



# Association Between Early Cardiac Rehabilitation and Long-term Survival in Cardiac Transplant Recipients

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## Abstract

**Objective:** To determine whether participation in early cardiac rehabilitation (CR) after heart transplant (HTx) affects long-term survival.

**Patients and Methods:** A retrospective review was conducted in 201 patients who underwent HTx at Mayo Clinic between June 1, 2000, and July 31, 2013. Patients were excluded with multiorgan transplant, no CR data, and follow-up less than 90 days after HTx. Demographic and exercise data at baseline before HTx were collected. Post-HTx exercise capacity, biopsy, CR data, and medications were collected at 1 through 5 and 10 years.

**Results:** Overall survival at 1, 5, and 10 years was 98%, 88%, and 82%, respectively; 29 patients died. Number of CR sessions attended in the first 90 days after HTx predicted survival in multivariate regression, controlling for baseline post-HTx 6-minute walk test (6MWT) results and rejection episodes (hazard ratio, 0.90; 95% CI, 0.82-0.97;  $P=.007$ ). Additional univariate predictors of survival included pre-HTx 6MWT results, weight at HTx, and body mass index and systolic blood pressure at CR enrollment. Pre-HTx 6MWT results, body mass index, and post-HTx were associated with improvement in peak oxygen consumption.

**Conclusion:** This report demonstrates, for the first time, an association between CR and long-term survival in patients after HTx. Further work should clarify the most beneficial aspects of CR.

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The use of heart transplant (HTx) has grown substantially during the past several decades and is now performed in more than 4000 patients per year internationally, with median posttransplant survival of approximately 11 years.<sup>1</sup> Improved surgical techniques and methods of management, including immunosuppressive drug regimens, infection control, and identification and management of coronary allograft vasculopathy and immunosuppressive-associated malignancies, among others, have resulted in improved survival.<sup>2</sup> Furthermore, quality of life (QoL) in HTx is improved early after transplant from pretransplant levels and compared with patients with advanced heart failure (HF).<sup>3,4</sup>

Exercise therapy and formalized cardiac rehabilitation (CR) programs are beneficial

to cardiopulmonary function in patients who have undergone HTx.<sup>5,6</sup> Four randomized trials of CR after HTx reported improvements in exercise capacity (notated as peak oxygen consumption [ $\text{VO}_2$ ]),<sup>7-9</sup> lean body mass,<sup>7,9</sup> muscle strength,<sup>7</sup> blood pressure,<sup>9</sup> workload,<sup>8,9</sup> ventilatory equivalent for carbon dioxide,<sup>8</sup> and bone mineral density<sup>10</sup> compared with control patients. A randomized trial involving exercise therapy in pediatric HTx patients also found improved 6-minute walk test (6MWT) results.<sup>11</sup>

Nonrandomized trials have reported improvements in several parameters in HTx patients who are involved in a regimented exercise program. These parameters include lean body mass,<sup>12</sup> resting heart rate,<sup>12-14</sup> respiratory exchange ratio at peak  $\text{VO}_2$ ,<sup>13</sup> work rate,<sup>13,14</sup> blood pressure,<sup>12</sup> minute



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ventilation during submaximal and maximal exercise,<sup>12</sup> and peak  $\text{VO}_2$ .<sup>13,14</sup> Notably, the use of exercise training does not increase the risk of acute rejection episodes<sup>8</sup> or significantly change the composition of circulating immune cells.<sup>15</sup> Nevertheless, CR remains underused.<sup>16-18</sup>

Despite the repeated demonstration of physiologic benefits of CR in HTx patients, few studies have focused on the medical benefits of CR, and no studies have found a long-term survival advantage. The purpose of this study was to explore whether participation in early CR could impart an improved long-term survival, independent of baseline medical debility. We believe that patients who perform a greater amount of CR have improved outcomes.

## METHODS

### Data Collection

A retrospective study was conducted in 201 of 211 consecutive patients who underwent single-organ HTx at Mayo Clinic in the modern era between June 1, 2000, and July 31, 2013. Not included in the analysis were 46 patients who had undergone multi-organ transplant at Mayo Clinic during this period. All the patients were enrolled in phase II CR. Patients were excluded from the analysis if they had died within 90 days after HTx ( $n=10$ ). All HTx patient records are kept in a database for administrative purposes. This study was approved by the Mayo Clinic Institutional Review Board.

Medical record review was used to obtain all the data. Baseline, pre-HTx demographic and clinical variables, including indication for transplant, United Network for Organ Sharing status, previous mechanical circulatory support, as well as renal function immediately before transplant, left ventricular ejection fraction, and serum creatinine level within 1 week of transplant, were obtained. Pre-HTx exercise data, including 6MWT results, cardiopulmonary exercise data, and weight, were obtained. Minimum follow-up was 1 year to allow for adequate analysis. Comprehensive follow-up occurred at Mayo Clinic; therefore, death was ascertained from the medical record.

All HTx patients are required to remain local to Mayo Clinic for the first 90 days after transplant to facilitate monitoring. Frequent contact is made with HTx patients while they stay locally to ensure compliance and address management concerns in the early post-HTx period. In addition, in the post-HTx period, patients are automatically enrolled in CR, generally within the first 2 weeks after hospital dismissal, except in cases of severe illness, and they are encouraged but not required to attend sessions. All the patients were enrolled in CR to be included in the present study.

Phase II CR progresses as follows. A baseline 6MWT is performed at enrollment, generally within 2 weeks after hospital dismissal. Patients typically progress to 30 to 45 minutes of supervised aerobic exercise and 10 to 15 minutes of strength training 3 days per week. On days not attending CR, patients are encouraged to exercise aerobically for at least 30 minutes. In addition to supervised exercise, CR sessions include counseling regarding topics such as nutrition and stress management, and patients receive social support from staff and other patients. In patients who satisfactorily complete the CR program, a cardiopulmonary exercise test is obtained at the end, generally 90 days after HTx. After the completion of CR, patients are encouraged to maintain a lifelong exercise regimen.

Number of CR sessions attended during the first 90 days after HTx was obtained through review of CR notes. Serial cardiopulmonary exercise test data were obtained as available at baseline (after transplant, after CR) and at years 1, 2, 3, 4, 5, and 10. At years 1, 5, and 10, use of antihypertensive, immunosuppressive, diuretic, corticosteroid, and statin medications was noted. Similarly, weight, body mass index (BMI [calculated as the weight in kilograms divided by the height in meters squared]), and blood pressure were obtained at these time points. Data from the first 10 endomyocardial biopsies were collected for each patient as well as from any biopsies revealing rejection (grade 2R or 3A/3B or greater).

### Data Analysis

Means between continuous variables were compared using a paired *t* test, which was

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