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Systolic Function as a Predictor of Mortality and Quality of Life in Long-term Survivors with Heart Failure

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ABSTRACT

Background: Patients with heart failure (HF) and preserved ejection fraction (EF) have been shown to have high mortality rates, comparable to those with reduced EF. Thus, long-term survivors of HF, regardless of ejection fraction, are a select group. Little is known about disease-related quality of life (QOL) and health status in these patients.

Hypothesis: Preserved EF in patients with heart failure independently predicts long-term survival, health related quality of life (QOL), or functional status.

Methods: The study followed a cohort of 413 patients consecutively hospitalized for HF between March 1996 and September 1998. In July 2005, information was collected about their mortality, health related QOL as defined by disease-specific Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, and functional decline as defined by limitations in Activities of Daily Living (ADL) scores.

Results: The primary outcomes were mortality, QOL, and functional decline. At follow-up, 8.1 years after enrollment, overall mortality was 76% (314/413). Adjusted for age, gender, renal insufficiency, diabetes mellitus, hypertension, HF, and respiratory disease, those with decreased ejection fraction (EF < 40%) had higher mortality compared with those with preserved ejection fraction (hazard ratio [HR] 1.42; confidence interval [CI] = 1.13, 1.80, p = 0.003). The KCCQ scores, including Clinical Summary Scores and Symptom Limitation Scores, as well as ADL limitations, were not significantly different in the survivors with preserved or decreased EF.

Conclusions: Heart failure patients with preserved EF have a modest survival advantage compared with those with decreased EF, but health related QOL scores and functional decline in survivors are similar regardless of systolic function.

Key words: heart failure, quality of life, mortality

Introduction

Prevalence of heart failure in patients with preserved ejection fraction (EF) is increasing. Although most studies have shown that patients with preserved EF have some survival advantage compared with those with decreased EF, others have found no significant difference in mortality between these groups. Regardless, mortality exceeds 10%–20% per year in both groups, making long-term survivors a very select group. Little is known about disease-related quality of life (QOL) and health status in these patients, particularly those with preserved ejection fraction.

Smith et al., analyzed data from 413 patients older than 50 years admitted to Yale-New Haven Hospital with clinical evidence of heart failure, who were followed for 6 months to examine mortality, readmission, and ability to perform activities of daily living (ADL). Mortality in these patients at 6 months was 13% in those with preserved EF versus 21% in those with decreased EF defined as EF < 40% (p = 0.02).

We tried to determine whether there continues to be an independent survival advantage for patients with preserved EF and whether preserved systolic function predicts long-term survival and health status. To address this question, survival in this cohort of heart failure (HF) patients was determined 8.1 years after initial hospitalization, with median follow-up of 1,168 days (3.2 years). Quality of life and functional status were measured in survivors.
Methods

Patient Population

After screening of 1,151 consecutive HF admissions at Yale-New Haven Hospital between March 1996 and September 1998, a cohort of 413 patients age 50 years and older was enrolled. Patients admitted with HF of noncardiac etiology were excluded, as were patients transferred from other hospitals, nursing homes and those with noncardiovascular terminal illness.10

Measures

Patients were interviewed during their index admission to obtain baseline clinical and demographic information and to ascertain functional status. Medical records abstraction was used to obtain information regarding medical comorbidities, cardiac history and EF measured during admission or within one year prior to admission. Preserved EF was categorized as greater than or equal to 40%.

Functional status was assessed at baseline and at six months after the index hospitalization with the Katz ADL Index, in which patients reported whether they needed help with 13 instrumental ADL in the preceding month. The ADL Index was again administered at this follow-up to all the surviving patients in this cohort who were able to participate in the survey. A proxy was required for 5 of the participants to complete the survey due to weakness or comorbidity. Of the remaining survivors, 8 were too frail or hard of hearing to participate in the survey and 5 refused. All investigations were conducted in accordance with the Declaration of Helsinki.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was also administered to all living enrollees able to participate in March 2005 during telephone interviews with a single interviewer to assess their disease-specific impairment in QOL. The KCCQ is a validated, frequently used HF-specific QOL survey.16 The KCCQ examines physical symptoms and limitations over the preceding 2 weeks, self-efficacy and knowledge, social interference, and contains an item to examine depressive symptoms.

Outcomes

Outcomes included survival days from index admission to death, health-related QOL, as defined by scores on the KCCQ, and functional status, as measured by ability to perform basic activities of daily living. Deaths were determined through a consecutive search of the National Death Index, hospital records, local and Internet directories, and next-of-kin. Patients were considered to have a functional decline in ADL performance if there was any increase in the number of limitations from baseline to the last follow-up measurement.

