidemia, diabetes, smoking status, MS, and number of MS risk factors], medications [immunosuppression agents, statins, antihypertensive agents, and hypoglycemic agents], biochemical parameters [eGFR, glucose, HbA1c%, hemoglobin, and all lipid parameters], and activity target and activity status), and (*3*) imaging (echocardiographic parameters [left atrial volume, LV volumes, LV ejection fraction, LV hypertrophy, E prime, and myocardial ischemia] and carotid IMT). Any variables with $P < 0.1$ on univariate analysis, which were not collinearly associated, then were entered into a multivariate regression analysis, and the final multivariate model was obtained using a stepwise backward elimination procedure of variables with $P > 0.05$. Standard regression diagnostics were performed for all models. R^2 values are reported only for significant results.

To assess the incremental value of imaging parameters over demographic and clinical variables, we performed a stepwise procedure in three steps. In the first step, a multivariate model of significant demographic variables was developed (model 1). In the second step, a multivariate model of significant clinical variables was developed and added to model 1 to give a multivariate model of demographic and clinical variables (model 2). In the third step, imaging parameters with $P < 0.1$ on univariate analysis were added to model 2. By using a stepwise backward elimination procedure of imaging variables with $P > 0.05$, a final model of independent demographic, clinical, and imaging variables was obtained (model 3). A significant improvement in model prediction between one model and the next was assessed from the difference in R^2 values and the P value associated with the F-statistic change. $P < 0.05$ was taken to be indicative of a significant increment between consecutive models.

Results

Clinical Characteristics

Seventy-one glucose-intolerant patients were recruited to the study (study cohort). Mean age of glucose-intolerant RTR was 54.4 ± 9.7 yr, and 55% were male. Median transplant duration was 5.7 yr (IQR 3.0 to 12.8 yr). Twenty-five RTR with normal glucose tolerance acted as a control cohort. Mean age of control subjects was 53.2 ± 11.2 yr ($P = 0.64$), 12 (47%) patients were male ($P = 0.48$), and median transplant duration was 6.4 yr (IQR 1.3 to 11.6 yr; $P = 0.56$). Individuals with abnormal glucose tolerance were heavier than those with normal glucose tolerance (28.3 ± 5.1 *versus* 25.6 ± 3.7 kg/m^2; $P = 0.04$).

Physical Activity, Exercise Testing, CF, and Myocardial Ischemia

In the study cohort, 33 (47%) RTR achieved activity target. Mean duration of treadmill exercise was 6.1 ± 2.9 min. Systolic and diastolic BP increased with exercise (135 ± 14 to 169 ± 24 mmHg [$P < 0.001$] and 81 ± 9 to 90 ± 8 mmHg [$P < 0.001$]; respectively). Forty-three (61%) RTR achieved target heart rate (>85% of age-predicted maximum), and 85% of RTR achieved a respiratory quotient >1. Reasons for terminating the test were fatigue ($n = 57$), dyspnea ($n = 3$), leg discomfort ($n = 6$), atrial fibrillation ($n = 3$), and poor coordination ($n = 2$). Peak VO_2 in the study cohort was 18.8 ± 7.1 ml/kg per min and was lower than both the peak VO_2 in the control cohort (23.3 ± 7.9 ml/kg per min; $P = 0.01$) and the predicted VO_2 (28.9 ± 6.3 ml/kg per min; $P < 0.001$). Only 7 (10%) RTR achieved predicted VO_2. Fourteen (20%) glucose-intolerant RTR had silent myocardial ischemia compared with four (16%) normal glucose tolerance control subjects ($P = 0.68$).

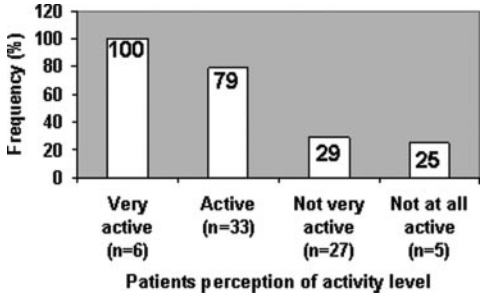

Figure 1. Percentage of patients within each self-perceived activity category who achieve recommended targets of moderate physical activity.

MS

Forty-five (63%) glucose-intolerant RTR had MS compared with five (20%) with normal glucose tolerance ($P < 0.001$). Table 2 shows the baseline characteristics of glucose-intolerant patients with and without MS. Patients with MS had lower HDL cholesterol, higher waist circumference, triglycerides, and fasting blood glucose levels and were more likely to have diabetes. The relationship between MS and (*1*) physical activity, (*2*) CF, and (*3*) imaging variables in the study cohort was explored further.

