Six-Minute Walk Test and Cardiopulmonary Exercise Testing in Patients With Chronic Heart Failure
A Comparative Analysis on Clinical and Prognostic Insights

Marco Guazzi, MD, PhD, FACC; Kenneth Dickstein, MD, PhD; Marco Vicenzi, MD; Ross Arena, PhD, FAHA

Background—The six-minute walk test (6MWT) and cardiopulmonary exercise testing (CPET) are the 2 testing modalities most broadly used for assessing functional limitation in patients with heart failure (HF). A comprehensive comparison on clinical and prognostic validity of the 2 techniques has not been performed and is the aim of the present investigation.

Methods and Results—Two hundred fifty-three patients diagnosed with systolic (n=211) or diastolic (n=42) HF (age: 61.9±10.1 years; New York Heart Association Class: 2.2±0.78) underwent a 6MWT and a symptom-limited CPET evaluation and were prospectively followed up. During the 4-year tracking period, there were 43 cardiac-related deaths with an annual cardiac mortality rate of 8.7%. The 6MWT distance correlated with CPET-derived variables (ie, peak VO₂, VO₂ at anaerobic threshold, and VE/VCO₂ slope) and was significantly reduced in proportion with lower peak VO₂ and higher VE/VCO₂ slope classes and presence of an exercise oscillatory breathing (EOB) pattern (P<0.01). However, no significant differences were observed in distance covered between survivors and nonsurvivors (353.2±95.8 m versus 338.5±76.4 m; P=NS). At univariate and multivariate Cox proportional analyses, the association of the 6MWT distance with survival was not significant either as a continuous or dichotomized variable (≤300 m). Conversely, CPET-derived variables emerged as prognostic with the strongest association found for EOB (systolic HF) and VE/VCO₂ slope (entire population with HF and patients with a 6MWT≤300 m).

Conclusions—The 6MWT is confirmed to be a simple and reliable first-line test for quantification of exercise intolerance in patients with HF. However, there is no supportive evidence for its use as a prognostic marker in alternative to or in conjunction with CPET-derived variables. (Circ Heart Fail. 2009;2:549-555.)

Key Words: exercise ▪ heart failure ▪ prognosis ▪ ventilation

Exercise intolerance is a cardinal feature of heart failure (HF) that carries important prognostic information. Its precise quantification is of value for studying pathogenetic mechanisms involved in functional limitation and for objectively staging the clinical severity of HF. Basically, 2 methods for defining the extent of exercise limitation, the 6-minute walk test (6MWT) and the cardiopulmonary exercise testing (CPET), are currently used in daily clinical practice. The 2 testing modalities are consistently different. The 6MWT is a measure of distance, which is considered submaximal and perhaps more closely approximates the capacity to perform activities of daily living. Its clinical appeal also lies in the fact that it can be performed by almost all patients without the need of sophisticated equipment. Nonetheless, it does not allow for a thorough investigation into the pathogenetic mechanisms involved in dyspnea and fatigue sensation. The CPET requires a maximal effort and provides a direct measure of oxygen consumption (VO₂) along with a series of measured and derived respiratory variables with a robust body of evidence supporting its prognostic ability. In addition, its interpretative and integrated analysis is valuable in the definition of pathophysiological correlates and mechanistic insights that lead to exercise limitation.

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With these established differences both tests are still commonly used for measuring functional limitation, assessing the response to different interventions, and for stratifying morbidity and mortality risk in populations with HF.

A comprehensive head-to-head clinical and prognostic comparison for patients with HF has not been systematically performed before and is, thus, the primary aim of the present investigation.

Methods
Study Design and Population
This is a prospective study consisting of patients with HF referred to the cardiopulmonary exercise laboratory at San Paolo Hospital, Milan. Two hundred fifty-three consecutive subjects diagnosed with HF who underwent a symptom-limited CPET between June 1999 and December 2008 were included. Subjects with significant obstructive lung disease, evidenced by a forced expiratory volume in 1
CPET Procedure and Data Collection
Symptom-limited CPET was performed on a bicycle ergometer after written informed consent had been obtained from all patients. Individualized ramp protocols were designed to obtain a test duration between 8 and 10 minutes. Ventilatory expired gas analysis was performed using a SensorMedics metabolic cart (Vmax, SensorMedics, Yorba Linda, Calif). The metabolic cart was calibrated according to the manufacturer’s specifications before each test.

Standard 12-lead electrocardiograms were obtained at rest, each minute during exercise, and for at least 5 minutes during the recovery phase; blood pressure was measured using a standard cuff sphygmomanometer. Minute ventilation (Ve, BTPS), oxygen uptake (VO2, STPD), carbon dioxide output (VCO2, STPD), and other cardiopulmonary variables were acquired breath by breath, averaged over 30 seconds, and printed using rolling averages every 10 seconds. The V-slope method was used to measure the anaerobic threshold. Ten-second averaged ventilation (Ve) and carbon dioxide (VCO2) data, from the initiation to peak exercise, were input into spreadsheet software (Microsoft Excel, Microsoft Corp, Bellevue, Wash) to analyze the CPET-based ventilatory classification8 and Weber classification systems.23 Tukey’s honestly significant difference was used to determine which ventilatory class (VC) groups were significantly different. Pearson product moment correlation was used to assess the relationships between echocardiography with tissue Doppler imaging and both CPET variables and 6MWT distance. Pearson product moment correlation and linear regression analysis were also used to assess the relationship between peak VO2 and 6MWT distance and the latter variables ability to predict the former. Univariate and multivariate Cox regression analyses assessed the ability of CPET variables and 6MWT distance. Pearson product moment correlation and linear regression analysis were also used to determine the presence or absence of EOB during CPET. One-way analysis of variance assessed the difference in 6MWT distance according to the CPET-based ventilatory classification8 and Weber classification systems.

