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Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease

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Background. Exercise capacity is reduced in end-stage renal disease (ESRD). Exercise requires the integrated function of multiple vital organs, and low exercise capacity is an independent predictor of mortality in a number of clinical populations. We analyzed the value of exercise capacity, characterized as peak oxygen uptake (VO_2), for predicting survival in a cohort of 175 hemodialysis patients over a median follow-up of 39 months.

Methods. Survival status was determined for 175 ESRD patients who had participated in previous studies for which peak VO_2 and other clinical data had been determined. Chi-square and Kaplan-Meier survival analyses were performed, and a minimal model of factors related to mortality was developed by Cox multiple regression.

Results. There were 23 deaths during the follow-up period. Peak VO_2 (>17.5 mL/min/kg) was a powerful predictor of survival ($P = 0.009$ by Kaplan-Meier). Age (<65 years), dialysis vintage (<39 months), pulse pressure (<54 mm Hg), and absence of diagnoses of diabetes or heart failure were also associated with better survival on univariate analyses. On multivariate analysis peak VO_2 contributed significantly to the minimal explanatory model relating clinical variables to mortality (overall $\chi^2 = 25.5$, $P = 0.00001$).

Conclusion. Among these ambulatory ESRD patients, peak VO_2 was a stronger predictor of survival than many traditional prognostic variables, some of which are subject to ceiling effects. Exercise capacity may thus provide incremental prognostic information concerning healthier ESRD patients. Because peak VO_2 may be modified by exercise training, the potential of exercise as an intervention to improve survival is suggested.

Many variables have been identified as predictive of mortality among patients with end-stage renal disease (ESRD). These include laboratory [1–5] and anthropometric [6] variables reflecting nutritional state, the presence of chronic inflammation [7, 8], the burden of comorbid or complicating medical conditions [9, 10], and cardiovascular function [11–14]. Exercise capacity, characterized by maximal or peak exercise oxygen uptake (VO_2), is influenced by many of the same factors as are reflected in the previously characterized predictive variables in ESRD. As a group, patients with ESRD have marked reductions in peak VO_2, reflecting limited capacity for physical work [15, 16]. In addition to characterizing functional capability, however, peak VO_2 has been identified as an independent predictor of mortality or survival in a number of chronic diseases [17–19]. Thus, in this analysis we sought to test the hypothesis that peak VO_2 would predict survival among patients receiving chronic hemodialysis for ESRD. Outcome data were collected for hemodialysis patients whose baseline exercise capacity and clinical status were carefully assessed during their participation in two completed clinical trials, and the relationship of peak VO_2 to survival was evaluated.

Key words: oxygen uptake, VO_2, exercise, mortality, end-stage renal disease, hemodialysis.

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METHODS

Study subjects

The analysis made use of a database of clinical, demographic, and exercise variables for patients with ESRD who participated in two clinical trials of L-Carnitine (Carnitor®) supplementation in chronic hemodialysis (CHIEF studies) [20]. Key inclusion criteria for those studies included ESRD on thrice weekly hemodialysis for at least 6 months with Kt/V value of ≥1.2, clinical stability, and ability to perform incremental exercise testing to symptomatic maximum. Study participation was six months' duration, during which time peak VO_2 was determined at three-month intervals using a standardized cycle ergometry exercise testing protocol. Patients were excluded from study if they could not cooperate with testing or if an initial screening exercise test had to be terminated because of adverse reactions such as ischemic changes or arrhythmia on electrocardiogram, or pathologic blood pressure response. The present analysis is based on peak VO_2 measures determined on a baseline test performed on a separate day from the screening test.

