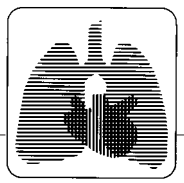

exercise and the heart

Clinical and Exercise Test Determinants of Survival After Cardiac Transplantation*

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Background: **Cardiac transplantation (CTX) is now a viable option for patients with end-stage heart failure, but there remains a paucity of available donor hearts relative to the demand for them. Establishing prognosis after CTX can help direct this resource to patients most likely to benefit, as well as to help guide therapy for CTX recipients. Clinical, exercise, and hemodynamic factors associated with survival after CTX have not been well established.**

Methods: **One hundred seventy-four randomly selected patients who underwent heart transplantation between 1983 and 1999 at Rikshospitalet University Hospital were included in the study. Data were collected as a part of routine posttransplantation management a mean of 3.5 ± 2.1 years (± SD) after CTX. Clinical, cardiopulmonary exercise testing, and hemodynamic measures were performed, including measures of peak oxygen uptake ($\dot{V}O_2$), ejection fraction, cardiac index, pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure, creatinine, and the presence of coronary artery disease. Patients were followed up for a mean of 7.1 ± 2.1 years; all-cause mortality was used as the end point for survival analysis.**

Results: **During the follow-up period, 39 patients died; the average annual mortality was 3.6%. Peak $\dot{V}O_2$ was 19.6 ± 5.6 mL/kg/min, representing 70.5 ± 6.7% of the age-predicted value. Only right atrial pressure and PCWP differed between those who survived and those who died; both were slightly higher among those who died. By Cox proportional hazard analysis, there were no age-adjusted univariate or multivariate predictors of survival among continuous variables. Exploring various cut points revealed that serum creatinine > 118 μmol/L, PCWP > 12 mm Hg, and mean pulmonary artery pressure > 25 mm Hg were significant univariate predictors of mortality. These cut points for PCWP and pulmonary artery pressure generated hazard ratios of 2.3 and 2.9, respectively.**

Conclusion: **Long-term survival after CTX was comparatively high in our cohort, with 5-year survival > 80%. Standard clinical, hemodynamic, and cardiopulmonary exercise test variables were not strong predictors of mortality in CTX patients a mean of 7 years after CTX. The association between elevated hemodynamic pressures and mortality, although weak, suggests that ventricular compliance, pulmonary vascular resistance, or both, may predict long-term survival after CTX.**

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Key words: cardiac transplantation; cardiopulmonary exercise testing; survival

Abbreviations: BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; CTX = cardiac transplantation; EF = ejection fraction; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RER = respiratory exchange ratio; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = oxygen uptake

Cardiac transplantation (CTX) is now a widely accepted therapeutic option for patients with end-stage heart failure; overall 5-year survival is currently estimated to be 65 to 75%.[1] Although many advances have occurred in transplantation medicine over the last 2 decades, factors influencing short-term and long-term survival after CTX are not well defined. Several clinical challenges persist in regard to treatment of CTX recipients that influence their long-term survival. These include accelerated coronary atherosclerosis and associated complications,[2–5] infection,[5,6] and stability of ventricular function.[3]

Table 1—*Patient Characteristics With Univariate Comparison Between Those Who Died and Those Who Survived

