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ORIGINAL RESEARCH

Initiation of Dialysis Is Associated With Impaired Cardiovascular Functional Capacity

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BACKGROUND: The transition to dialysis period carries a substantial increased cardiovascular risk in patients with chronic kidney disease. Despite this, alterations in cardiovascular functional capacity during this transition are largely unknown. The present study therefore sought to assess ventilatory exercise response measures in patients within 1 year of initiating dialysis.

METHODS AND RESULTS: We conducted a cross-sectional study of 241 patients with chronic kidney disease stage 5 from the CAPER (Cardiopulmonary Exercise Testing in Renal Failure) study and from the intradialytic low-frequency electrical muscle stimulation pilot randomized controlled trial cohorts. Patients underwent cardiopulmonary exercise testing and echocardiography. Of the 241 patients (age, 48.9 [15.0] years; 154 [63.9%] men), 42 were predialytic (mean estimated glomerular filtration rate, 14 mL·min^{-1}·1.73 m^{-2}), 54 had a dialysis vintage ≤12 months, and 145 had a dialysis vintage >12 months. Dialysis vintage ≤12 months exhibited a significantly impaired cardiovascular functional capacity, as assessed by oxygen uptake at peak exercise (18.7 [5.8] mL·min^{-1}·kg^{-1}) compared with predialysis (22.7 [5.2] mL·min^{-1}·kg^{-1}; P<0.001). Dialysis vintage ≤12 months also exhibited reduced peak workload, impaired peak heart rate, reduced circulatory power, and increased left ventricular mass index (P<0.05 for all) compared with predialysis. After excluding those with prior kidney transplant, dialysis vintage >12 months exhibited a lower oxygen uptake at peak exercise (17.0 [4.9] mL·min^{-1}·kg^{-1}) compared with dialysis vintage ≤12 months (18.9 [5.9] mL·min^{-1}·kg^{-1}; P=0.033).

CONCLUSIONS: Initiating dialysis is associated with a significant impairment in oxygen uptake at peak exercise and overall decrements in ventilatory and hemodynamic exercise responses that predispose patients to functional dependence. The magnitude of these changes is comparable to the differences between low-risk New York Heart Association class I and higher-risk New York Heart Association class II to IV heart failure.

Key Words: aerobic capacity ■ cardiopulmonary exercise testing ■ dialysis ■ end-stage renal disease ■ oxygen uptake at peak exercise

The incident dialysis period is a life-altering transition characterized by a heightened risk for cardiovascular disease and mortality in patients with end-stage kidney disease (ESKD). In chronic kidney disease (CKD), the development of cardiovascular disease is attributed to both traditional and nontraditional risk factors that lead to alterations of the heart, vascular, musculoskeletal, and respiratory systems and collectively contribute to impairment of cardiovascular function.[1] The transition to dialysis dependency

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CLINICAL PERSPECTIVE

What Is New?

- Cardiovascular functional capacity (as assessed by oxygen uptake at peak exercise) is severely impaired after initiation of dialysis compared with patients with advanced chronic kidney disease predialysis.
- The mean oxygen uptake at peak exercise for patients on dialysis in their first year of dialysis was <20.1 $mL \cdot min^{-1} \cdot kg^{-1}$, which has been identified as a critical threshold below which the ability to live independently is at risk.
- Although most cardiovascular changes occur within the first year of initiating dialysis, cardiovascular functional capacity may continue to decline with increasing dialysis vintage in the absence of kidney transplantation.

What Are the Clinical Implications?

- Our findings indicate that the transition to dialysis marks a period of rapid decline in cardiovascular functional capacity that may predispose patients to functional dependence, which suggests that patients in this transition are an exceptionally vulnerable population.
- Our data provide rationale for further prospective studies that will assess cardiovascular functional changes using cardiopulmonary exercise testing during the transition to dialysis period.

Nonstandard Abbreviations and Acronyms

CPET	cardiopulmonary exercise testing
ESKD	end-stage kidney disease
HRpeak	heart rate at peak exercise
VE/VCO_2	ratio of minute ventilation/carbon dioxide production
Vin1	dialysis vintage ≤12 months
Vin2	dialysis vintage >12 months
VO_2AT	oxygen uptake at anaerobic threshold
VO_2Peak	oxygen uptake at peak exercise

introduces additional stressors, such as rapid fluid and electrolyte shifts, repetitive myocardial ischemia secondary to coronary microvascular dysfunction and intradialytic hypotension, increased inflammation attributable to blood contact with the dialysis membrane and catheters, and increased myocardial oxygen demand attributable to access-associated augmentation in cardiac output.[2–4] Accordingly, cardiovascular mortality rate in patients with ESKD is at its highest during the first year of dialysis, and ≈80% of cardiovascular deaths in patients on dialysis are secondary to primary arrythmia or sudden cardiac death.[5,6]

There are currently no uniformly accepted standardized diagnostic tools available to help screen and identify patients with CKD who are at increased risk of cardiovascular events in clinical practice today. Emerging data suggest that conventional resting heart imaging studies do not reliably predict functional performance and may not accurately reflect the risk of premature death in patients with ESKD.[7,8] In addition, gross alterations in left ventricular (LV) structure and function are largely absent during the transition to dialysis period,[9] and neither the high prevalence of coronary artery disease nor heart failure can fully explain the excess of sudden cardiac death in patients on dialysis.[10] Functional field tests, such as the 6-minute walk test, have been shown to have some prognostic value in patients with chronic heart failure,[11] but may lack sensitivity and provide limited information. Moreover, given the multisystemic alterations that occur throughout the oxygen transport chain,[1] an integrated approach to the assessment of cardiovascular function is needed to better understand the evolution of cardiovascular disease during this high-risk transition. These complex alterations can be collectively assessed using state-of-the-art cardiopulmonary exercise testing (CPET). CPET provides an objective integrated assessment that takes into account alterations of the heart (fibrosis and hypertrophy), lungs (impaired lung function), and musculoskeletal system (sarcopenia), and molecular changes that can occur in CKD by incorporating ventilatory gas exchange measurements during incremental exercise.[12]

Assessment of oxygen uptake at peak exercise (VO_2Peak) is widely accepted as a robust measure of cardiovascular functional capacity.[13] In addition, studies have shown that submaximal indexes, such as oxygen uptake at anaerobic threshold (VO_2AT), are also powerful measures of cardiovascular functional capacity and are independent of a patient's volitional effort.[14,15] These CPET indexes have been shown to predict risk of death in both the populations with general heart failure and CKD.[8,12] We recently demonstrated impaired VO_2Peak and VO_2AT in nontransplanted patients with ESKD and that CPET was sensitive enough to detect a significant decline in these indexes after 1-year follow-up in the CAPER (Cardiopulmonary Exercise Testing in Renal Failure and After Kidney Transplantation) study.[16] To date, the natural history and pattern of alterations in cardiovascular functional capacity during the first-year incident dialysis period are unknown. The overall goal of this study was to interrogate cardiovascular functional changes (as assessed by CPET) in patients within the first year of dialysis initiation compared with predialysis patients and those with a dialysis vintage over 1 year. We hypothesized that initiation of dialysis

is associated with significant impairment in VO_2Peak and exercise ventilatory gas exchange responses, and further impairment with increasing dialysis vintage.

METHODS

Data are available from the authors on reasonable request.

Study Design and Cohorts

We performed secondary analysis of data from a total of n=241 patients: 171 patients with advanced predialytic CKD and patients on dialysis were analyzed from the recently published CAPER study cohort[16] and an additional 70 patients receiving dialysis from the intradialytic low-frequency electrical muscle stimulation pilot randomized controlled trial were included in this study.[17] All patients in the present study were on the kidney transplant waitlist. All patients on hemodialysis were on thrice-weekly conventional hemodialysis. All patients on peritoneal dialysis were receiving either automated peritoneal dialysis with nightly 5 cycles of exchanges or continuous ambulatory peritoneal dialysis with 4 exchanges over 24 hours. In addition, all patients were recruited from the same center at the University Hospital Coventry and Warwickshire National Health Service Trust, Coventry, UK, as previously described.[16,17] Patients were aged ≥18 years. The intradialytic low-frequency electrical muscle stimulation pilot trial[17] protocol was approved by the West Midlands Research Ethics Committee (13/WM/0494) and registered with ClinicalTrials.gov: NCT02874521. The CAPER study[16] was approved by the Black Country Research Ethics Committee. Both studies adhered to the Declaration of Helsinki. All participants provided written informed consent.