Table 1. Patient characteristics

Variable	Units	All patients	Survivors	Non-survivors	P value[a]
N		175	152	23	
Age	*years*	46 ± 13	44 ± 12	56 ± 16	0.000074
Gender	*% male*	65	65	61	0.69
Peak VO_2	*mL/min/kg*	18.6 ± 6.5	19.2 ± 6.6	14.9 ± 4.9	0.003
Dialysis vintage	*months*	41.5 ± 15	40 ± 13	52 ± 18	0.0002
Serum albumin	*g/dL*	3.97 ± 0.28	3.99 ± 0.27	3.87 ± 0.30	0.06
Serum creatinine	*mg/dL*	10.9 ± 2.9	11.2 ± 2.8	9.6 ± 3.2	0.02
Blood pressure, resting					
Systolic	*mm Hg*	138 ± 23	136 ± 23	149 ± 22	0.01
Diastolic	*mm Hg*	82 ± 13	83 ± 13	80 ± 13	0.37
Pulse pressure	*mm Hg*	55 ± 19	53 ± 18	68 ± 20	0.0003
Hemoglobin	*g/dL*	11.2 ± 1.1	11.3 ± 1.1	10.9 ± 1.0	0.11
Race	*% non-white*	69	71	52	0.60
Diabetes	*%*	19	15	44	0.001
CHF	*%*	10	7	26	0.004
BMI	*kg/m^2*	24.5 ± 4.1	24.5 ± 4.1	24.7 ± 4.3	0.87

Abbreviations are: CHF, chronic heart failure; pulse pressure, systolic pressure minus diastolic pressure; BMI, body mass index. Values are mean ± 1 SD.
[a]For differences between survivors and non-survivors [by analysis of variance (ANOVA) for continuous variables and χ^2 for categorical variables].

Approximately three years after completion of the CHIEF studies, a questionnaire was mailed to each participating site to ascertain survival status and dates and causes of deaths as of October 1, 2001 for patients who had been enrolled in the trials. Ten of the original 12 study sites participated in the follow-up. Collection and use of these data for the present analysis was reviewed and approved by the institutional review board of the Harbor-UCLA Research and Education Institute.

Analyses

Patient characteristics as related to outcomes were summarized using descriptive statistics. Group values are reported as mean and SD unless otherwise noted. The primary outcome measure was survival during the follow-up period. Simple descriptive statistics were used to characterize survivors and non-survivors, who were compared using either analysis of variance (ANOVA) or chi-square analysis with Yate's correction where applicable. Survival status was analyzed as a function of exercise capacity, expressed as peak VO_2 in mL/kg/min, and of other selected clinical variables. Chi-square analysis was used to compare crude death rates and univariate survival analyses were performed using the log-rank test on survival curves created with the method of Kaplan-Meier. For these purposes stratification of the population for continuous variables was done using values previously utilized in survival analyses for this patient population (for age and serum albumin), or using the observed group median value (for peak VO_2, dialysis vintage, serum creatinine, blood pressures, and hemoglobin). Sensitivity analyses were also conducted for some of these variables, using different cut-off points. Survival data were not censored at the time of kidney transplantation. To control for covariance of exercise capacity with other variables recognized to have prognostic significance in this population, Cox's proportional-hazards multivariate regression was performed. All potentially relevant variables identified from Kaplan-Meier survival analyses ($P < 0.15$) were entered into the Cox model; a minimal explanatory model predicting mortality was then derived using a backward selection approach. All analyses were performed using Statistica v. 5.1 software (StatSoft, Inc., Tulsa, OK, USA).

RESULTS

Data were available for all patients from the 10 reporting study sites, representing 175 of 193 patients enrolled in the CHIEF studies. Survival status and dates of deaths were determined approximately 3.5 years after the initial baseline assessments were performed (mean follow up: 1242 ± 273 days). There were a total of 23 deaths (13%) during the follow-up period. Cardiovascular causes were reported for seven deaths (including cardiac arrest, cardiomyopathy, and cerebral ischemia), infectious causes for seven (including sepsis, abscess, and pneumonia), and malignancy for two. Causes of the remaining seven deaths were reported as unknown. Forty-four patients received kidney transplants during the follow-up period, and two of the deaths occurred among these patients.

Subject characteristics

Baseline characteristics for all patients and for the subgroups of surviving and non-surviving patients are shown in Table 1. Patients averaged 46 ± 13 years of age and had been on dialysis an average of 41 ± 15 months at the time of the baseline evaluations. Group mean values for clinical variables reflect, in part, the entry criteria for the original study which included requirements of clinical stability, adequate dialysis as reflected in a Kt/V of at least 1.2, and treatment with erythropoietin in accordance with prevailing standards of clinical practice.

