Long-term survival in patients hospitalized with congestive heart failure: relation to preserved and reduced left ventricular systolic function

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Aims The purpose of this study was to evaluate the influence of left ventricular systolic function on the survival in a large consecutive cohort of patients hospitalized with congestive heart failure and to determine how left ventricular systolic function interacts with co-morbid conditions in terms of prognosis.

Methods and results Analysis of survival data from 5491 patients admitted for new or worsening heart failure to 34 departments of cardiology or internal medicine in Denmark from 1993–1996 was carried out. A standardized echocardiogram was available for 95% of the patients, and left ventricular systolic function was estimated using wall motion index score. Follow-up time was 5–8 years. Patients with preserved systolic function were older, more frequently female, and had less evidence of ischemia than patients with systolic dysfunction. After 1 year, 24% of the patients had died. Low wall motion index was a potent independent predictor of death (risk ratio for one unit increase, 0.60 (0.56–0.64)), and was of greater prognostic significance in younger patients and patients with a history of myocardial ischemia. However, even in patients with preserved systolic function, mortality was high (1 year mortality, 19%).

Conclusion In hospitalized heart failure patients, particularly in younger patients with ischemic heart disease, mortality risk is inversely related to left ventricular systolic function.

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KEYWORDS
Prognosis; Mortality; Ejection fraction; Myocardial infarction; Diastolic dysfunction

Introduction

Among the patients with congestive heart failure (CHF), approximately 50% have normal systolic function.\textsuperscript{1,2} Most studies have indicated that the patients with normal or near-normal left ventricular ejection fraction (LVEF) have a better prognosis than those with depressed LVEF.\textsuperscript{1,3,4} However, the reported prognosis in absolute terms for these patients is subject to considerable variation, and indeed recently published studies have not demonstrated any difference in the outcome between patients with normal or depressed LVEF.\textsuperscript{2,5,6} The
reason for the discrepancy between the studies is not entirely clear, but may be related to differences in the selection of the study population. Few studies have evaluated the influence of LVEF on the long-term prognosis in patients hospitalized with CHF, and these studies were relatively small, lacked estimates of LVEF in a significant number of patients, had short or intermediate follow-up time, or they were restricted to elderly patients or patients with advanced systolic heart failure.

The aim of the present study was to investigate the influence of LVEF on long-term mortality in a large consecutive cohort of patients hospitalized with CHF, and to evaluate which clinical co-variates might influence the effect of LVEF on prognosis.

**Methods**

**Patients**

Patients were obtained from the screened population in the Danish Investigations of Arrhythmia and Mortality (DIAMOND)--CHF study. Details of the design of study have been previously described. The DIAMOND study was a multicentre, randomized, double blind, placebo controlled trial of the efficacy of the class III antiarrhythmic agent dofetilide on the mortality in patients with acute myocardial infarction (MI) or CHF. The results of the CHF arm of the study, which included 27% of the screened patients with CHF, showed no significant effect of dofetilide when compared with placebo. The study was conducted at departments of cardiology or internal medicine in 34 hospitals in Denmark. University hospitals, as well as medium and small-sized county hospitals participated in the study. In total, 5548 consecutive patients hospitalized with new or worsening CHF were screened for entry into the study between November 1993 and July 1996. These patients comprise the DIAMOND--CHF screening registry. To meet the criteria for inclusion into the DIAMOND--CHF registry, a clinical diagnosis of heart failure was required, together with at least one episode within the preceding month of shortness of breath, either on minimal exertion or at rest (New York Heart Association (NYHA) functional class III or IV), or paroxysmal nocturnal dyspnoea. Heart failure was not necessarily the primary diagnosis at admission. The decision on whether the underlying cause of the symptoms was cardiac or not was made by the investigators. Patients with acute MI within the last 7 days were screened for entry into the DIAMOND--MI arm and, therefore, heart failure patients with recent MI are not included in the DIAMOND--CHF screening registry. At screening, a clinical history, a physical examination and an ECG were obtained. Furthermore, an echocardiogram was recorded on videotape and evaluated in a central laboratory. Left ventricular systolic function was assessed by calculation of wall motion index as previously described, using a 16-segment model of the left ventricle. Wall motion index (WMI) multiplied by 0.3 gives an estimate of ejection fraction. Left ventricular systolic function and geometry were further characterized by measurements of mitral E-point ventricular septum separation (EPSS) and left ventricular end-diastolic diameter obtained from 2-D recordings (apical 2-chamber view). Creatinine clearance was calculated from serum creatinine values using the formula by Cockcroft and Gault.