Statistical Analysis

Demographic and clinical characteristics were compared between patients with preserved and decreased EF using the Pearson chi-square test for categorical variables and the t-test for continuous variables.

Survival curves were constructed using multivariable Cox proportional hazards regression to examine whether EF was an independent predictor of survival adjusted for age, gender, respiratory disease, renal insufficiency, hypertension, history of HF, and diabetes mellitus. Analyses included covariates that had either been previously identified in studies of mortality or were thought to be clinically significant.1,3,17

Mean numbers of ADL limitations at baseline and at follow-up were compared by EF using t-tests to determine whether one group had significantly more limitations than another and whether there were significant differences in functional decline over time. Transplant recipients (n = 4) and those who were too frail to give meaningful survey responses were excluded from analyses of functional status and QOL analyses. Mean KCCQ scores were also compared by EF using t-test to assess for significant differences by EF group. To assess the effect of cut-off value, additional analyses were performed limiting the definition of preserved systolic function as EF ≥ 50%, with exclusion of 60 patients with EF 40%–49%. This more restrictive classification of preserved systolic function was tested as varying definitions have been used in published studies.1,3,13

Results

Approximately half of the 413 patient cohort (n = 213) had a decreased EF (< 40%) (Figure 2), and approximately half were men (n = 213). The mean age was 72 years and the majority had a history of HF (Table 1). Baseline comparisons revealed that patients with preserved systolic function were significantly more likely to be older, to be women, and to have a history of hypertension. Patients with a decreased EF were more likely to have a history of HF, myocardial infarction, coronary artery disease, and arrhythmia.

Mortality

Eight years after initial hospitalization (median of 3.2 years of follow-up), crude mortality was 75.5% for those with preserved EF and 76.5% for those with decreased EF. Crude and adjusted survival curves are shown in Figure 1(A) and (B), respectively. Those with decreased EF tended to have increased mortality compared with those with preserved EF (HR = 1.23, 95% CI = 0.98, 1.53 p = 0.07). After adjusting for age, gender, renal insufficiency, respiratory disease, hypertension, diabetes, and history of HF, the increased mortality for those with systolic dysfunction persisted (HR = 1.42, CI = 1.13, 1.80, p = 0.003).
TABLE 1: Baseline characteristics in preserved versus decreased ejection fraction

<table>
<thead>
<tr>
<th>Description</th>
<th>Preserved</th>
<th></th>
<th>Decreased</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>%</td>
<td>#</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>200</td>
<td></td>
<td>213</td>
<td></td>
<td></td>
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<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: mean (SD)</td>
<td>73</td>
<td>11</td>
<td>70</td>
<td>11</td>
<td>0.0060</td>
</tr>
<tr>
<td>Male</td>
<td>73</td>
<td>37</td>
<td>140</td>
<td>65</td>
<td>0.0000</td>
</tr>
<tr>
<td>Cardiac history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>131</td>
<td>65</td>
<td>167</td>
<td>78</td>
<td>0.0035</td>
</tr>
<tr>
<td>Hypertension</td>
<td>160</td>
<td>80</td>
<td>138</td>
<td>65</td>
<td>0.0006</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>80</td>
<td>40</td>
<td>110</td>
<td>52</td>
<td>0.0177</td>
</tr>
<tr>
<td>Pacer</td>
<td>19</td>
<td>10</td>
<td>42</td>
<td>19</td>
<td>0.0034</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>85</td>
<td>42</td>
<td>113</td>
<td>53</td>
<td>0.0319</td>
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<tr>
<td>Coronary artery bypass</td>
<td>38</td>
<td>19</td>
<td>67</td>
<td>31</td>
<td>0.0037</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>76</td>
<td>38</td>
<td>81</td>
<td>38</td>
<td>0.9953</td>
</tr>
<tr>
<td>Non-cardiac history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency (Cr &gt; 1.5)</td>
<td>74</td>
<td>37</td>
<td>71</td>
<td>33</td>
<td>0.4353</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>65</td>
<td>32</td>
<td>57</td>
<td>26</td>
<td>0.2014</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>31</td>
<td>15</td>
<td>32</td>
<td>15</td>
<td>0.8929</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>97</td>
<td>48</td>
<td>96</td>
<td>45</td>
<td>0.4851</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>54</td>
<td>27</td>
<td>51</td>
<td>24</td>
<td>0.4759</td>
</tr>
</tbody>
</table>

