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Original research

Cardiorespiratory fitness and cardiovascular burden in chronic kidney disease

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ABSTRACT

Objectives: Reduced functional capacity is associated with poor prognosis. In patients with chronic kidney disease the factors that contribute to low cardiorespiratory fitness are unclear. The objective of this study was to evaluate the cardiorespiratory and cardiovascular response to exercise in chronic kidney disease patients, and secondly investigate the relationships between cardiorespiratory fitness and cardiovascular burden.
Design: Cross-sectional analysis.
Methods: Baseline demographic, anthropometric and biochemical data were examined in 136 patients with moderate chronic kidney disease (age 59.7 ± 9.6 yrs, eGFR 40 ± 9 ml/min/1.73 m^2, 55% male, 39% with a history of cardiovascular disease, 38% diabetic and 17% current smokers). Cardiorespiratory fitness was measured as peak VO_2, left ventricular morphology and function using echocardiography, central arterial stiffness by aortic pulse wave velocity and left ventricular afterload using augmentation index. Physical activity levels were assessed using the Active Australia questionnaire.
Results: Peak VO_2 (22.9 ± 6.5 ml/kg/min) and peak heart rate (148 ± 22 bpm) were 17% and 12% lower than the age-predicted values, respectively. The low fit group were significantly older, and were more likely to have type II diabetes, cardiovascular disease, a higher BMI and be less active than the high fit group ($P < 0.05$). The independent predictors of peak VO_2 were age, type II diabetes, hemoglobin level, physical activity, aortic pulse wave velocity, augmentation index, and global longitudinal strain.
Conclusions: In patients with chronic kidney disease, the peak VO_2 and heart rate response is markedly impaired. Reduced cardiorespiratory fitness is independently associated with increased aortic stiffness, increased left ventricle afterload, poor left ventricle function and higher burden of cardiovascular risk.

Chronic kidney disease (CKD) is associated with a significant reduction in exercise capacity and a marked increase in the risk of atherosclerosis and cardiovascular disease (CVD),[1] which is not fully explained by a high number of traditional risk factors. Like the general population, low cardiorespiratory fitness[2] (CRF) and physical activity[3] are associated with increased risk of morbidity and mortality in CKD. It has been irrefutably demonstrated over the past 50 years that higher levels of physical activity and CRF lowers the risk of CVD in the general population.[4–6] Whether higher levels of fitness and physical activity contribute beneficially to lower cardiovascular risk in patients with CKD is unknown.

CKD patients have an increased burden of CVD, which includes ischemic heart disease, systolic and diastolic dysfunction and increased arterial stiffness.[1,7] Moreover, a large proportion of patients are obese and inactive,[8] which perpetuates deconditioning, muscle wasting and chronic low-grade inflammation,[9] and may lower fitness. Surprisingly, the relationship between CRF and possible contributory factors has not been previously evaluated in this population. Due to the integrative nature and coordinated response of multiple systems, CRF is an excellent indicator of overall cardiovascular health. Therefore the aim of this study was to evaluate the cardiorespiratory and cardiovascular response to exercise in CKD patients, and secondly investigate the relationship between CRF and cardiovascular burden. We hypothesized that individuals

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with CKD and higher CRF would demonstrate enhanced cardiovascular function as assessed by left ventricular (LV) and vascular function, and better traditional cardiovascular risk factor profiles than individuals with lower fitness.

1. Methods

This study was a cross-sectional analysis of patients with stage 3 and 4 CKD enrolled in an interventional randomized controlled trial of cardiovascular risk modification. Details of the interventional study have been published.[10] Briefly, patients were eligible for inclusion if they were aged 18–75 yrs, had moderate CKD (eGFR 25–60 ml/min/1.73 m^2) and one or more uncontrolled cardiovascular risk factors. Exclusion criteria for the study were: Intervention for or symptomatic coronary artery disease (within 3 months), current heart failure (NYHA class III and IV) or significant valvular heart disease, pregnant or planning to become pregnant, life expectancy or anticipated time to dialysis or transplant <6 months as determined by their treating nephrologist. Participants provided written informed consent and the study complied with the Declaration of Helsinki. The study protocol was approved by the Princess Alexandra Human Research Ethics Committee (HREC 2007/190), and was registered at www.anzctr.org.au (Registration Number ANZCTR12608000337370).

All patients were pre-screened by the study research nurse. Detailed medical histories were obtained including prior history of CVD, for example myocardial infarction, coronary angioplasty, coronary artery bypass surgery, stroke, transient ischemic attack and/or peripheral vascular disease. Patients were subsequently screened for the presence of inducible myocardial ischemia as indicated by a positive exercise stress echocardiogram.