CPET and Echocardiography

We assessed baseline data from both cohorts of patients who had undergone CPET. For dialysis-dependent participants, CPET was performed on a nondialysis day at least 12 hours after the last dialysis session. Patients on peritoneal dialysis had their fluid drained before CPET. CPET assessments were conducted uniformly for all patients by a trained exercise physiologist or physician who was blinded to the dialysis status of the study participant, as previously described.[7,17] Participants performed maximum incremental exercise on an upright cycle ergometer (Ergoselect 100; Ergoline), and continuous breath-by-breath gas exchange analysis (VIASYS; MasterScreen CPX) was performed. In addition, patients included in the CAPER study cohort had also undergone 2-dimensional Doppler and tissue Doppler transthoracic echocardiography using Vivid 7 (GE Healthcare) and assessment of arterial stiffness (SphygmoCor; AtCor Medical Pty Ltd).

Study End Points

Our primary end point was baseline VO_2Peak (in $mL{\cdot}min^{-1}{\cdot}kg^{-1}$) assessed via CPET. The secondary end points included ventilatory gas exchange measures (VO_2AT, ratio of minute ventilation/carbon dioxide production [VE/VCO_2] slope, and respiratory exchange ratio), hemodynamic measures (heart rate at peak exercise [HRpeak], O_2 pulse, and circulatory power), peak workload, cardiac structural indexes, and arterial stiffness. VO_2Peak and VO_2AT were normalized for body weight to facilitate intersubject comparisons.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics measures. Continuous variables were summarized by mean (SD) if normally distributed or median (interquartile range [IQR]) otherwise. Categorical variables were summarized by frequency (relative frequency in percentage). *t*-Tests, Mann-Whitney *U* tests, and Fisher exact tests were applied when appropriate to evaluate potential effects of initiating dialysis by comparing between predialysis and dialysis vintage ≤12 months (Vin1) groups. Vin1 and dialysis vintage >12 months (Vin2) groups were compared to further assess potential effects of increasing dialysis vintage. We adjusted for factors associated with VO_2Peak using multiple linear regression analysis. Covariates were selected on the basis of a combination of biological plausibility and known factors from published studies, and those that were significantly different between predialysis and Vin1. Comparative box plots were used to display group differences of outcome variables before and after adjusting for covariates. Pearson correlation coefficients were calculated to identify factors associated with VO_2Peak by dialysis vintage groups. $P<0.05$ was considered statistically significant, and missing observations were excluded. Statistical software STATA (16.1; Stata Corp LLC, College Station, TX) and SAS version 9.4 (SAS Institute, Cary, NC) were used for data analysis.

RESULTS

Characteristics of the Study Population

Baseline characteristics of the study population, including predialysis patients (n=42) and patients with a dialysis vintage ≤12 months (Vin1; n=54; mean dialysis vintage, 7.6 [3.9] months) and >12 months (Vin2; n=145; dialysis vintage, 60.1 [41.3] months) are shown in Table 1 (all patients) and Table S1 (excluding those with prior kidney transplant).

Predialysis Patients and Patients With a Dialysis Vintage ≤12 Months

Comparing between predialysis and Vin1, there was a lower proportion of White patients but higher proportions of Asian and Black patients (P=0.040) in Vin1. Vin1 also had a lower mean level of albumin (P=0.022) and a higher mean concentration of troponin T (P<0.001), NT-proBNP (N-terminal pro-B-type natriuretic peptide) (P<0.001), intact parathyroid hormone (P=0.039), and CRP (C-reactive protein) (P=0.003) compared with predialysis.

Characteristics of Patients With a Dialysis Vintage >12 Months

Comparing between Vin2 and Vin1, Vin2 had a longer duration of antihypertensive treatment (P=0.003) and a higher mean concentration of troponin T (P=0.002), NT-proBNP (P=0.001), corrected calcium (P=0.014), and intact parathyroid hormone (P=0.038).

There were no significant group differences (predialysis versus Vin1 and Vin1 versus Vin2) in age, sex, body mass index, hypertension, smoking status, diabetes, cardiovascular disease, phosphorous, hemoglobin, or glycated hemoglobin (P≥0.05 for all).

Cardiovascular Functional and Structural Changes With Initiating Dialysis

Functional and structural cardiovascular measures in predialysis and Vin1 are shown in Table 2 and Figure 1. Patients in Vin1 exhibited a significantly impaired VO_2Peak (18.7 [5.8] mL·min^{-1}·kg^{-1}) compared with predialysis (22.7 [5.2] mL·min^{-1}·kg^{-1}; P<0.001), even after adjusting for age, diabetes, race, diuretic use, and intact parathyroid hormone levels (Figure 2 and Table S2). These patients also had a lower VO_2AT (11.4 [2.8] mL·min^{-1}·kg^{-1}) compared with predialysis (12.6 [2.0] mL·min^{-1}·kg^{-1}; P=0.015); however, this difference was no longer significant after adjusting for covariates. No significant differences were observed in percentage predicted VO_2Peak, AT as percentage predicted VO_2Peak, or VE/VCO_2 slope (P≥0.05 for all) between groups.

In addition, Vin1 patients exhibited a blunted Hrpeak (130.3 [29.4] beats per minute) compared with predialysis (142.7 [22.9] beats per minute; P=0.027) and lower circulatory power (2367.6 [782.5] mm Hg·mL of O_2·min^{-1}·kg^{-1}) compared with predialysis (2799.4 [694.4] mm Hg·mL of O_2·min^{-1}·kg^{-1}; P=0.012). No significant differences were observed in O_2 pulse (P=0.2) between groups.

Peak workload was lower in Vin1 patients (98.6 [36.7] W) compared with predialysis (133.2 [58.0] W; P=0.001). No significant group differences were observed in endurance time (P=0.08).

Vin1 patients had a greater LV mass index (117.2 [40.5] g·m^{-2}) compared with predialysis (95.0 [26.6] g·m^{-2}; P=0.002); however, this difference was no longer significant after adjusting for race and diuretic use. LV ejection fraction was also reduced in Vin1 patients (58.2% [10.3%]) compared with predialysis (61.9% [7.0%]; P=0.043). Deceleration time was shorter in Vin1 compared with predialysis (P=0.040). Vin1 also had a lower averaged annular (septal and lateral) transmitral velocity compared with predialysis (P=0.010) and a higher ratio of early transmitral ventricular filling velocity/annular mitral velocity compared with predialysis patients (P<0.001). No significant group differences were observed in LV end-diastolic volume index, left atrial volume index, or the ratio of peak early/late transmitral ventricular filling velocities (P≥0.05 for all). Vin1 patients also exhibited a shorter time to reflection on applanation tonometry compared with predialysis (P<0.001). No significant group differences were noted between augmentation index standardized at 75 beats per minute (P=0.1) or pulse wave velocity (P=0.7).

Cardiovascular Functional Changes With Increasing Dialysis Vintage

There were no significant differences in VO_2Peak and other functional cardiovascular measures between Vin1 and Vin2 on analysis of the entire study population regardless of prior transplant status (Table 2 and Figure 1). Because there was a significantly higher proportion of Vin2 patients who had a prior kidney transplant (33 [22.8%]) compared with the Vin1 patients (5 [9.3%]; P=0.041), we therefore reevaluated the cohort to exclude those patients who had a prior kidney transplant. After exclusion of patients with prior transplant (Table 3 and Figure 1), Vin2 patients exhibited a significantly impaired VO_2Peak (17.0 [4.9] mL·min^{-1}·kg^{-1}) compared with Vin1 (18.9 [5.9] mL·min^{-1}·kg^{-1}; P=0.033). However, this difference was no longer significant after adjusting for covariates (Figure 2).