Functional Status and Quality of Life

Of the 77 survivors who were eligible to participate in the study, 64 (84%) were able to complete the entire survey. Of those, 33 had a decreased EF, including 4 patients who underwent transplant in the interim period since enrollment (Figure 2). There was no significant difference in the percentage of the entire cohort who were able to complete the survey between EF groups (29/213 versus 31/200, p = 0.59) or in percentage of survivors who could not participate in the survey or refused (7/36 versus 6/37, p = 0.72). Baseline characteristics were generally similar in those who could participate compared with those who could not, with the exception that a greater percentage of the excluded patients had a history of cerebrovascular accident (31% versus 7%, p = 0.01) and a history of bypass surgery (38% versus 12%, p = 0.02). Additionally, those who refused or were unable to participate in the survey had a greater number of ADL limitations (p = 0.006).

Previous report of this cohort showed that functional limitation at baseline tended to be greater for those with preserved EF and that this difference was statistically significant on 6 month follow-up (p = 0.02). However, on long-term follow-up, no significant differences in functional status, percentage of survivors that declined in ADL function or in QOL as measured by the KCCQ were apparent between EF groups (Table 2). Sensitivity analysis assuming all patients who refused or were unable to participate in the follow-up survey experienced functional decline did not reveal any differential change in long-term functional status by EF.

Discussion

This investigation confirms previous studies that HF carries a poor prognosis after hospitalization regardless of ejection fraction, with long-term mortality rates approaching 80% at 8 years. Those with preserved ejection fraction were found...
LVEF: Decreased LVEF: Preserved

Survival rate (%)

Days from enrollment

Unadjusted Survival Curve

A)

LVEF: Decreased LVEF: Preserved

Survival rate (%)

Days from enrollment

Adjusted Survival Curve

B)

LVEF: Decreased LVEF: Preserved

Figure 1: (A) Unadjusted proportional hazards model of survival by EF HR 1.23 (0.98, 1.53) \( p = 0.07 \) EF = Ejection Fraction; LVEF = Left Ventricular Ejection Fraction; HR = Hazard Ratio. (B) Adjusted proportional hazards model of survival by EF HR 1.42 (1.13, 1.80) \( p = 0.003 \) EF = Ejection Fraction; LVEF = Left Ventricular Ejection Fraction; HR = Hazard Ratio.

to have a small survival advantage, independent of gender and comorbidity, compared with those with decreased ejection fraction. However, long-term survivors in both groups demonstrated objective measurements of health-related QOL and functional status consistent with New York Heart Association Class II.

Several prior studies have found a survival advantage for those with preserved EF. More recently, Owan et al. examined mortality rates in over 4,000 patients hospitalized in Olmsted County with HF and found a slight survival advantage (HR 0.96) for those with preserved systolic function, with one year rates of 29% compared to 32% for those with decreased EF and 5 year rates of 65% and 68%. However, another recent study of almost 3,000 patients admitted to Canadian hospitals with HF showed no significant difference in survival between those with preserved and decreased EF, with mortality of 22.2% and 25.5%, respectively. Our findings are consistent with the more recent reports identifying a smaller disparity in mortality by EF than previously found. Advances in medical interventions in those with decreased EF likely contribute to this change in the epidemiology of heart failure. For instance, angiotension converting enzyme inhibitors (ACEI) have been convincingly shown to decrease mortality in patients with decreased EF. The data are less convincing in those with preserved EF. In our cohort, ACEI were prescribed in 70% of those with decreased EF compared to 34% of those with preserved EF. Any disparity in survival between those with decreased and those with preserved EF may dissipate further as two proven strategies, beta-blocker therapy and internal cardiac defibrillators (ICDs), become more prevalent. Reflective of the evidence base at the time the patients in our cohort were initially discharged (1994–1998), only 34% of those with decreased EF and 40% with preserved EF were prescribed a beta-blocker. Information on ICD implantation was not collected.

Baseline QOL in patients with HF has been shown to be related to subsequent morbidity and mortality. In a recent study by Heidenreich, patients with KCCQ scores of \( \geq 75 \) and decreased EF had significantly lower rates of mortality and HF hospitalization at 1 year than those with scores of <25. For comparison, the long-term survivors in our cohort had scores in the 60–80 range. These scores were higher than might have been expected for people carrying the burden of this illness over a long period of time. However, this may simply represent the selection of stable New York Heart Association class I/II as long-term survivors.