MS and Physical Activity. In patients with MS, 19 (42%) perceived themselves to be active (very active $n = 2$; active $n = 17$) and the remainder (58%) considered themselves inactive (not very active $n = 19$; not at all active $n = 7$). In patients without MS, 18 (70%) perceived themselves to be active (very active $n = 4$; active $n = 14$) and the remaining 30% considered themselves not very active. Only 48% of patients with MS achieved the activity target compared with 76% without MS ($P = 0.02$). However, in both groups, there was a significant correlation between patients' self-perceived activity status and

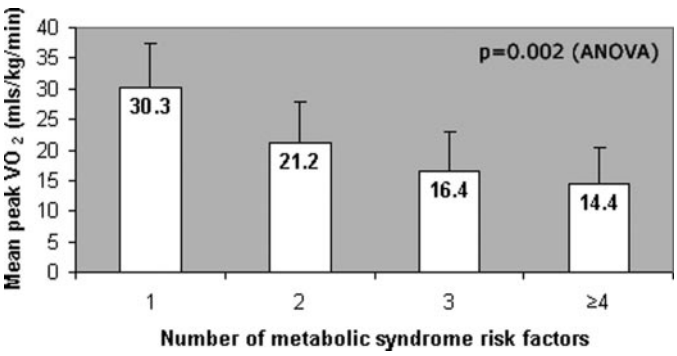

Figure 2. Relationship between number of metabolic syndrome (MS) risk factors and mean peak oxygen consumption (VO_2).

the percentage achieving activity target (Figure 1). On treadmill testing, patients with MS exercised for less time (5.5 ± 2.3 min *versus* 7.2 ± 3.6 min; $P = 0.01$).

MS and CF. Patients with MS had reduced peak VO_2 compared with those without MS (16.9 ± 5.9 *versus* 22.4 ± 7.5 ml/kg per min; $P = 0.001$). As the number of MS risk factors increased from one to four or more, mean peak VO_2 decreased ($P = 0.002$; Figure 2).

MS and Imaging Parameters. LV mass index was increased in RTR with MS (64 ± 22 *versus* 53 ± 17 g/m$^{2.7}$; $P = 0.04$), but there were no significant differences in other resting two-dimensional echo parameters. MS was not associated with myocardial ischemia or abnormal IMT (Table 2).

Predictors of Peak VO_2

The variables that were associated with peak VO_2 on univariate and multivariate analyses are shown in Table 3. No MS risk factors other than central obesity were associated with peak VO_2. Of note, eGFR did not independently predict CF. In the final multivariate model, peak VO_2 was positively correlated with male gender, height, and activity status and inversely correlated with the number of MS risk factors and carotid IMT (Table 3). The adjusted R^2 for this model was 0.66.

Incremental Value of Imaging Variables

The incremental value of imaging variables over demographic and clinical variables in determining CF is shown in Table 4 and Figure 3. In a multivariate model of significant demographic variables (gender and age, adjusted $R^2 = 0.42$), addition of independent clinical variables (previous cardiac event, activity status, and number of MS risk factors) improved the predictive power of the model (adjusted $R^2 = 0.63$, $P < 0.001$). The power of the model was improved further by addition of imaging variables (myocardial ischemia, LV end systolic volume, LV end diastolic volume, LV mass index, E prime, and carotid IMT), although only carotid IMT remained in the final model (adjusted $R^2 = 0.65$, $P = 0.04$), accounting for 13% of the variability in peak VO_2 in this group.

Discussion

Principal Findings

This study demonstrates that after adjustment for gender and height, the principal correlates of reduced CF in glucose-intolerant RTR are physical inactivity, an adverse cardiovascular risk factor profile as defined by the number of MS risk factors, and atherosclerotic burden. Furthermore, the incremental value of atherosclerotic burden over clinical variables suggests that noninvasive cardiovascular imaging may supplement clinical information in the investigation of CF in this high-risk patient group.

Physical Activity and CF in Glucose-Intolerant RTR

In this study, physical activity levels were impaired in glucose-intolerant RTR, with <50% of patients achieving currently recommended targets of physical activity. CF also was reduced, with only 10% of patients achieving predicted levels of peak VO_2 during exercise testing. Regular physical activity has been shown to improve CF and reduce the incidence of cardiovascular events, independent of any beneficial effects on cardiovascular risk factors in the general population (24). Only two studies have studied physical activity levels in RTR (25,26). Gallagher-Lepak *et al.* (25)

Table 3. Variables associated with peak VO_2 on univariate and multivariate linear regression analyses in glucose-intolerant renal transplant recipients ($n = 71$)