Correlation Analysis for Determinants of VO_2Peak

VO_2Peak in predialysis patients was associated with age (r=−0.411; P=0.007), CRP (r=−0.493; P=0.002), HRpeak (r=0.334; P=0.031), and peak workload (r=0.810; P<0.001; Table 4). Similarly, VO_2Peak in Vin1 patients was also correlated with age (r=−0.536; P<0.001), CRP (r=−0.353; P=0.038), HRpeak (r=0.521; P<0.001), and peak workload (r=0.656; P<0.001). VO_2Peak in Vin2 patients was associated with age (r=−0.506; P<0.001), hemoglobin (r=0.189; P=0.023), mean arterial pressure (r=0.170; P=0.042), HRpeak

Table 1. Baseline Characteristics of the Study Population

Characteristic*	Predialysis (n=42)	Dialysis vintage ≤12 mo (n=54)	Dialysis vintage >12 mo (n=145)	*P* value†	*P* value‡
Age, mean (SD), y	42 (14)	47 (16)	52 (14)	0.07	0.06
Men	24 (57.1)	32 (59.3)	98 (67.6)	0.8	0.3
Race				0.040	0.9
White	38 (90.5)	40 (74.1)	101 (69.7)	…	…
Asian	4 (9.5)	8 (14.8)	24 (16.6)	…	…
Black	0 (0.0)	6 (11.1)	20 (13.8)	…	…
BMI, mean (SD), $kg{\cdot}m^{-2}$	24.9 (4.0)	26.0 (4.6)	26.6 (5.5)	0.2	0.4
SBP, mean (SD), mm Hg	135.5 (15.4)	133.2 (25.3)	130.5 (25.7)	0.6	0.5
DBP, mean (SD), mm Hg	82.3 (9.4)	78.9 (14.6)	76.3 (18.3)	0.2	0.3
MAP, mean (SD), mm Hg	100.0 (9.0)	97.0 (16.8)	94.3 (18.8)	0.3	0.4
Hypertension	37 (88.1)	45 (83.3)	119 (83.2)	0.6	1.0
Antihypertensive treatment duration, median (IQR), mo	75 (24–180)	60 (24–140)	132.0 (60–238)	1.0	0.003
Previous kidney transplant	1 (2.4)	5 (9.3)	33 (22.8)	0.2	0.041
Blood pressure medication use					
ACEI or ARB blocker	23 (54.8)	23 (42.6)	40 (27.6)	0.2	0.043
Calcium antagonist	27 (64.3)	30 (55.6)	62 (42.8)	0.4	0.1
ß-Blocker	14 (33.3)	21 (38.9)	58 (40.0)	0.6	0.9
Diuretic	12 (28.6)	6 (11.1)	15 (10.4)	0.037	1.0
Smoking (ever)	20 (47.6)	33 (61.1)	78 (54.5)	0.2	0.4
Diabetes	2 (4.8)	10 (18.5)	25 (17.2)	0.06	0.8
Cardiovascular disease	2 (4.8)	3 (8.3)	13 (14.0)	0.7	0.6
Dialysis modality				…	0.05
Hemodialysis	…	45 (83.3)	135 (93.1)	…	…
Peritoneal dialysis	…	9 (16.7)	10 (6.9)	…	…
Dialysis vintage, mean (SD), mo	…	7.6 (3.9)	60.1 (41.3)	…	<0.001
Laboratory values					
eGFR, mean (SD), $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$	14 (3)	10 (5)	7 (3)	<0.001	0.002
Troponin T, median (IQR), $ng{\cdot}L^{-1}$	11.6 (8.2–16.5)	27.8 (18.2–41.2)	42.1 (27.7–59.7)	<0.001	0.002
NT-proBNP, median (IQR), $pg{\cdot}mL^{-1}$	39.7 (18.8–65.4)	143.4 (38.9–268.9)	305.3 (161.1–683.0)	<0.001	0.001
Albumin, mean (SD), $g{\cdot}dL^{-1}$	4.4 (0.3)	4.3 (0.4)	4.3 (0.4)	0.022	0.2
Corrected calcium, mean (SD), $mmol{\cdot}L^{-1}$	2.2 (0.1)	2.2 (0.2)	2.3 (0.2)	0.9	0.014
Phosphorus, mean (SD), $mmol{\cdot}L^{-1}$	1.4 (0.3)	1.6 (0.4)	1.6 (0.5)	0.1	0.3
iPTH, median (IQR), $pg{\cdot}mL^{-1}$	15.6 (6.9–23.0)	21.7 (12.5–43.6)	34.3 (13.3–61.1)	0.039	0.038
CRP, median (IQR), $mg{\cdot}L^{-1}$	1.4 (0.5–2.9)	2.7 (1.7–7.3)	3.5 (1.7–7.6)	0.003	0.5
Hemoglobin, mean (SD), $g{\cdot}dL^{-1}$	11.9 (1.2)	11.6 (1.5)	11.5 (1.4)	0.2	1.0
HbA1c level, median (IQR), %	5.6 (5.5–5.8)	5.3 (5.1–5.8)	5.4 (5.0–5.8)	0.08	0.9

Data are presented as number (percentage) of patients unless otherwise indicated. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; iPTH, intact parathyroid hormone; IQR, interquartile range; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and SBP, systolic blood pressure.

*Missing values excluded. Predialysis: 4 missing troponin T, 4 missing NT-proBNP, and 4 missing CRP; dialysis vintage ≤12 months: 2 missing SBP, 2 missing DBP, 2 missing MAP, 6 missing treatment duration, 18 missing cardiovascular disease, 9 missing eGFR, 19 missing troponin T, 19 missing NT-proBNP, 18 missing corrected calcium, 18 missing phosphorous, 1 missing iPTH, 19 missing CRP, 1 missing hemoglobin, and 18 missing HbA1c. Dialysis vintage >12 months: 1 missing SBP, 1 missing DBP, 1 missing MAP, 2 missing hypertension, 20 missing treatment duration, 1 missing number of blood pressure medications, 1 missing diuretic, 2 missing smoking, 42 missing eGFR, 60 missing troponin T, 60 missing NT-proBNP, 52 missing corrected calcium, 52 missing phosphorous, 3 missing iPTH, 60 missing CRP, and 52 missing HbA1c.

†Comparison between predialysis and dialysis vintage ≤12 months.

‡Comparison between dialysis vintage ≤12 months and dialysis vintage >12 months.

Table 2. Functional and Structural Cardiovascular Measures

Variable*	Predialysis	Dialysis vintage ≤12 mo	Dialysis vintage >12 mo	*P* value†	*P* value‡
VO_2Peak, mL·min^{-1}·kg^{-1}	22.7 (5.2)	18.7 (5.8)	17.8 (5.2)	<0.001	0.3
VO_2Peak, % predicted	73.9 (16.0)	66.9 (17.8)	67.3 (16.1)	0.07	0.9
VO_2AT, mL·min^{-1}·kg^{-1}	12.6 (2.0)	11.4 (2.8)	10.8 (2.5)	0.015	0.2
AT, % predicted VO_2Peak	41.6 (9.5)	41.4 (10.3)	40.4 (8.5)	0.9	0.6
VE/VCO_2 slope	32.1 (5.6)	29.9 (5.3)	29.7 (5.7)	0.08	0.9
Peak workload, W	133.2 (58.0)	98.6 (36.7)	95.6 (34.0)	0.001	0.6
Endurance time, min	11.2 (2.2)	10.4 (1.9)	10.2 (1.8)	0.08	0.6
RER at AT	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.001	1.0
RER at peak exercise	1.2 (0.1)	1.3 (0.1)	1.3 (0.1)	0.037	0.6
HRpeak, bpm	142.7 (22.9)	130.3 (29.4)	126.8 (23.7)	0.027	0.4
HRpeak, % predicted	79.9 (10.9)	75.1 (14.9)	75.5 (14.2)	0.07	0.8
Oxygen pulse, mL·min^{-1} of O_2	12.1 (4.7)	10.7 (3.6)	10.9 (3.1)	0.2	0.8
Circulatory power, mm Hg·mL of O_2·min^{-1}·kg^{-1}	2799.4 (694.4)	2367.6 (782.5)	2274.6 (769.0)	0.012	0.5
VO_2Peak <20.1 mL·min^{-1}·kg^{-1}, n (%)	17 (40.5)	34 (63.0)	101 (69.7)	0.039	0.4
VO_2Peak ≤17.5 mL·min^{-1}·kg^{-1}, n (%)	7 (16.7)	23 (42.6)	76 (52.4)	0.008	0.3
Cardiac measures					
LVMI, g·m^{-2}	95.0 (26.6)	117.2 (40.5)	122.8 (48.1)	0.002	0.5
LVEDV index, mL·m^{-2}	47.3 (15.9)	50.2 (16.5)	51.1 (17.8)	0.4	0.7
LA volume index, mL·m^{-2}	23.4 (11.1)	24.9 (9.7)	31.6 (16.0)	0.5	0.005
LVEF, %	61.9 (7.0)	58.2 (10.3)	59.8 (10.0)	0.043	0.3
E/A	1.1 (0.3)	1.0 (0.4)	1.0 (0.5)	0.1	0.6
Deceleration time, ms	226.9 (55.3)	200.8 (54.6)	214.2 (62.6)	0.040	0.3
Mean e', m·s^{-1}	11.2 (3.6)	9.1 (3.2)	8.8 (2.7)	0.010	0.6
E/mean e'	7.0 (2.2)	9.4 (4.4)	10.2 (4.7)	<0.001	0.1
Arterial indexes					
Time to reflection, ms	145.9 (12.6)	136.7 (10.5)	137.5 (12.8)	<0.001	0.7
Augmentation index at 75 bpm, %	17.9 (14.9)	22.6 (13.2)	25.7 (11.4)	0.1	0.2
Pulse wave velocity, m·s^{-1}	8.0 (2.3)	8.2 (2.6)	9.0 (2.8)	0.7	0.1