Variables	Total (n = 175)	Survived (n = 135)	Died (n = 39)	p Value
Age, yr	52 ± 12	51 ± 12	53 ± 11	0.30
Height, cm	177 ± 7	177 ± 7	177 ± 6	0.81
Weight, kg	80 ± 13	79 ± 13	80 ± 13	0.68
BMI	25.4 ± 3.7	25.4 ± 3.7	25.6 ± 3.6	0.75
Follow-up, yr	7.1 ± 2.1	6.7 ± 2	8.3 ± 1.7	< 0.001
Resting HR, beats/min	96 ± 16 (n = 141)	94 ± 17	100 ± 14	0.07
Maximal HR, beats/min	147 ± 22	146 ± 22	150 ± 20	0.27
Maximal systolic BP, mm Hg	191 ± 31 (n = 150)	191 ± 31	191 ± 31	0.95
Maximal diastolic BP, mm Hg	93 ± 16 (n = 149)	93 ± 17	96 ± 15	0.40
Maximal $\dot{V}O_2$, L/min	1.5 ± 0.48	1.6 ± 0.5	1.5 ± 0.4	0.29
Maximal RER	1.19 ± 0.14	1.19 ± 0.14	1.18 ± 0.12	0.72
Maximal $\dot{V}E$, L/min	65.6 ± 19.7	65.9 ± 20.1	64.8 ± 18.4	0.78
% age-predicted $\dot{V}O_2$	70.5 ± 16.7	70.8 ± 17.5	69.8 ± 13.7	0.75
Peak W	135.5 ± 43.5	137.6 ± 43.6	128.8 ± 43.6	0.27
LVEDP, mm Hg	11.6 ± 5.6 (n = 135)	11.4 ± 5.2	12.5 ± 6.7	0.33
EF, %	72.1 ± 18.9 (n = 130)	70.8 ± 20.4	76.8 ± 11.7	0.13
Creatinine, μmol/L	125 ± 39 (n = 145)	123 ± 37	134 ± 43	0.14
RAP, mm Hg	4.7 ± 3.2 (n = 157)	4.6 ± 3.1	5.3 ± 3.8	0.29
MPAP, mm Hg	17.4 ± 5.5 (n = 160)	16.9 ± 5.3	19.2 ± 5.7	0.03
a-$\dot{V}O_2$ difference	48.6 ± 12.1 (n = 159)	48.7 ± 12.3	48.1 ± 12	0.77
PCWP, mm Hg	9.2 ± 4.6 (n = 160)	8.9 ± 4.4	10.6 ± 5.2	0.05
Cardiac index, L/min	2.63 ± 0.60 (n = 160)	2.64 ± 0.61	2.59 ± 0.58	0.63
TxCAD, %	69 (n = 155)	72	62	0.09
Cardiac output, L/min	5.2 ± 1.2 (n = 160)	5.2 ± 1.2	5.1 ± 1.1	0.65
pANP, mmol/L	1,729 ± 1,195 (n = 102)	1,713 ± 1,117	1,677 ± 1,425	0.90
CYA dose, mmol/L	237 ± 70	238 ± 73	232 ± 60	0.61

*Data are presented as mean ± SD unless otherwise indicated. a-$\dot{V}O_2$ difference = arterial-venous O_2 difference; pANP = end terminal atrial natriuretic peptide; TxCAD = presence of CAD; CYA dose = cyclosporine-A dose.

The knowledge that particular clinical, hemodynamic, exercise, or neuroendocrine variables unique to CTX patients may be associated with survival is useful, in that it helps to direct therapy and optimize prognosis. In addition, further defining donor and recipient characteristics that predict outcomes after CTX helps to direct scarce donor hearts to patients who are most likely to benefit.

In recent years, the exercise test has been increasingly recognized for its value in stratifying risk in patients with cardiovascular disease.[7,8] Specifically, exercise capacity expressed as peak oxygen uptake ($\dot{V}O_2$) has become an important factor in selecting or listing patients with chronic heart failure for CTX.[9] Less is known, however, about factors associated with risk after CTX; few data are available on the association between clinical and exercise test responses and survival after CTX. Moreover, previous studies have tended to be small, and there have been few integrated approaches that have included relevant demographic, clinical, hemodynamic, and exercise data. The purposes of the present study were as follows: (1) to characterize the exercise response of patients after CTX; and (2) to address the relation between clinical, hemodynamic, and exercise test variables and survival among CTX patients evaluated over a 12-year period.

Materials and Methods

Patients

One hundred seventy-four patients who underwent heart transplantation between 1983 and 2001 at Rikshospitalet University Hospital, Oslo were included in the study. The Regional Ethics Committee approved the study, and informed consent was obtained. Data were collected as a part of routine posttransplantation management, which included maximal exercise testing and hemodynamic assessment. The indication for CTX was coronary artery disease (CAD) in 57%, idiopathic dilated cardiomyopathy in 37%, and other indications in 6%. Clinical characteristics of the patients are presented in Table 1. All patients were in clinically stable condition with no history of recent rejection or concurrent

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