Table 2. Crude mortality rates for 175 patients with ESRD stratified according to selected clinical variables

Variable	Stratification	Deaths/group (%)	total	*P* value[a]
Age *years*	<65	17/157 (11)	175	0.02
	≥65	6/18 (33)		
Peak VO_2 *mL/min/kg*	≤17.5	19/88 (22)	175	0.002
	>17.5	4/87 (5)		
Dialysis vintage *months*	≤39	6/88 (7)	175	0.02
	>39	17/87 (20)		
Serum albumin *g/dL*	<4.0	14/75 (19)	173[b]	0.15
	≥4.0	9/98 (9)		
Serum creatinine *mg/dL*	≤10.8	16/90 (18)	175	0.17
	>10.8	7/85 (8)		
Systolic blood pressure *mm Hg*	≤138	7/88 (8)	175	0.07
	>138	16/87 (18)		
Pulse pressure *mm Hg*	≤54	6/88 (7)	175	0.02
	>54	17/87 (20)		
Hemoglobin *g/dL*	≤11.3	14/86 (16)	171[b]	0.38
	>11.3	9/85 (11)		
Diagnosis of CHF	Yes	6/17 (35)	175	0.01
	No	17/158 (11)		
Diagnosis of diabetes	Yes	10/33 (30)	175	0.003
	No	13/142 (9)		

Abbreviations are: pulse pressure, systolic pressure minus diastolic pressure; CHF, chronic heart failure.
[a]By Yates' χ^2 test.
[b]Due to missing values (albumin, 2; hemoglobin, 4).

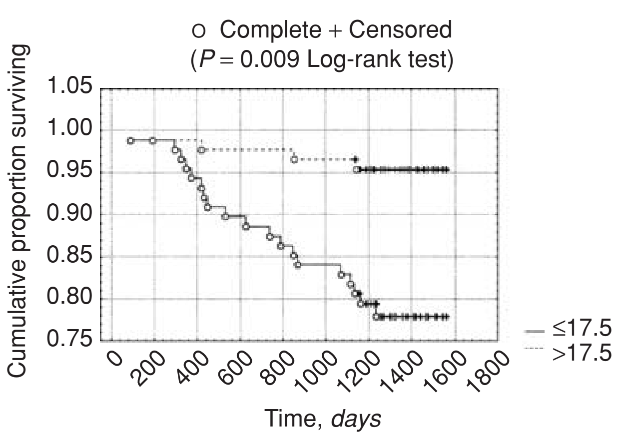

Fig. 1. Survival as a function of baseline value of peak exercise VO_2 for 175 ambulatory patients with end-stage renal disease. Patients with peak VO_2 above the median value of 17.5 mL/min/kg (interrupted line) had significantly better survival than those with lower values (solid line) ($P = 0.009$ by log-rank test).

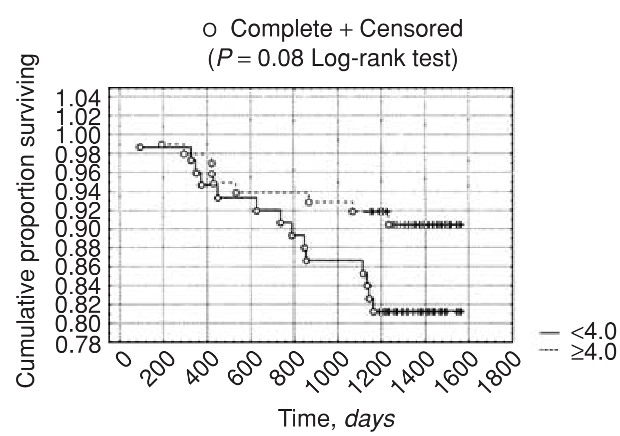

Fig. 2. Survival as a function of baseline serum albumin for 175 ambulatory patients with end-stage renal disease. Serum albumin concentration at or above the group median value of 4.0 gm/dL (interrupted line) showed a trend toward better survival than those with lower values (solid line) ($P = 0.08$ by log-rank test).