Data are presented as mean (SD) unless otherwise indicated. AT indicates anaerobic threshold; bpm, beats per minute; E/A, ratio of peak early/late transmitral ventricular filling velocities; e', annular mitral velocity; HRpeak, heart rate at peak exercise; LA, left arterial; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; RER, respiratory exchange ratio of carbon dioxide production to oxygen consumption; VE/VCO_2, relationship between minute ventilation and carbon dioxide production; VO_2AT, oxygen uptake at AT; and VO_2Peak, oxygen uptake at peak exercise.

*Missing values excluded. Dialysis vintage ≤12 months: 18 missing VO_2Peak, % predicted, 18 missing AT, 18 missing VE/VCO_2 slope, 1 missing peak workload, 18 missing oxygen pulse, 18 missing circulatory power, 1 missing LVMI, 1 missing LVEDV index, 1 missing LVEF, 1 missing E/A, 18 missing deceleration time, 18 missing mean e', 1 missing E/mean e', 18 missing time to reflection, 18 missing augmentation index, and 18 missing pulse wave velocity. Dialysis vintage >12 months: 52 missing VO_2Peak, % predicted, 1 missing VO_2AT, 53 missing AT, 52 missing VE/VCO_2 slope, 52 missing endurance time, 1 missing RER at AT, 1 missing HRpeak, 1 missing HRpeak, % predicted, 53 missing oxygen pulse, 52 missing circulatory power, 2 missing LVMI, 4 missind LVEDV index, 52 missing LA volume index, 4 missing LVEF, 4 missing E/A, 52 missing deceleration time, 55 missing mean e', 9 missing E/mean e', 52 missing time to reflection, 53 missing augmentation index, and 52 missing pulse wave velocity.

†Comparison between predialysis and dialysis vintage ≤12 months.

‡Comparison between dialysis vintage ≤12 months and dialysis vintage >12 months.

(*r*=0.283; *P*<0.001), and peak workload (*r*=0.708; *P*<0.001).

After exclusion of patients with prior kidney transplant, VO_2Peak in Vin1 patients was associated with LV mass index (*r*=−0.292; *P*=0.044) in addition to age, CRP, HRpeak, and peak workload. Vin2 was associated with CRP (*r*=−0.304; *P*=0.025) in addition to age, hemoglobin, HRpeak, and peak workload but was no longer correlated with mean arterial pressure.

DISCUSSION

The present study is the first to comprehensively assess ventilatory gas exchange patterns of cardiovascular function in parallel with structural changes during the incident transition to dialysis period. The findings of this study suggest that cardiovascular functional capacity (as assessed by VO_2Peak) is severely impaired after initiation of dialysis compared with patients with

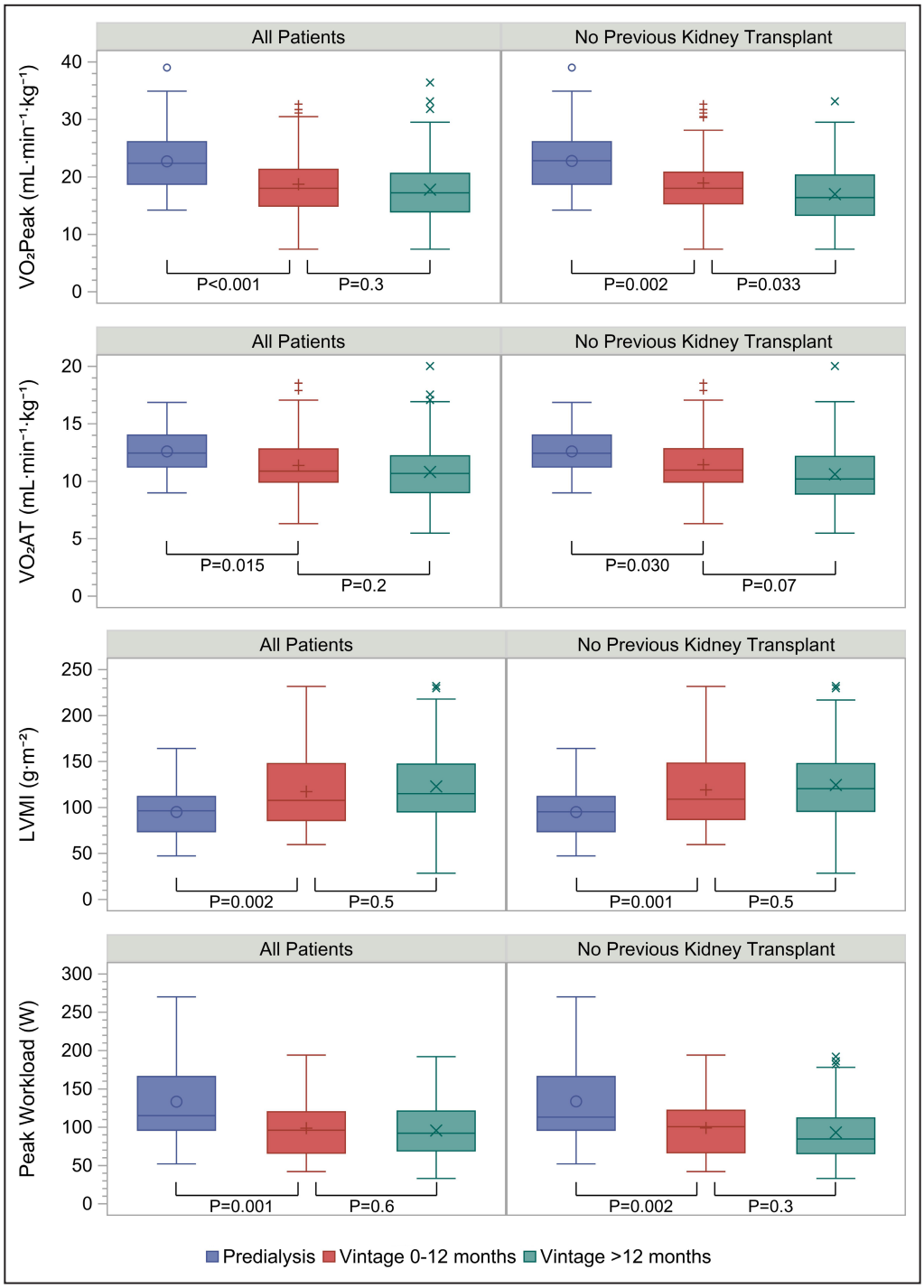

Figure 1. Differences in oxygen uptake at peak exercise (VO_2Peak), oxygen uptake at anaerobic threshold (VO_2AT), left ventricular mass index (LVMI), and peak workload between groups (unadjusted).