Variable	Univariate Analysis[a]		Multivariate Analysis	
	R^2	P	R^2	P
Gender	0.27	<0.001	0.04	0.003
Age (yr)	0.09	0.005	—	—
Height (m)	0.29	<0.001	0.30	0.01
Previous cardiac event	0.08	0.01	—	—
Hemoglobin (g/dl)	0.10	0.006	—	—
Physical activity status	0.15	0.002	0.17	0.001
Activity target	0.11	0.005	—	—
MS	0.14	0.001	—	—
No. of MS risk factors	0.10	0.003	0.11	0.001
Myocardial ischemia	0.05	0.052	0.01	0.06
LV end systolic volume (ml)	0.08	0.02	—	—
LV end diastolic volume (ml)	0.11	0.004	—	—
LV mass index (g/m$^{2.7}$)	0.09	0.01	—	—
E prime (cm/s)	0.15	0.001	—	—
Carotid IMT (mm)	0.12	0.002	0.06	0.001

[a]On univariate analysis, peak VO_2 was positively correlated with male gender, height, hemoglobin, physical activity status, and activity target and inversely correlated with age, previous cardiac event, MS and number of MS risk factors, myocardial ischemia, LV volumes, LV mass index, E prime, and carotid IMT.

Table 4. Incremental value of cardiovascular imaging variables over demographic and clinical variables in predicting peak VO_2 in glucose-intolerant renal transplant recipients ($n = 71$)

	Univariate Analysis		Multivariate Analysis		Model R^2
	R^2	P	R^2	P	
Model 1					0.42
gender	0.27	<0.001	0.36	<0.001	
age (yr)	0.09	0.005	0.07	<0.001	
Model 2					0.63
gender	0.27	<0.001	0.28	<0.001	
age (yr)	0.09	0.005	0.10	<0.001	
previous cardiac event	0.08	0.01	0.03	0.03	
activity status	0.15	0.002	0.17	0.002	
no. of MS risk factors	0.10	0.003	0.08	<0.001	
Model 3					0.65
gender	0.27	<0.001	0.28	<0.001	
age (yr)	0.09	0.005	0.02	0.04	
previous cardiac event	0.08	0.01	0.03	0.07	
activity status	0.15	0.002	0.17	<0.001	
no. of MS risk factors					
myocardial ischemia	0.05	0.052	—	—	
LV end systolic volume (ml)	0.08	0.02	—	—	
LV end diastolic volume (ml)	0.11	0.004	—	—	
LV mass index ($g/m^{2.7}$)	0.09	0.01	—	—	
E prime (cm/s)	0.15	0.001	—	—	
Carotid IMT (mm)	0.12	0.002	0.13	0.04	

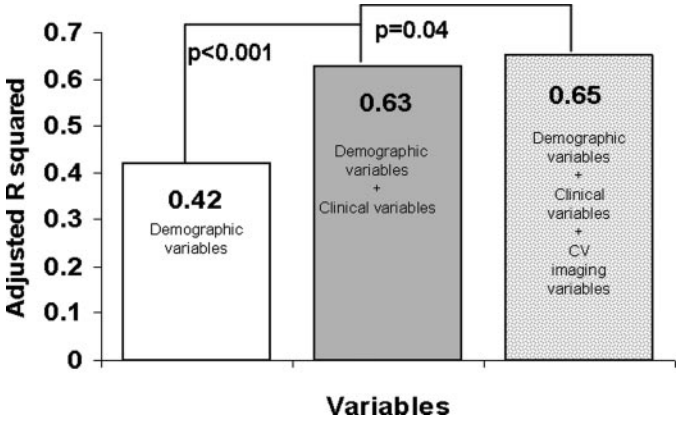

Figure 3. Incremental value of clinical and imaging variables in predicting peak VO_2. Left bar, model 1 (age and gender); middle bar, model 2 (age, gender, previous cardiac event, activity status, and number of MS risk factors); right bar, model 3 (age, gender, previous cardiac event, activity status, number of MS risk factors, and intima-media thickness).

monitored self-reported physical activity levels in nine patients before transplantation and at 6 and 16 wk after transplantation and observed a significant increase in physical activity during the 16-wk follow-up. In another study, the impact of transplantation on physical activity in both the short and the long term was evaluated in 32 patients who were assessed immediately before transplantation and then at 3, 6, 12, and 60 mo after transplantation (26). The results identified that RTR had a 30% increase in physical activity levels by 1 yr after transplant that was maintained at 5 yr. Although both studies identified an improvement in physical activity with renal transplantation, neither study assessed whether posttransplantation levels of physical activity were comparable with recommended levels.

Data on CF using peak VO_2 assessment in RTR are similarly limited and pertain mainly to the benefits of regular physical activity on CF (5,27). In a study of 167 RTR who were randomly assigned at 1 mo after transplantation into an exercise intervention group and a usual care group and tested at baseline, 6 mo, and 12 mo, there was a statistically significant improvement in CF in RTR in the exercise intervention group compared with baseline (5). The long-term benefits of regular exercise with respect to CF and cardiovascular outcomes in RTR remain uncertain.