**Mortality**

Survival status was obtained by means of the Danish Central Personal Registry. In Denmark, all residents are given a central person registry number and all deaths in the country are registered within 2 weeks. A computerized search of the register was performed in autumn 2002, resulting in a follow-up time ranging from 5 to 8 years. Survival status was available for 5491 patients. The remaining 57 patients were lost to follow-up due to either immigration or incorrectly recorded central personal registry number.

**Ethics**

The study was conducted in accordance with the Declaration of Helsinki II, and was approved by the Central Danish Ethics Committee.

**Statistical analysis**

Baseline variables were compared using continuity adjusted Chi-square test for discrete variables and Wilcoxon rank sum tests for continuous variables. Differences in time to death between groups were analyzed by a two-sided log–rank test. The Kaplan–Meier method was used to construct life-table plots. Relative risks (RR) and 95% confidence intervals (CI) were calculated as hazard ratios obtained from Cox proportional-hazard models. Significant predictors of mortality in the multivariate model were identified using a backward selection procedure. The assumption of log-linearity was tested and confirmed for the relationship between WMI and survival. Interaction analysis was performed using a likelihood ratio test in a multivariate Cox
model. All the calculations were made using the Statistical Analysis System software (SAS Institute, Cary, NC). A $P$ value $<0.05$ was considered significant.

Results

Patients were elderly (mean age, 71.7±10.2 years), almost exclusively Caucasian (99.9%), and most often males. Mean (±SD) duration of heart failure was 28±46 months. In one quarter of the patients, heart failure had been diagnosed within 5 days of screening. Most patients (57%) had a history of ischemic heart disease and more than one-third of the patients had previously suffered an MI. Valvular disease of hemodynamic significance was present in 4% of patients with mitral valve regurgitation, accounting for almost half of the cases (1.8%). A history of hypertension was present in 24% of the patients, but many of the hypertensive patients (58%) also had a history of ischemic heart disease. Therefore, hypertension in the absence of known ischemic heart disease was rather uncommon, and since the prevalence of valve disease was relatively low, it must be anticipated that ischemic heart disease was the underlying cause of heart failure in most subjects. In the vast majority of the patients with ischemic heart disease, chronic rather than subacute myocardial ischemia was responsible for the cardiac decompensation, since patients with acute MI within 1 week before the index hospitalization were not included in the registry, and also because only 3% had experienced an MI within the last 8 weeks.

In 63% of the cases, patients were admitted with a primary diagnosis of heart failure or due to dyspnea. Suspected acute coronary syndrome was the cause of admission in 17% and arrhythmia in 7%. Infection (2%), valve disease (0.1%) and other reasons (11%) accounted for the remaining admissions. Patients with depressed systolic function (WMI<1.6) were more often admitted with a primary diagnosis of CHF compared to the patients with normal systolic function ($P<0.0001$). In contrast, the frequency of dyspnea being the primary cause for admission was not significantly different in patients with normal and depressed systolic function.

Patients were most often in NYHA class II–III at the time of screening. Few patients (5.1%) were in NYHA class I. It must be anticipated that the functional status of these patients had improved considerably in the interval between admission and screening (up to 7 days), or that they were primarily admitted for conditions other than CHF.

Left ventricular systolic function was obtained in 95% of the screened patients, and the baseline data for the different levels of systolic function are presented in Table 1. Forty-one percent of the patients had moderate to severe systolic dysfunction (WMI≤1.2). In 37% of the patients, a normal or near-normal systolic function was found (WMI>1.6). As expected, the patients with preserved systolic function were older, more frequently female, and had less evidence of ischemic heart disease. Hypertension was less common in the group of patients with the most severe LV dysfunction. Chronic obstructive pulmonary disease was reported more frequently in the group of patients with WMI>1.6, which may reflect either that co-existing pulmonary disease is particularly common in patients with primarily diastolic dysfunction, or that a number of patients in this group, primarily suffering from pulmonary disease, were misclassified as having CHF. Severe renal dysfunction with an estimated creatinine clearance less than 20 ml/min was only found in 2.6% of the patients and there was no clear relationship with the degree of systolic dysfunction. Data presented in Table 1 further shows that in terms of mean values, a good concordance between mitral EPSS and WMI existed. As expected, an inverse relationship between WMI and left ventricular end-diastolic dimension was found.