VO_2Peak, VO_2AT, LVMI, and peak workload in predialysis patients (blue), patients with a dialysis vintage ≤12 months (red), and patients with a dialysis vintage >12 months (green).

advanced CKD predialysis. There was a significant decrease in VO_2Peak of a mean of 4.0 mL·min^{-1}·kg^{-1} between predialysis patients and Vin1 patients, and an even greater decrease of a mean of 6.2 mL·min^{-1}·kg^{-1} between Vin1 and hypertensive controls (24.9 [7.1] mL·min^{-1}·kg^{-1}) in the CAPER study.[16] The magnitude of this decline is comparable to the discriminatory differences between low-risk patients with New York Heart Association class I heart failure (VO_2Peak >20 mL·min^{-1}·kg^{-1}) and higher-risk symptomatic

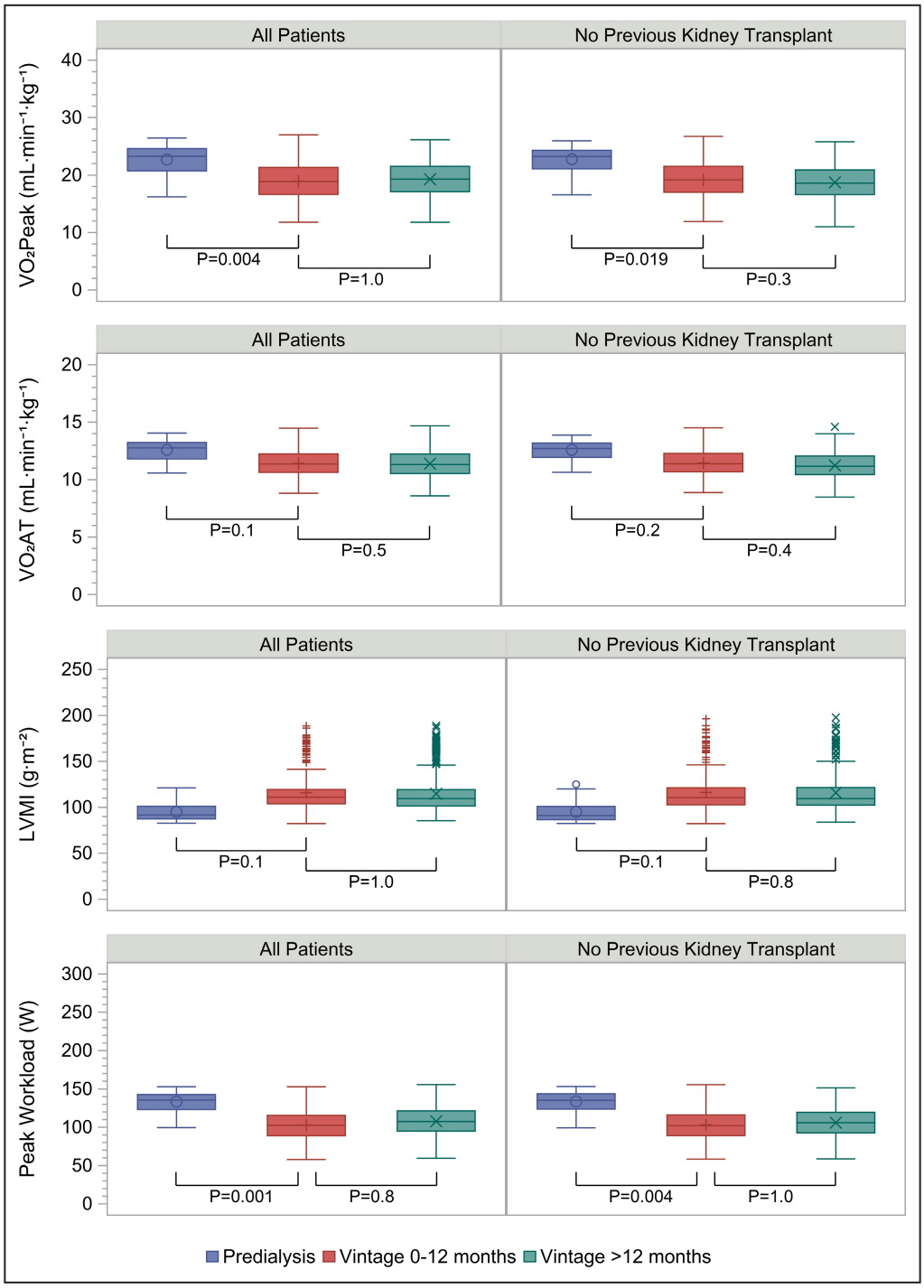

Figure 2. Differences in oxygen uptake at peak exercise (VO_2Peak), oxygen uptake at anaerobic threshold (VO_2AT), left ventricular mass index (LVMI), and peak workload between groups (adjusted).

VO_2Peak, VO_2AT, LVMI, and peak workload in predialysis patients (blue), patients with a dialysis vintage ≤12 months (red), and patients with a dialysis vintage >12 months (green). Comparisons were adjusted for age, diabetes, race, diuretic use, and intact parathyroid hormone levels.

patients with New York Heart Association class II to IV heart failure (VO_2Peak 14–20 mL·min^{-1}·kg^{-1}).[18] In addition, the mean VO_2Peak for the Vin1 group was <20.1 mL·min^{-1}·kg^{-1}, and a significantly higher proportion of Vin1 patients (63%) were below this level compared with predialysis (40.5%; *P*=0.039), which has been identified as a critical threshold below which the ability to live independently is at risk.[19] This finding suggests

Table 3. Functional Cardiovascular Measures, Excluding Those With Prior Kidney Transplant

Variable*	Predialysis	Dialysis vintage ≤12 mo	Dialysis vintage >12 mo	*P* value†	*P* value‡
VO_2Peak, mL·min^{-1}·kg^{-1}	22.7 (5.3)	18.9 (5.9)	17.0 (4.9)	0.002	0.033
VO_2Peak, % predicted	74.7 (15.5)	68.7 (17.5)	67.9 (16.0)	0.1	0.8
VO_2AT, mL·min^{-1}·kg^{-1}	12.6 (2.0)	11.4 (2.9)	10.6 (2.6)	0.030	0.07
AT, % predicted VO_2Peak	42.0 (9.4)	42.2 (10.7)	42.1 (9.0)	0.9	0.9
VE/VCO_2 slope	32.1 (5.7)	29.7 (5.2)	30.1 (6.2)	0.06	0.7
Peak workload, W	133.6 (58.7)	98.9 (35.6)	93.0 (35.0)	0.002	0.3
Endurance time, min	11.3 (2.2)	10.5 (1.9)	10.4 (1.8)	0.1	0.8
RER at AT	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.002	0.4
RER at peak exercise	1.2 (0.1)	1.2 (0.1)	1.3 (0.1)	0.06	0.8
HRpeak, bpm	143.5 (22.5)	129.8 (29.5)	126.7 (24.0)	0.016	0.5
HRpeak, % predicted	80.4 (10.4)	75.1 (14.9)	76.4 (14.3)	0.048	0.6
Oxygen pulse, mL·min^{-1} of O_2	12.1 (4.8)	10.9 (3.6)	10.6 (3.3)	0.3	0.7
Circulatory power, mm Hg·mL of O_2·min^{-1}·kg^{-1}	2811.8 (698.3)	2436.5 (753.4)	2146.9 (675.7)	0.032	0.07
VO_2Peak <20.1 mL·min^{-1}·kg^{-1}, n (%)	16 (39.0)	31 (63.3)	81 (72.3)	0.034	0.3
VO_2Peak ≤17.5 mL·min^{-1}·kg^{-1}, n (%)	7 (17.1)	20 (40.8)	67 (59.8)	0.020	0.039
Cardiac measures					
LVMI, g·m^{-2}	94.9 (26.9)	119.1 (41.0)	124.4 (50.1)	0.001	0.5
LVEDV index, mL·m^{-2}	47.1 (16.0)	50.8 (16.2)	52.1 (17.5)	0.3	0.7
LA volume index, mL·m^{-2}	23.4 (11.2)	25.9 (10.0)	30.9 (16.7)	0.3	0.09
LVEF, %	62.2 (6.8)	58.0 (9.9)	58.9 (10.6)	0.022	0.6
E/A	1.1 (0.3)	1.0 (0.4)	1.0 (0.5)	0.1	0.6
Deceleration time, ms	227.2 (56.0)	196.7 (57.3)	213.3 (61.2)	0.027	0.2
Mean e', m·s^{-1}	11.1 (3.6)	9.3 (3.3)	8.6 (2.3)	0.028	0.3
E/mean e'	7.0 (2.2)	9.3 (4.2)	10.2 (4.6)	0.002	0.3
Arterial indexes					
Time to reflection, ms	145.3 (12.3)	136.4 (10.1)	137.5 (13.7)	0.002	0.7
Augmentation index at 75 bpm, %	18.0 (15.0)	23.4 (11.5)	26.0 (12.2)	0.1	0.3
Pulse wave velocity, m·s^{-1}	7.9 (2.3)	8.4 (2.7)	9.2 (3.0)	0.4	0.2

Data are presented as mean (SD) unless otherwise indicated. AT indicates anaerobic threshold; bpm, beats per minute; E/A, ratio of peak early/late transmitral ventricular filling velocities; /e', annular mitral velocity; HRpeak, heart rate at peak exercise; LA, left arterial; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; RER, respiratory exchange ratio of carbon dioxide production to oxygen consumption; VE/VCO_2, relationship between minute ventilation and carbon dioxide production; VO_2AT, oxygen uptake at AT; and VO_2Peak, oxygen uptake at peak exercise.