Impact of MS on Physical Activity and CF

In the nontransplant population, metabolic parameters have been identified as important determinants of CF in a number of studies (6–8). Furthermore, MS prevalence is higher in individuals who have reduced CF and are physically inactive (28–30). Recent evidence also suggests that reduced CF is itself an independent predictor of incident MS (31,32). Thus, the interrelation between MS and CF is well established in the general population.

In the renal transplant population, the relationship among

MS, physical activity, and CF has not been explored previously. In this study, glucose-intolerant RTR with MS were physically inactive with reduced CF compared with those without MS. In addition, the *number* of MS risk factors was an independent determinant of CF. Although this association was demonstrated recently in nontransplant individuals (33), to the best of our knowledge, this is the first study to identify a dose–response association between the number of metabolic components and CF in RTR. Painter *et al.* (34) reported on the relationship between coronary heart disease (CHD) risk using the Framingham risk equation and CF in RTR. They examined the effects of exercise training on CF and CHD risk in 96 RTR who were randomly assigned to an exercise training group and a usual care group at 1 mo after transplantation. After 1 yr, physical activity levels and CF improved in patients in the exercise training group. However, there was no change in 10-yr CHD risk by Framingham, either over time or between the groups over time. Moreover, there was a significant negative correlation between CF and CHD risk ($r = -0.406$, $P < 0.001$).

In this study, several other markers of CVD, including a previous cardiac event, and echocardiographic parameters such as increased LV mass, increased LV volumes, and myocardial ischemia, all correlated with reduced CF on univariate analysis. Furthermore, abnormal IMT added incremental value to clinical variables in determining CF. IMT is associated with atherogenic risk factors and cardiovascular events in RTR (35,36) and is a useful marker of subclinical atherosclerosis even in the absence of clinical evidence of CVD (37,38). This finding provided supplementary evidence of a strong link between cardiovascular risk and reduced CF in glucose-intolerant RTR.

Limitations

Although this study has identified an important relationship among CF, physical activity, and MS in RTR, there were a number of limitations. These included the small sample size and the exclusion of individuals with normal glucose tolerance in the statistical analyses. By only assessing glucose-intolerant RTR, we were unable to evaluate the impact, if any, of glucose intolerance on CF, which casts doubt on the generalizability of these findings to all RTR. It should be noted, however, that because mean peak VO_2 was significantly higher in an age- and gender-matched cohort of normal glucose-tolerant transplant recipients, it is possible that disorders of glucose homeostasis indeed may be important in contributing to reduced CF in RTR. Further studies should include glucose intolerance as a categorical variable in any statistical analyses to explore this association further.

Although data were collected on activity status, we did not determine the specific reasons for inactivity in patients who perceived themselves as inactive. This supplementary information may have proved useful in further evaluating the limitations to CF, particularly because deconditioning and patient motivation are difficult to quantify accurately. Furthermore, data on physical activity would have been useful in individuals with normal glucose tolerance.

A further limitation was that baseline spirometry was not performed before exercise testing. This information could have helped to exclude significant ventilatory limitation that contributed to reduced CF in RTR, rather than relying on estimated ventilatory limitation. However, the significant positive correlation between estimated ventilatory limitation and peak VO_2 in the patient group ($r = 0.6$, $P < 0.001$), along with the small proportion of patients observed to terminate exercise because of dyspnea, suggest that respiratory dysfunction was unlikely to be a significant factor limiting CF in the group as a whole. Finally, the observational nature of this study makes it impossible to determine whether markers of cardiovascular risk, such as number of MS risk factors and subclinical atherosclerosis are direct *causes* of reduced CF or are *consequences* or associated phenomena. Further studies are required to evaluate this association further.

Conclusion

Despite these limitations, the findings from this study are important. Physical inactivity, MS, and reduced CF are major risk factors for CVD in the general population (1,39–41). Similar factors may operate in the pathogenesis of CVD in RTR. The cardiovascular benefits of regular exercise and optimal CF are well established in the general population. However, whether similar benefits are afforded to RTR is uncertain. Prospective studies are needed to address whether physical activity and modification of cardiovascular risk factors translate into improved CF and long-term cardiovascular outcomes in RTR and the precise impact of disorders of glucose homeostasis on CF in this patient group. Furthermore, the prognostic significance of silent myocardial ischemia needs to be clarified before increased physical activity is prescribed routinely in all RTR.

Acknowledgments

K.A. was supported by a Clinical Centre of Research Excellence Award from the National Health and Medical Research Council of Australia and a Cardiovascular Lipid Research Grant awarded by Pfizer.

We gratefully acknowledge the help with data collection provided by Rachael Pidcock and Linda Orazio, the advice provided by Neil Smart (exercise physiologist), and Elaine Beller (statistician) and the assistance of the staff and patients in the Renal Unit at the Princess Alexandra Hospital, Brisbane.

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