On admission, patients were mostly treated with diuretics and to a lesser extent with ACE inhibitors and digoxin. The proportion of the patients being treated with diuretics at discharge was somewhat higher than at admission (85 vs. 73%), as was the proportion of patients receiving ACE inhibitors and digoxin (51 vs. 27% and 52 vs. 33%, respectively). A clear inverse correlation between left ventricular systolic function and utilization of ACE inhibitors at discharge existed (Table 1). Among the patients with moderate to severe systolic dysfunction (WMI≤1.2), 77% of the discharged patients were on ACE-inhibitor treatment. Few patients (13%) were treated with beta-blockers.

Mortality

During the follow-up period 3955 (72%) patients died and the crude 1-year mortality was 24%. Left ventricular systolic function was a potent predictor of death (Fig. 1). To investigate which clinical parameters and laboratory values were independent predictors of early death, a multivariate analysis was performed including all available baseline data mentioned in Table 1, except EPSS, because it essentially denotes the same as WMI. Also, medications were not included in the analysis, since
patients were not randomized to this treatment, which, therefore, could be a source of bias. In the multivariate analysis, decreasing left ventricular systolic function, male gender, increasing age, diabetes, the presence of significant valve disease, decreasing renal function, history of COPD and duration of heart failure emerged to have independent, negative influence on survival of the patients with CHF, after admission to hospital (Table 2). A RR of 0.60 for one unit increase in WMI can be interpreted as an approximately 40% increase in risk of death in patients with a LVEF of 0.30 (WMI/1) compared to the patients with a normal LVEF of 0.60 (WMI/2).

WMI interacted significantly with age (P<0.0001), meaning that WMI was of less prognostic importance in patients aged 80 and over (Fig. 2). In these patients, however, low WMI, was still a significant risk factor for early death (RR for one unit increase in WMI is 0.80 (0.69–0.92)). Furthermore, WMI interacted with a history of previous MI and history of ischemic heart disease (P<0.0001 and P<0.05, respectively). The effect of a history of ischemic heart disease on the prognostic importance of WMI is shown in Fig. 2. The results for previous MI are similar, RR for one unit increase in WMI in patients with previous MI history being 0.49 (0.43–0.56) vs. 0.65 (0.60–0.72) in patients without MI. Also, there was a significant interaction between the presence of atrial fibrillation and WMI (P<0.001). However, the influence of atrial fibrillation on WMI was modest: RR for one unit increase in WMI in patients with atrial fibrillation was 0.68 (0.59–0.78) vs. 0.57 (0.52–0.62) in patients without such history of atrial fibrillation.

**Discussion**

The population of the present study was elderly with a minor predominance of men, which is in accordance with the most epidemiological heart failure studies. The local investigators did not specifically address the underlying cause of heart failure, but presumably ischemic heart disease was responsible in the majority of cases. The high prevalence of known ischemic heart disease and previous MI, together with a rather low prevalence of isolated hypertension and valvular disease, leaves ischemia as the probable major cause. Moreover, it is likely that the group of patients

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**Table 1** Baseline data according to left ventricular systolic function