*Missing values excluded. Dialysis vintage ≤12 months: 18 missing VO_2Peak, % predicted,18 missing AT, 18 missing VE/VCO_2 slope, 1 missing peak workload, 19 missing endurance time, 18 missing oxygen pulse, 18 missing circulatory power, 1 missing LVMI, 1 missing LVEDV index, 18 missing LA volume index, 1 missing LVEF, 1 missing E/A, 18 missing deceleration time, 18 missing mean e', 1 missing E/mean e', 18 missing time to reflection, 18 missing augmentation index, and 18 missing pulse wave velocity. Dialysis vintage >12 months: 52 missing VO_2Peak, % predicted, 1 missing VO_2AT, 53 missing AT, 52 missing VE/VCO_2 slope, 52 missing endurance time, 1 missing RER at AT, 1 missing HRpeak, 1 missing HRpeak, % predicted, 53 missing oxygen pulse, 52 missing circulatory power, 2 missing LVMI, 4 missing LVEDV index, 52 missing LA volume index, 4 missing LVEF, 4 missing E/A, 52 missing deceleration time, 53 missing mean e', 8 missing E/mean e', 52 missing time to reflection, 53 missing augmentation index, and 53 missing pulse wave velocity.

†Comparison between predialysis and dialysis vintage ≤12 months.

‡Comparison between dialysis vintage ≤12 months and dialysis vintage >12 months.

that the transition to dialysis marks a period of rapid decline in cardiovascular functional capacity that may predispose patients to functional dependence. Furthermore, a significantly higher proportion of Vin1 patients had a VO_2Peak ≤17.5 mL·min^{-1}·kg^{-1} (42.6%) compared with predialysis (16.7%; *P*=0.008), which has previously been identified as a threshold for higher risk of death in patients with ESKD.[20] This finding supports the notion that the period of incident dialysis is a life-threatening transition in patients with ESKD.

The blunted chronotropic responses observed in Vin1 patients compared with predialysis patients are a novel finding. Chronotropic incompetence in patients with ESKD reflects autonomic dysfunction resulting from uremia, sympathetic overactivity, and vagal withdrawal.[21] Circulatory power is a surrogate of peak exercise cardiac power that incorporates heart rate, stroke volume, blood pressure, and arterial oxygen extraction responses to exercise. More important, circulatory power has been shown to be a robust predictor of poor

Table 4. Pearson Correlation Analysis of VO_2Peak

	All patients						Excluding those with prior kidney transplant					
	Predialysis		Dialysis vintage ≤12 mo		Dialysis vintage >12 mo		Predialysis		Dialysis vintage ≤12 mo		Dialysis vintage >12 mo	
Measure*	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Age	−0.411	0.007	−0.536	<0.001	−0.506	<0.001	−0.423	0.006	−0.580	<0.001	−0.425	<0.001
eGFR	0.054	0.7	−0.260	0.09	−0.056	0.6	0.053	0.7	−0.311	0.05	−0.089	0.5
Calcium	−0.225	0.2	−0.075	0.7	−0.058	0.6	−0.215	0.2	−0.053	0.8	0.055	0.7
Phosphorus	−0.015	0.9	0.030	0.9	0.083	0.4	−0.001	1.0	0.115	0.5	0.163	0.2
iPTH†	−0.130	0.4	−0.019	0.9	0.113	0.2	−0.109	0.5	0.004	1.0	0.061	0.5
CRP†	−0.493	0.002	−0.353	0.038	−0.191	0.08	−0.493	0.002	−0.392	0.032	−0.304	0.025
Hemoglobin	0.105	0.5	0.212	0.1	0.189	0.023	0.115	0.5	0.258	0.08	0.223	0.018
LVMI	0.119	0.5	−0.262	0.06	0.081	0.3	0.121	0.5	−0.292	0.044	0.122	0.2
LVEF	−0.116	0.5	0.017	0.9	0.126	0.1	−0.143	0.4	0.010	0.9	0.105	0.3
Mean arterial pressure	−0.107	0.5	0.258	0.06	0.170	0.042	−0.113	0.5	0.206	0.2	0.134	0.2
HRpeak	0.334	0.031	0.521	<0.001	0.283	<0.001	0.325	0.038	0.528	<0.001	0.293	0.002
Peak workload	0.810	<0.001	0.656	<0.001	0.708	<0.001	0.810	<0.001	0.661	<0.001	0.719	<0.001

CRP indicates C-reactive protein; eGFR, estimated glomerular filtration rate; HRpeak, heart rate at peak exercise; iPTH, intact parathyroid hormone; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; and VO_2Peak, oxygen uptake at peak exercise.

*Missing values excluded. Predialysis: 4 missing CRP. Dialysis vintage ≤12 months: 9 missing eGFR, 18 missing calcium, 18 missing phosphorous, 1 missing iPTH, 19 missing CRP, 1 missing hemoglobin, 1 missing LVMI, 1 missing LVEF, 2 missing mean arterial pressure, and 1 missing peak workload. Dialysis vintage >12 months: 42 missing eGFR, 52 missing calcium, 52 missing phosphorous, 3 missing iPTH, 60 missing CRP, 2 missing LVMI, 4 missing LVEF, 1 missing mean arterial pressure, and 1 missing HRpeak.

†Log transformed before analysis.

outcome in patients with heart failure.[22] In the present study, the mean circulatory power in Vin1 patients was lower than previously reported values in patients with heart failure who died or underwent heart transplantation.[22] This suggests that peak exercise cardiac power is significantly impaired following initiation of dialysis and is a significant contributor to impaired functional reserve.

Our echocardiography findings point to worsening LV hypertrophy and dysfunction in the transition to dialysis. The increase in LV mass is believed to be an adaptive response to both sustained pressure and volume overload that initially normalizes wall stress and maintains a normal systolic function. However, sustained fluid overload and uremia may progress to maladaptive hypertrophy, characterized by myocardial fibrosis and reduced compliance and contractility. Furthermore, dialysis-induced myocardial stunning has been shown to lead to LV dysfunction,[23] which may blunt peak cardiac output and VO_2Peak in patients receiving dialysis. Interestingly, hemoglobin concentration significantly correlated with VO_2Peak in the Vin2 group but not in Vin1 or predialysis. Anemia is associated with reduced exercise capacity in CKD and contributes to exercise intolerance by lowering oxygen-carrying capacity.[24] The effects of anemia can be compensated by increased cardiac output and/or peripheral oxygen extraction. However, our findings suggest these compensatory mechanisms may decline with increasing dialysis vintage, leading to a reduction in VO_2Peak.