There are conflicting data in the literature regarding the relationship between health-related QOL and systolic
function. Indirectly, QOL has been shown to decrease with increases in New York Heart Association functional class. More directly, in a recent study, patients with a reduced EF had lower measurements of health-related QOL, as measured by the Minnesota Living with Heart Failure. However, several studies showed minimal differences in QOL scores between those with preserved and decreased, consistent with our findings.

Functional limitations have been shown to be independent predictors of mortality in patients with both preserved and decreased EF. In our cohort, functional decline and ADL limitations were similar between survivors with preserved and decreased EF. Considering the duration of time these patients have carried the burden of HF, the quality of their functional status is perhaps higher than expected. Additionally, the differences found at 6 months dissipated over time. These findings raise the possibility that our measurements of functional status and QOL are surrogate markers of another characteristic intrinsic to survivors that has not yet been defined. While the small number of survivors in this study make it difficult to generalize, the survivors with preserved EF were significantly less likely to have chronic renal insufficiency (p = 0.001) or respiratory insufficiency (p = 0.002) than those who died. The survivors with decreased EF were significantly less likely to have a history of MI (p = 0.001), cardiac bypass graft (CABG) (p = 0.03), or arrhythmia (p = 0.007) than those who died. Survivors in both groups were less likely to have functional ADL limitations at baseline (p = 0.001, 0.02).

Despite the thoroughness of characterization of this cohort and longer follow-up than previous studies, limitations in this analysis exist including the small number of surviving members of the initial cohort. Second, only information regarding systolic function was available, so it was not possible to determine if patients had diastolic dysfunction. However, clinical decisions are usually made based on EF rather than more invasive assessments. Third, the KCCQ was unavailable at cohort inception, precluding evaluation of the trajectory of health-related QOL over time. Finally, the details of the causes of death were limited.

# Table 2: Quality of life and functional status in survivors by ejection fraction

<table>
<thead>
<tr>
<th>Description</th>
<th>Total</th>
<th>LVEF</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>%/SD</td>
<td>#</td>
<td>%/SD</td>
</tr>
<tr>
<td>All</td>
<td>60</td>
<td></td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Age: mean (SD)</td>
<td>65</td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28</td>
<td>47%</td>
<td>10</td>
<td>32%</td>
</tr>
<tr>
<td>Baseline ADL limitations: mean (SD)</td>
<td>2.9</td>
<td>3</td>
<td>3.0</td>
<td>3</td>
</tr>
<tr>
<td>Follow-up ADL Limitations: mean (SD)</td>
<td>3.6</td>
<td>4</td>
<td>3.7</td>
<td>5</td>
</tr>
<tr>
<td>Functional Decline</td>
<td>23</td>
<td>38%</td>
<td>10</td>
<td>32%</td>
</tr>
<tr>
<td>Overall summary score: mean (SD)</td>
<td>77</td>
<td>23</td>
<td>76</td>
<td>25</td>
</tr>
<tr>
<td>Clinical summary score: mean (SD)</td>
<td>76</td>
<td>22</td>
<td>75</td>
<td>24</td>
</tr>
<tr>
<td>Self-efficacy score: mean (SD)</td>
<td>74</td>
<td>21</td>
<td>73</td>
<td>22</td>
</tr>
<tr>
<td>Physical limitation score: mean (SD)</td>
<td>78</td>
<td>24</td>
<td>74</td>
<td>30</td>
</tr>
<tr>
<td>Symptom stability score: mean (SD)</td>
<td>54</td>
<td>17</td>
<td>51</td>
<td>12</td>
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<tr>
<td>Quality of life score: mean (SD)</td>
<td>75</td>
<td>26</td>
<td>75</td>
<td>29</td>
</tr>
<tr>
<td>Symptom limitation score: mean (SD)</td>
<td>81</td>
<td>26</td>
<td>82</td>
<td>26</td>
</tr>
<tr>
<td>Total symptom score: mean (SD)</td>
<td>74</td>
<td>23</td>
<td>74</td>
<td>24</td>
</tr>
</tbody>
</table>

ADL = activities of daily living; LVEF = left ventricular ejection fraction; SD = standard deviation

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In summary, the high mortality of patients with HF selects a small group who survive long-term. These survivors appear to have a relatively good health-related QOL and functional status, regardless of systolic function. As the population ages and prevalence of patients with HF, particularly those with preserved systolic function increases, studies will be needed to evaluate strategies both to improve morbidity and to allow us to identify those who are likely to survive.

References