Factors influencing survival

Crude death rates for patients stratified by selected clinical variables are shown in Table 2. Patients with a peak VO_2 above the group median value of 17.5 mL/min/kg had a significantly better crude survival rate than those with lower peak VO_2 (Table 2); this finding was confirmed by univariate Kaplan-Meier analysis ($P = 0.009$) (Fig. 1). Similar results were obtained if peak VO_2 was stratified at 14 or 15 mL/min/kg ($P = 0.0016$ and 0.00064, respectively; data not shown). Patients younger than age 65, those with resting pulse pressure of less than 54, and those without a diagnosis of diabetes, or without a diagnosis of chronic heart failure, had a better crude survival than those who were older, had a higher pulse pressure, were diabetic, or suffered from chronic heart failure. There was a trend ($P = 0.15$) toward better crude survival for those whose serum albumin was at or above the group median value of 4.0 g/dL (Table 2), and this trend was confirmed on univariate Kaplan-Meier analysis ($P = 0.08$) (Fig. 2). In contrast, hemoglobin and serum creatinine were not significantly related to mortality in this analysis (Table 2), nor were race or gender (data not shown).

Multivariate analysis was somewhat limited by the relatively low number of deaths and the large number of variables available. Nonetheless, a highly significant

Table 3. Independent variables and minimal model of factors related to mortality in 175 patients with ESRD

Variable	Initial variables		Minimal model	
	Beta	*P* value	Beta	*P* value
Age *years*	0.04	0.40	0.05	0.002
Peak VO_2 *mL/min/kg*	−0.09	0.17	−0.001	0.05
Diabetes *yes*	0.06	0.90	—	—
CHF *yes*	1.12	0.04	1.04	0.03
Hb *g/dL*	−0.06	0.80	—	—
Albumin *g/dL*	−0.24	0.78	—	—
Systolic blood pressure *mm Hg*	0.00	0.99	—	—
Pulse pressure *mm Hg*	0.02	0.32	—	—
Dialysis vintage *months*	−0.01	0.84	—	—
Creatinine *mg/dL*	−0.08	0.40	—	—

Abbreviations are: pulse pressure, systolic pressure minus diastolic pressure; CHF, chronic heart failure. Initial variables were those found to be related to survival on Kaplan-Meier analysis at $P < 0.15$.

minimal model (overall $\chi^2 = 25.5$, $P = 0.00001$) was developed that included age, peak VO_2, and the diagnosis of chronic heart failure as predictors of mortality (Table 3).

DISCUSSION

In this analysis of data from 175 ambulatory hemodialysis patients, peak VO_2 was a powerful predictor of survival status over an average follow-up of approximately 3.5 years. In a multivariate minimal explanatory model, the only additional factors significantly enhancing this predictive value were age and the presence or absence of chronic heart failure.

Individual variables related to prognosis in hemodialysis populations include functions of nutrition, inflammation, cardiovascular status, and comorbid medical conditions. Serum concentrations of albumin [1], prealbumin [2], and creatinine [1] all have positive relationships to survival, consistent with their relationship to protein balance and nutritional state. There are negative associations between inflammatory markers and survival [8, 21], which may relate in part to the negative effect of inflammation on protein balance [22] as well as pathogenic processes underlying vascular disease [7]. More distal measures of cardiovascular dysfunction, including left ventricular hypertrophy [14] and pulse pressure [12], or chronic heart failure, are associated with mortality, as is the diagnoses of diabetes [10, 23]. Not surprisingly, many of these factors covary, reflecting both commonality of cause and physiologic interactions among the processes. Consistent with this, in the present analysis a number of variables including serum albumin, serum creatinine, and dialysis vintage, which were each significantly related to outcome on univariate analysis, were effectively incorporated into a smaller number of variables on mulitvariate regression.