VE/VCO_2 slope, an index of ventilatory efficiency, has recently emerged as a reliable prognostic variable in advanced heart failure.[25] A VE/VCO_2 slope <30 is considered normal.[25] In the present study, Vin1 patients had lower VE/VCO_2 slope (29.7 [5.2]) compared with predialysis patients (32.1 [5.7]), although this did not reach statistical significance. Elevated VE/VCO_2 slope has previously been reported in patients with CKD stage 3 to 4 compared with healthy controls.[26] Another study, however, reported no significant differences in VE/VCO_2 slope in a mixed cohort of non–dialysis- and dialysis-dependent patients with ESKD compared with hypertensive controls.[7] Elevated VE/VCO_2 slope has been associated with lower cardiac output, higher pulmonary vascular resistance, and increased ventilation-perfusion mismatching,[27,28] all of which have been reported in CKD.[1] Therefore, the degree to which each of these pathophysiological factors may independently contribute to ventilatory efficiency in CKD is unknown. Future studies using invasive CPET, which combines pulmonary and systemic hemodynamics along with gas analysis, are warranted to elucidate the mechanisms behind changes in ventilatory efficiency in the transition to dialysis.

Impaired cardiovascular functional capacity in the Vin1 group may also be a result of uremic burden and subsequent deconditioning. Analysis of patient-reported outcomes among patients undergoing incident dialysis in the CHOICE (Choices for Health Outcomes in Caring for ESRD[End-Stage Renal Disease]) study and the LUCID (Longitudinal US/Canada Incident Dialysis) study found that anorexia (44% and 44%, respectively), nausea/vomiting (36% and 43%, respectively), pruritus (72% and 63%, respectively), sleepiness (86% and 68%, respectively), difficulty concentrating (55% and 57%, respectively), fatigue (89% and 77%, respectively), and pain (82% and 79%, respectively) were highly prevalent.[29] In fact, >80% of patients had ≥3 of these symptoms, and we postulate that these complications contribute to low physical activity. In addition, in a study of 1547 incident dialysis patients in the US Renal Data System Comprehensive Dialysis Study, self-reported physical activity for men was below the 25th percentile of healthy men; and for women, it was below the 1st percentile of healthy women.[30] Low physical activity was associated with poorer health-related quality of life in both the physical and mental domains, and these results taken together suggest that low physical performance is a major comorbidity in patients undergoing incident dialysis. We postulate that deconditioning of patients and reduced physical activity may be major determinants of impaired VO_2Peak levels observed in the early stages of dialysis.

We have previously shown that kidney transplantation is associated with improved VO_2Peak,[16] and the regression of LV hypertrophy after renal transplantation has been shown to persist into the fourth posttransplant year.[31] In the present study, our initial analysis indicated no significant changes in VO_2Peak associated with dialysis vintage. Because a significantly higher proportion of Vin2 patients had a prior kidney transplant compared with the Vin1 patients, we excluded patients who had a prior kidney transplant and reevaluated differences in VO_2Peak associated with increasing dialysis vintage. We found that VO_2Peak was significantly further impaired in the Vin2 group compared with Vin1 group after exclusion of patients who had a prior transplant. This finding suggests that although most cardiovascular changes occur within the first year of initiating dialysis,[2] cardiovascular functional capacity may continue to decline with increasing dialysis vintage in the absence of kidney transplantation. Therefore, our findings suggest that preemptive renal transplantation could prevent further decrements in cardiovascular functional capacity in patients with CKD.

Data from the Frequent Hemodialysis Network Daily and Nocturnal Trials demonstrated that frequent dialysis (6 times per week) reduced LV hypertrophy.[32] However, studies evaluating the effects of frequent dialysis on VO_2Peak are lacking and have yielded

conflicting results. One study showed no improvements in VO_2Peak in patients who changed from conventional hemodialysis to short daily hemodialysis (3 hours, 5–6 days/week) after 6 months.[33] Another study found that conversion from conventional hemodialysis to nocturnal hemodialysis (8–10 hours, 5–6 nights/week) progressively enhanced VO_2Peak at 2 and 6 months.[34] Further adequately powered prospective trials are desperately needed to determine whether more frequent dialysis and other interventions, such as exercise programs, can confer cardiovascular functional improvement in patients undergoing incident dialysis and halt further cardiovascular functional declines with increasing dialysis vintage.

Limitations

Our results should be interpreted in the context of the limitations of the study. We did not assess differences in noncardiac determinants of VO_2Peak, such as peripheral O_2 extraction and skeletal muscle properties. Therefore, the impact of initiating dialysis on noncardiac determinants of cardiovascular functional capacity remains unknown. Our patient population was limited to those on the renal transplant waitlist. Further studies including nonwaitlisted patients are needed. Another limitation of our study was the lack of baseline physical activity data. Physical activity levels have been shown to worsen as CKD progresses and are lowest in patients receiving dialysis.[35] Survey data have found that fatigue, reduced walking ability, and shortness of breath are the most common barriers to physical activity in patients on dialysis.[36,37] Physical activity level is also influenced by age, chronic inflammation, cardiovascular disease, protein energy wasting, obesity, and diabetes in this population.[38] Exercise training interventions have been shown to improve VO_2Peak in patients on dialysis.[39,40] Therefore, potential differences in physical activity levels between the predialysis group and the Vin1 group may influence changes in cardiovascular functional capacity. In addition, prospective studies evaluating changes in cardiovascular functional capacity serially over time following the initiation of dialysis and comparing the various forms of dialysis modalities would yield important insights.

CONCLUSIONS

The present study is the first to comprehensively describe cardiovascular functional changes and exercise ventilatory response patterns using state-of-the-art CPET technology in the transition to dialysis period. The data presented provide strong rationale for new prospective studies that will further assess cardiovascular functional changes during the incident dialysis period and across the span of dialysis vintage. In addition, the present study has unveiled ventilatory and hemodynamic indexes that could have potential prognostic utility in risk stratifying patients with advanced CKD. Cardiovascular outcome studies linking ventilatory and hemodynamic indexes during incremental exercise testing during CPET in patients with advanced CKD are therefore critically needed.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of the study population excluding those with prior kidney transplant

Characteristic*	Predialysis (PreD) N=41	Dialysis Vintage ≤12 months (Vin1) N=49	Dialysis Vintage >12 months (Vin2) N=112	*p*-value†	*p*-value‡
Age, y, mean (SD)	42 (14)	48 (17)	54 (14)	0.06	0.022
Male	23 (56.1)	29 (59.2)	77 (68.8)	0.8	0.3
Race				0.022	0.8
White	38 (92.7)	36 (73.5)	77 (68.8)	-	-
Asian	3 (7.3)	7 (14.3)	21 (18.8)	-	-
Black	0 (0.0)	6 (12.2)	14 (12.5)	-	-
BMI, $kg \cdot m^{-2}$, mean (SD)	25.1 (3.9)	26.0 (4.6)	27.3 (5.8)	0.3	0.2
SBP, mm Hg, mean (SD)	135.6 (15.6)	134.3 (25.6)	130.1 (26.4)	0.8	0.4
DBP, mm Hg, mean (SD)	82.3 (9.5)	78.6 (14.5)	74.8 (19.2)	0.1	0.2
MAP, mm Hg, mean (SD)	100.1 (9.1)	97.2 (16.8)	93.2 (19.3)	0.3	0.2
Hypertension	36 (87.8)	40 (81.6)	91 (82.7)	0.6	1.0
Anti-hypertensive treatment duration, months, median (IQR)	78.0 (24.0-180.0)	51.0 (16.0-120.0)	51.0 (16.0-120.0)	0.6	0.001
Previous Kidney Transplant	0 (0.0%)	0 (0.0)	0 (0.0)	-	-
Blood Pressure medication use					
ACEI or ARB blocler	23 (56.1)	22 (44.9)	32 (28.6)	0.3	0.044
Calcium Antagonist	26 (63.4)	26 (53.1)	45 (40.2)	0.3	0.1
ß-Blocker	13 (31.7)	18 (36.7)	40 (35.7)	0.6	0.9
Diuretic	11 (26.8)	5 (10.2)	8 (7.2)	0.05	0.5
Smoking (ever)	19 (46.3)	30 (61.2)	60 (54.5)	0.2	0.5
Diabetes	2 (4.9)	10 (20.4)	21 (18.8)	0.06	0.8
Cardiovascular disease	2 (4.9)	3 (9.7)	11 (18.3)	0.6	0.4
Dialysis Modality				-	0.07
Hemodialysis	-	41 (83.7)	105 (93.8)	-	-
Peritoneal Dialysis	-	8 (16.3)	7 (6.3)	-	-
Dialysis Vintage, months, mean (SD)	-	7.4 (4.0)	59.1 (41.7)	-	<0.001
Laboratory Values					
eGFR, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, mean (SD)	14 (3)	10 (5)	7.2 (2.7)	<.001	<.001
Troponin T, $ng \cdot L^{-1}$, median (IQR)	11.2 (8.2-16.5)	41.8 (30.3-59.7)	27.5 (17.9 - 40.5)	<.001	0.001
ntProBNP, $pg \cdot mL^{-1}$, median (IQR)	39.7 (18.8-63.9)	268.4 (138.2-571.1)	133.9 (37.4 - 268.9)	0.001	0.018
Albumin, $g \cdot dL^{-1}$, mean (SD)	4.4 (0.3)	4.3 (0.5)	4.4 (0.4)	0.028	0.2