<table>
<thead>
<tr>
<th>WMI</th>
<th>&lt;0.8 (n=695)</th>
<th>0.8–1.2 (n=1452)</th>
<th>1.3–1.6 (n=875)</th>
<th>&gt;1.6 (n=2218)</th>
<th>All (n=5491)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.4±11.1</td>
<td>71.0±10.6</td>
<td>72.6±9.7</td>
<td>72.9±9.5</td>
<td>71.7±10.2</td>
</tr>
<tr>
<td>Male gender</td>
<td>524 (75%)</td>
<td>984 (68%)</td>
<td>512 (59%)</td>
<td>1125 (51%)</td>
<td>3302 (60%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8±4.4</td>
<td>25.6±4.6</td>
<td>25.5±4.3</td>
<td>26.4±5.0</td>
<td>25.9±4.8</td>
</tr>
<tr>
<td>Duration of CHF</td>
<td>36±48</td>
<td>29±45</td>
<td>27±49</td>
<td>26±45*</td>
<td>28.4±4.6</td>
</tr>
<tr>
<td>History of IHD</td>
<td>444 (64%)</td>
<td>902 (62%)</td>
<td>553 (63%)</td>
<td>1078 (49%)</td>
<td>3119 (57%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>323 (46%)</td>
<td>686 (47%)</td>
<td>376 (43%)</td>
<td>547 (25%)</td>
<td>2025 (37%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>123 (18%)</td>
<td>362 (25%)</td>
<td>220 (25%)</td>
<td>555 (25%)</td>
<td>1333 (24%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>116 (17%)</td>
<td>290 (20%)</td>
<td>158 (18%)</td>
<td>295 (13%)</td>
<td>900 (16%)</td>
</tr>
<tr>
<td>Valve disease</td>
<td>39 (6%)</td>
<td>51 (4%)</td>
<td>27 (3%)</td>
<td>86 (4%)**</td>
<td>208 (4%)</td>
</tr>
<tr>
<td>AF</td>
<td>148 (21%)</td>
<td>342 (24%)</td>
<td>210 (24%)</td>
<td>580 (26%)</td>
<td>1337 (24%)</td>
</tr>
<tr>
<td>VT/VF</td>
<td>21 (3%)</td>
<td>38 (3%)</td>
<td>18 (2%)</td>
<td>16 (1%)**</td>
<td>98 (2%)</td>
</tr>
<tr>
<td>COPD</td>
<td>135 (19%)</td>
<td>297 (20%)</td>
<td>157 (17%)</td>
<td>577 (26%)*</td>
<td>1226 (22%)</td>
</tr>
<tr>
<td>NYHA III–IV</td>
<td>428 (63%)</td>
<td>898 (62%)</td>
<td>557 (64%)</td>
<td>1370 (62%)</td>
<td>3444 (63%)</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>59±7.5</td>
<td>53±7.3</td>
<td>46±7.5</td>
<td>41.2±6.8*</td>
<td>48.0±10.4</td>
</tr>
<tr>
<td>EPSS (mm)</td>
<td>22.8±6.7</td>
<td>16.8±6.7</td>
<td>9.9±6.9</td>
<td>3.4±4.9*</td>
<td>11.2±9.5</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min) a&lt;20</td>
<td>10 (1%)</td>
<td>44 (3%)</td>
<td>27 (3%)</td>
<td>46 (2%)</td>
<td>135 (3%)</td>
</tr>
<tr>
<td>21–40</td>
<td>200 (30%)</td>
<td>375 (27%)</td>
<td>207 (26%)</td>
<td>487 (24%)</td>
<td>1315 (26%)</td>
</tr>
<tr>
<td>41–60</td>
<td>220 (33%)</td>
<td>488 (35%)</td>
<td>293 (36%)</td>
<td>691 (34%)</td>
<td>1764 (34%)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>240 (36%)</td>
<td>482 (35%)</td>
<td>282 (35%)</td>
<td>811 (40%)**</td>
<td>1915 (37%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>482 (69%)</td>
<td>890 (61%)</td>
<td>553 (52%)</td>
<td>939 (42%)</td>
<td>2879 (52%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>650 (94%)</td>
<td>1337 (92%)</td>
<td>738 (84%)</td>
<td>1739 (78%)*</td>
<td>4675 (85%)</td>
</tr>
<tr>
<td>ACEI</td>
<td>562 (81%)</td>
<td>1083 (75%)</td>
<td>469 (54%)</td>
<td>568 (26%)*</td>
<td>2792 (51%)</td>
</tr>
</tbody>
</table>

Number of patients (%) or mean±SD
IHD=ischemic heart disease; VT/VF=ventricular tachycardia/ventricular fibrillation; AF=atrial fibillation/flutter; BMI=body mass index; COPD=chronic obstructive pulmonary disease; EPSS=mitral E-point ventricular septum separation; LVEDD=left ventricular end-diastolic dimension; ACEI=angiotensin converting enzyme inhibitor.

Drug treatment was recorded at discharge.

*P<0.001; **P<0.05.

aIncludes all patients irrespective of knowledge of WMI (missing in 251).
bCreatinine clearance missing in 362 patients.
without known ischemic heart disease contained a considerable number of subjects with significant, but undiagnosed coronary artery disease.\textsuperscript{25}

Ischemic heart disease being the most common underlying disorder is in accordance with most of the earlier large-scale analyses\textsuperscript{26,27} except the Framingham study in which hypertension was the most important single cause.\textsuperscript{28}

Taking into consideration the fact that the study population was hospitalized and of advanced age, it is not surprising that comorbidities, such as diabetes, chronic obstructive pulmonary disease or renal dysfunction were frequently present along with CHF. Since the heart failure diagnosis in this study was purely based on clinical judgement, it is possible that some patients primarily suffering from diseases other than left ventricular dysfunction were classified as having CHF. This may be particularly true for patients with intact or near-normal systolic function, who were reported to have chronic obstructive pulmonary disease (see Table 1). It should be emphasized, however, that 74\% of the patients with WMI>1.6 did not have pulmonary disease, and the frequency of severe renal dysfunction was low. There was no difference in functional status (NYHA class) between the patients with normal and depressed systolic function, and it must be anticipated that diastolic dysfunction of the left ventricle was responsible for, or contributed to, the heart failure symptoms in a significant number of subjects in this group of patients.