Exercise capacity of healthy persons is intrinsically dependent on many of the same variables that predict survival in hemodialysis patients [24, 25]. Specifically, the capacity to transport oxygen is determined by cardiovascular function and hemoglobin concentration, and the capacity for utilization of oxygen is related to skeletal muscle mass and function, which are dependent on nutritional status. Both diabetes and hypertension, which may predict poor outcome in ESRD, are associated with reduced exercise capacity even in persons without renal failure [26, 27]. We have previously reported correlations between exercise capacity of hemodialysis patients and a number of these variables, including hemoglobin concentration, serum albumin, and the diagnosis of diabetes [28]. It is thus reasonable to expect that peak exercise VO_2 would represent an integrated measure of multiple important prognostic variables in ESRD, and therefore would itself be related to outcome. Apart from serving indirectly as a marker of other prognostic factors, however, peak VO_2 directly reflects the capacity to increase cardiac output in response to the physiologic stress of exercise. As such, it is likely to correspond to the capacity to survive pathologic stresses related to acute illness or injury, as well.

The patients included in this analysis represent a healthy subset of the hemodialysis population, reflected in an overall mortality rate that was far lower than that reported for United States hemodialysis patients in general [29]. By initial study inclusion criteria, the patients were judged to be clinically stable and able to perform maximal exercise testing. Non-ambulatory, frail, or unstable patients, who would be predicted to be at highest risk for mortality based on commonly used prognostic variables, are, thus, not represented. This may explain why serum albumin was a relatively weak predictor of survival in this study, despite being among the strongest reported prognostic variables in large ESRD cohorts [1]. Patients who had findings of significant exercise-induced EKG abnormalities on screening exercise tests were also excluded from the study, although a substantial proportion of the observed mortality was nevertheless attributed to cardiovascular disease. The prognostic power of peak VO_2 in this relatively healthy subset of the dialysis population is thus of particular interest, as the mortality risk of these patients may be less readily predicted by other assessments due to threshold effects [30].

Exercise capacity has been recognized as an independent predictor of survival across a broad range of values within healthy populations [31–34]. A similar relationship between exercise capacity and prognosis has been identified in certain clinical conditions, particularly cardiovascular diseases [19, 35]. This is particularly well-documented in chronic heart failure [17], and has practical application in prioritization and timing of heart transplantation. In that setting, peak VO_2 values less than 14 mL/min/kg have been used as a criteria for heart transplant eligibility [36], based on observations that higher values predicted a two-year survival as good as that of coincident new transplant recipients. In neither the heart failure population [17] nor among apparently healthy men [34] does there appear to be a ceiling above which the relationship between peak VO_2 and prognosis is lost, even after control for other commonly used clinical and demographic risk factors.

The number of deaths in the present study was low, limiting the statistical power of multivariate analyses to fully explore the relationships between peak VO_2, other clinical factors, and mortality. The highly significant relationship between exercise capacity and survival on univariate analysis, and its contribution to the multivariate model supports further investigation of this, however, particularly with respect to risk stratification of the healthiest and most functional ESRD patients.

Ultimately, the value of identifying predictors of survival or mortality lies in the identification of modifiable factors to target for intervention. It is noteworthy therefore that peak VO_2 may be increased by physical exercise training. Furthermore, it appears that training reduces mortality in the general population [37, 38] and perhaps among patients with heart failure [39]. Among patients with ESRD exercise training has been demonstrated to increase peak VO_2 [40] and functional capacity [41]. It has also recently been reported [42] that dialysis patients who identify themselves as sedentary have higher mortality than those who report being ambulatory. Whether sedentary behavior contributes causally to increased mortality in this setting, or is simply a marker of more extensive disease and poorer prognosis is not clear. Thus, it remains to be seen whether increasing peak VO_2 by exercise training might modify mortality rate in this population.

CONCLUSION

In this study peak VO_2 was found to be a highly significant predictor of survival among a stable ambulatory cohort of hemodialysis patients. This finding is consistent with other data demonstrating that nutritional status, cardiovascular factors, and exercise behavior are significant factors related to outcome in ESRD, and suggests that exercise testing may represent a useful approach to risk stratification among the most functional patients with ESRD. The potential for interventions targeting exercise function to further enhance survival in this population is deserving of further study.

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