Corrected Ca, mmol·L^{-1}, mean (SD)	2.2 (0.1)	2.2 (0.2)	2.3 (0.2)	1.0	0.001
Phosphorus, mmol·L^{-1}, mean (SD)	1.4 (0.3)	1.5 (0.4)	1.7 (0.5)	0.3	0.1
iPTH, pg·mL^{-1}, median (IQR)	15.4 (6.9-22.8)	32.7 (15.7-55.8)	20.9 (8.6 - 45.0)	0.048	0.046
CRP, mg·L^{-1}, median (IQR)	1.3 (0.5-2.9)	5.1 (2.2-8.1)	2.9 (1.6 - 8.3)	0.005	0.3
Hemoglobin, g·dL^{-1}, mean (SD)	11.9 (1.2)	11.5 (1.6)	11.5 (1.4)	0.2	1.0
HbA1c level, %, median (IQR)	5.6 (5.5-5.8)	5.4 (5.0-5.9)	5.3 (5.1 - 5.8)	0.1	0.7

Abbreviations: BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure; BP, Blood Pressure; IQR, Interquartile range; SD, Standard Deviation; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker; eGFR, Estimated Glomerular Filtration Rate; ntProBNP, N-terminal pro–B-type natriuretic peptide; Ca, calcium; iPTH, intact parathyroid hormone; CRP, C-reactive protein; HbA1c, glycated hemoglobin; IQR, Interquartile Range.

Data are presented as number (%) of patients unless otherwise indicated

*Missing values excluded. Predialysis: 4 missing Troponin T, 4 ntProBNP, 4 CRP; dialysis vintage ≤12 months: 2 missing SBP, 2 DBP, 2 MAP, 6 treatment duration, 18 cardiovascular disease, 9 eGFR, 19 Troponin T, 19 ntProBNP, 18 corrected Ca, 18 phosphorous, 1 iPTH, 19 CRP, 1 hemoglobin, 18 HbA1c. Dialysis vintage >12 months: 1 missing SBP, 1 DBP, 1 MAP, 2 hypertension, 20 treatment duration, 1 number of BP meds, 1 diuretic, 2 smoking, 42 eGFR, 60 Troponin T, 60 ntProBNP, 52 corrected Ca, 52 phosphorous, 3 iPTH, 60 CRP, 52 HbA1c.

†Comparison between predialysis and dialysis vintage ≤12 months

‡Comparison between dialysis vintage ≤12 months and dialysis vintage >12months

Table S2. Multiple linear regression analysis of VO_2Peak, VO_2 AT, LVMI, and peak workload

Variable	VO_2Peak					
	Model 1		Model 2		Model 3	
	ß (SE)	*p*-value	ß (SE)	*p*-value	ß (SE)	*p*-value
Age	-0.17 (0.02)	<0.001	-0.17 (0.02)	<0.001	-0.17 (0.02)	<0.001
Diabetes	-2.35 (0.85)	0.006	-2.37 (0.87)	0.007	-2.12 (0.89)	0.018
Group (Overall)	–	0.002	–	0.004	–	0.005
(PreD vs. Vin1)	2.67 (0.95)	0.005	2.66 (0.98)	0.007	2.86 (0.99)	0.004
(Vin2 vs. Vin1)	-0.24 (0.73)	0.7	-0.21 (0.74)	0.8	-0.01 (0.76)	1.0
Race (Overall)			–	0.9	–	0.8
(Asian vs. Caucasian)			-0.04 (0.86)	1.0	-0.45 (0.89)	0.6
(Black vs. Caucasian)			-0.33 (0.99)	0.7	-0.51 (1.03)	0.6
Diuretic Use			-0.17 (0.90)	0.9	-0.14 (0.91)	0.9
iPTH					0.00 (0.01)	0.7
Variable	VO_2AT					
	Model 1		Model 2		Model 3	
	ß (SE)	*p*-value	ß (SE)	*p*-value	ß (SE)	*p*-value
Age	-0.07 (0.01)	<0.001	-0.06 (0.01)	<0.001	-0.06 (0.01)	<0.001
Diabetes	-0.69 (0.42)	0.1	-0.76 (0.43)	0.1	-0.59 (0.44)	0.2
Group (Overall)	-	0.045	-	0.1	-	0.047
(PreD vs. Vin1)	0.75 (0.48)	0.1	0.69 (0.49)	0.2	0.88 (0.49)	0.1
(Vin2 vs. Vin1)	-0.29 (0.37)	0.4	-0.27 (0.37)	0.5	-0.23 (0.37)	0.5
Race (Overall)			-	0.9	-	0.6
(Asian vs. Caucasian)			0.12 (0.43)	0.8	-0.26 (0.44)	0.6
(Black vs. Caucasian)			-0.17 (0.49)	0.7	-0.48 (0.50)	0.3
Diuretic Use			0.22 (0.45)	0.6	0.14 (0.45)	0.8
iPTH					0.01 (0.00)	0.1
Variable	LVMI					
	Model 1		Model 2		Model 3	
	ß (SE)	*p*-value	ß (SE)	*p*-value	ß (SE)	*p*-value
Age	0.26 (0.20)	0.2	0.26 (0.19)	0.2	0.31 (0.19)	0.1
Diabetes	2.18 (8.26)	0.8	4.06 (7.66)	0.6	4.19 (7.64)	0.6

Group (Overall)	-	0.007	-	0.030	-	0.1
(PreD vs. Vin1)	-20.42 (9.07)	0.025	-16.57 (8.54)	0.1	-15.06 (8.46)	0.1
(Vin2 vs. Vin1)	4.49 (7.04)	0.5	3.68 (6.46)	0.6	0.31 (6.49)	1.0
Race (Overall)			-	<0.001	-	<0.001
(Asian vs. Caucasian)			1.72 (7.41)	0.8	-0.85 (7.54)	0.9
(Black vs. Caucasian)			54.75 (8.52)	<0.001	50.34 (8.72)	<0.001
Diuretic Use			15.72 (7.84)	0.046	14.15 (7.78)	0.1
iPTH					0.16 (0.07)	0.029
	Peak Workload					
	Model 1		**Model 2**		**Model 3**	
Variable	***ß* (SE)**	***p*-value**	***ß* (SE)**	***p*-value**	***ß* (SE)**	***p*-value**
Age	-0.81 (0.17)	<0.001	-0.84 (0.17)	<0.001	-0.85 (0.18)	<0.001
Diabetes	-16.53 (6.92)	0.018	-16.58 (7.05)	0.020	-15.58 (7.30)	0.034
Group (Overall)	-	<0.001	-	<0.001	-	0.001
(PreD vs. Vin1)	27.84 (7.78)	<0.001	27.24 (8.02)	<0.001	26.96 (8.15)	0.001
(Vin2 vs. Vin1)	0.49 (6.03)	0.9	0.88 (6.06)	0.9	1.59 (6.28)	0.8
Race (Overall)			-	0.5	-	0.5
(Asian vs. Caucasian)			-6.83 (6.95)	0.3	-6.89 (7.28)	0.3
(Black vs. Caucasian)			4.43 (8.01)	0.6	4.49 (8.43)	0.6
Diuretic Use			3.33 (7.27)	0.6	4.27 (7.51)	0.6
iPTH					-0.01 (0.07)	0.9

Abbreviations: PreD, predialysis group; Vin1, dialysis vintage ≤12 months group; Vin2, dialysis vintage >12 months group; SE, Standard Error; VO_2Peak, peak oxygen consumption; VO_2 AT, oxygen consumption at the point of anaerobic threshold; LVMI, left ventricular mass index; iPTH, intact parathyroid hormone.