Peak VO_2 was determined from a graded treadmill exercise test to exhaustion with 12-lead ECG monitoring (CASE V6.51, GE Medical Systems, Milwaukee, WI, USA). Participants completed a Duke Activity Status Index to assist in determining which exercise protocol to use. Based on their response, patients performed either a Bruce, Balke or Naughton exercise protocol. Breath-by-breath gas analysis (Vmax29c, SensorMedics, CA, USA) and ventilatory volumes were measured continuously, and VO_2 peak was determined from the peak 20 s average during the final minute of exercise. Peak exercise blood pressure (BP) was measured in the last minute of exercise using a mercury sphygmomanometer. Achieved VO_2 peak was compared to sex specific normative VO_2 data for women [VO_2 peak = $(14.7 - (0.13 \times \text{age}) \times 3.5)$][11] and men [$VO_2$ peak = $(18.4 - (0.16 \times \text{age}) \times 3.5)$].[12] Predicted maximal heart rate (HR) was determined by the following formula [$208 - (0.7 \times \text{age})$].[13] Chronotropic incompetence was evaluated using heart reserve, where the difference between resting and peak heart rate was divided by the difference between resting heart rate and age predicted maximal heart rate. Failure to attain ≥80% of the heart reserve was used to identify chronotropic incompetence, as previously reported.[14] To minimize diurnal influence on testing parameters all participants were tested between 9 am and 11 am.

Imaging was performed by an experienced sonographer using a standard echocardiography machine (Vivid 7, General Electric Medical Systems, Milwaukee, WI) with a 3.5 MHz transducer. Images were acquired in the standard parasternal and apical views and were digitally recorded for offline analysis. Early (E) and late (A) diastolic mitral inflow velocities were measured from transmitral flow profile, recorded in apical four-chamber view with the sample volume placed at the level of the mitral valve leaflets in diastole. Pulsed wave tissue Doppler was used to measure the early diastolic relaxation velocity (e') at the septal mitral annulus. The E/e' ratio was calculated as an index of LV filling pressures.[15] Left atrial (LA) volume was measured using the area-length method and indexed to body surface area (LA volume index, LAVI). The LV end-systolic and end-diastolic volumes were assessed using the modified Simpson biplane method and indexed to body surface area. LV mass was assessed according to the method of Devereux and indexed to body surface area (LVMI). Global longitudinal strain and strain rate were measured with speckle tracking echocardiography off-line using specialized software (Echopac BT 2008, GE Medical Systems) and reported as the average of 6 basal segments from 3 standard apical views as previously reported.[16]

Central arterial stiffness was non-invasively determined by aortic pulse wave velocity (aPWV). The pulse wave distance was taken as the sternal notch-to-femoral distance minus the sternal notch-to-carotid distance. Radial tonometry was used to estimate central BP using a validated generalized transfer function (SpygmoCor 8.1, AtCor Medical, Sydney, Australia). The radial artery waveform was calibrated with brachial BP acquired in duplicate at the time of the measurement. Augmentation index (AIx) a marker of LV afterload was calculated as the ratio of augmented pressure to central pulse pressure. As AIx is influenced by HR, we used the value normalized for HR of 75 bpm (AIx75).[17]

Self-reported physical activity was measured using items from the Active Australia questionnaire.[18] Patients were classified as meeting physical activity guidelines if they reported performing ≥600 MET minutes per week.[19]

Exercise capacity was assessed by patients completing the six-minute walk test (6MWT) according to published recommendations.[20] METs were derived by the treadmill from the time, speed and grade at test termination.

Grip strength was measured using a hand-grip dynamometer (Jamar 5030 J1, Illinois, United States). The protocol was standardized and the peak value from three trials was recorded.[21] For muscular power, patients completed the "get up and go" test.[22]

After an overnight fast, patients provided blood and urine samples for the measurement of serum/plasma concentrations of creatinine, hemoglobin, glucose and lipids (total cholesterol, LDL cholesterol, and HDL cholesterol) using standard automated techniques. Kidney function was determined as eGFR using the standard MDRD-175 formula.

Results are reported as mean ± SD, median (interquartile range [IQR]), or frequencies (%) depending on the distribution of the data. Patients were grouped post hoc into tertiles based on their fitness (VO_2 peak) as low, moderate and high fitness. Analysis of variance (ANOVA), the Kruskal Wallis test or the Pearson X^2 test, were used as appropriate to assess group differences. Post hoc comparisons were performed using the Fishers Least Significant Difference test. Students paired t-test was used to compare achieved and predicted exercise variables (peak VO_2 and predicted maximum HR). An analysis of covariance (ANCOVA) was performed to determine the influence of increasing age on VO_2 peak in CKD patients. Univariate correlation (Pearson's and Spearman Rho) were used to determine the relationship between peak VO_2 and covariates (clinical variables – sex, age, history of CVD, type II diabetes, previous myocardial infarction, creatinine, eGFR, albumin, total cholesterol, HDL and LDL cholesterol, hemoglobin, BP, physical activity; vascular variables – AIx75, aPWV, peripheral pulse pressure, central pulse pressure; and cardiac variables – intraventricular relaxation time (IVRT), LAVI, e', s', E/e', ejection fraction, LVMI, EDVI, global longitudinal strain, average strain rate) and are reported in the Supplementary material. Multivariable regression models were developed to evaluate clinical and cardiovascular parameters that were predictors of peak VO_2 using three nested models. Standard regression diagnostics were performed and co-linearity tested. Statistical significance was defined as $\alpha < 0.05$. Statistical analysis was performed using commercially available software (SPSS v 20, SPSS Inc, Chicago, IL).