The pharmacological treatment pattern on admission was characterized by infrequent utilization of ACE inhibitors (26\%). This presumably reflects that several patients (~25\%) were admitted with newly diagnosed CHF, along with the rather large proportion of patients, who had normal or only slightly depressed left ventricular systolic function. The fact that 77\% of the patients with WMI≤1.2 were discharged on ACE-inhibitor therapy is in accordance with the results of two
contemporary epidemiological studies, which included patients hospitalized with chronic heart failure. It must be anticipated that the 26% of the patients with a WMI>1.6 who received an ACE inhibitor were treated with this class of drugs for arterial hypertension. Few patients were treated with beta-blockers despite a high prevalence of ischemic heart disease and/or hypertension. This result is probably due to the fact that screening took place prior to the emergence of solid evidence for a beneficial effect of beta blockade in heart failure patients.

The present study confirms that patients hospitalized with CHF carry a dismal prognosis. The 1-year mortality rate of 24% is substantially higher than the ~10% mortality rate reported for heart failure patients in most randomized clinical trials, underscoring the difference between consecutive series of patients and patients selected for drug trials. In contrast, the figure is well in accordance with the previously published consecutive series of unselected patients hospitalized with CHF, of which most have reported a 1-year mortality rate of approximately 25%, although lower and higher values have been found as well.

In the current study, left ventricular systolic function was a potent predictor of mortality. This is in accordance with the most of the previous studies, although several recent studies have reported no effect of baseline LVEF on mortality. The reason for the differences in the outcomes of the numerous analyses is not clear. The controversy of LVEF and prognosis in CHF was recently reviewed by Senni, who concluded that the evidence against a different prognosis in systolic and non-systolic heart failure was growing, and that the studies showing an inverse relationship between mortality and LVEF were often biased by exclusion of the older patients. Age-dependent bias is not present in the current study, where the mean age is comparable to epidemiological heart failure studies in general. An alternative explanation for the discrepant results might be that information about ejection fraction is unavailable in a substantial fraction of the patients in the majority of the studies in which no difference in mortality between systolic and non-systolic heart failure was found. Other studies with a similar outcome were potentially biased by the fact that patients were selected on the basis of availability of LVEF. Generally, patients lacking an estimate of LVEF carry a worse prognosis than patients in whom the information is available. One cannot safely assume that the effect of mortality of LVEF in patients without an estimate of systolic function is identical to that in patients with a known LVEF. Therefore, caution should be exerted when drawing conclusions on the effect of LVEF in mortality if information about systolic function is missing in a considerable fraction of the study population. One strength of the current analysis is the availability of LVEF measurements in nearly all patients. Therefore, we feel that the present work adds important information to the debate by showing that in a consecutive population, in which information on LVEF is available in 95% of the patients, LVEF is an important, independent predictor of mortality.

Nevertheless, it should be underlined that 1-year mortality in the group of patients with near-normal or normal systolic function (WMI>1.6) was considerable (19%). Clearly, more information about this group of patients is needed, and the results of clinical trials to improve their outcome are awaited with the greatest interest.

In the present study, an important interaction between coronary heart disease, expressed either by a history of ischemia or by a history of MI, and LVEF was found. To our knowledge, this interaction has not been previously described. This may relate to the fact that very few studies have investigated interactions between LVEF and co-morbid factors in CHF, probably due to the need for very large sample sizes. The physiological background for the interaction is not entirely clear, but one may speculate that patients with a history of ischemia are at high risk for a new ischemic event, and that patients with poor contractile reserve may not tolerate ischemia or infarction as well, as those with preserved LVEF. A possible reason for the observed interaction between age and WMI is that the older patients are more likely to die from causes not directly related to heart failure, meaning that WMI looses some of its prognostic power in this group. Since, unfortunately we do not have information on the cause of death, we are not able to test this hypothesis in the current study.

In conclusion, this analysis of a large consecutive cohort of contemporary CHF patients demonstrates that hospitalization with CHF is associated with a worse prognosis if the heart failure symptoms are accompanied by a low ejection fraction. It is further demonstrated that the prognostic impact of systolic function, to some extent, depends on the presence or absence of other risk factors, particularly age and ischemia. Although a low ejection fraction clearly predicts a worse prognosis, mortality remains high in patients with preserved systolic function.
Acknowledgement
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