Follow-Up on Survival
No patients were lost to follow-up. The mean follow-up duration was 20.4 ± 16.6 months. There were 43 cardiac-related deaths during the 4-year tracking period with an annual cardiac mortality rate of 8.7%. Two of the subjects underwent heart transplantation during the tracking period and were treated as censored cases. None of the subjects included in this study suffered a noncardiac-related death. The mortality rate in patients diagnosed with systolic (17.1%, 36 of 211) and diastolic HF (16.7%, 7 of 42) was the same.

Baseline Characteristics
Table 1 reports demographic, clinical, and echocardiographic characteristics for the overall group as well as differences between survivors and nonsurvivors. Non-survivors were slightly but significantly older than survivors and had a higher NYHA functional classes, LV end-systolic volume, LV mass, E/A, and E/E' ratios. With respect to therapy distribution, patients with diastolic HF were receiving diuretic, inotropic therapy as well as cardiac resynchronization therapy and LV assist devices in a lower rate. The distribution of patients receiving cardiac resynchronization therapy was similar in survivors and nonsurvivors, whereas LV assist device distribution was higher in nonsurvivors.

As reported in Table 2, systolic and diastolic HF presented for the most part with similar baseline characteristics, although patients with diastolic HF presented with lower velocities. The ratio of early transmitral flow velocity to annular mitral velocity of the lateral LV wall (E/E') was taken as an estimate of LV filling pressure.
NYHA functional classes and smaller LV end-systolic volume. Patients with diastolic HF were receiving diuretic, inotropic therapy as well as cardiac resynchronization therapy and LV-assist devices in a lower rate.

**CPET Data**
Average peak VO$_2$ was 15 mL·kg$^{-1}$·min$^{-1}$ with a peak respiratory exchange ratio of 1.05, suggesting that the majority of subjects exercised close to their maximal capacity. Nonsurvivors compared with survivors had a significantly lower peak VO$_2$, a higher VE/VCO$_2$ slope, and presented with EOB more frequently (Table 1). No complications were recorded as a result of CPET, and tests were terminated because of dyspnea (63%) or fatigue (37%).

**6MWT**
The mean distance covered during the 6MWT was 350.7±92.8 m. The average distance covered was equivalent for subjects with systolic and diastolic HF (350.3±88.7 versus 352.5±112.7 m, respectively; $P=NS$; Table 2). None of the tests was terminated prematurely. Eight patients required a rest stop, and 25% complained of symptoms (fatigue and dyspnea) during the test. Day-by-day 6MWT reproducibility was tested in 80 patients with a correlation coefficient of 0.78. The comparison of the average 6MWT distance in survivors versus nonsurvivors showed that the distance walked was slightly lower in nonsurvivors, but statistical significance was not reached. No differences were observed between the groups for reported symptoms or rest stops during the 6MWT. Figure 1 shows the average 6MWT distance covered according to the peak VO$_2$ Weber’s subgroups (A), the ventilatory classification system (B), and the NYHA (average)* classification system (C). A significant difference was found among all classes ($P<0.01$), with the exception of VC-I versus VC-IV with a significant difference being observed among all groups ($P<0.01$) with the exception of VC-I versus VC-II. Finally, patients with EOB exhibited a significantly lower 6MWT distance versus no EOB (315.5±86.8 m versus 379.5±87.8 m; $P<0.01$).
Study of Correlations

No correlation was found between 6MWT distance, LVEF, and E/A ratio. There was a weak but significant correlation between distance walked and LVESV and E/E* ratio (Table 3). A weak but significant correlation was found between peak VO2 and E/E* ratio, whereas the VE/VCO2 slope correlated with LVEF and E/E* ratio (Table 3).

A strong correlation was noted between peak VO2 and VO2 at anaerobic threshold versus 6MWT distance, and a weaker but a statistical significant correlation was also observed between the Ve/VCO2 slope and 6MWT distance (Figure 2).

Cox Regression Univariate and Multivariate Analyses

Cox regression analyses performed for systolic HF documented EOB as the strongest predictor ($\chi^2$, 18.4; $P<0.001$) with Ve/VCO2 slope adding value (residual $\chi^2$, 4.0; $P<0.05$), whereas peak VO2 and 6MWT distance were not retained into the model (residual $\chi^2$, <2.0; $P>0.10$). When the analysis was performed including the entire population with HF, Ve/VCO2 slope emerged as the strongest predictor ($\chi^2$, 25.0, $P<0.001$) with EOB adding value (residual $\chi^2$, 12.6; $P<0.001$). Peak VO2 and 6MWT were not retained (residual $\chi^2$, <1.0, $P>0.40$; Table 4).

Table 3. Correlation Coefficients Between 6MWT Distance and CPET Variables Versus Echocardiographic Data

<table>
<thead>
<tr>
<th></th>
<th>Peak Vo2</th>
<th>Ve/VCO2 Slope</th>
<th>6MWT Distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>0.12</td>
<td>-0.22*</td>
<td>0.06</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>-0.17†</td>
<td>0.10</td>
<td>-0.13†</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>-0.07</td>
<td>0.04</td>
<td>-0.02</td>
</tr>
<tr>
<td>E/E* ratio</td>
<td>-0.21*</td>
<td>0.30*</td>
<td>-0.15†</td>
</tr>
</tbody>
</table>

*P<0.01.
†P<0.05.
Table 4. Cox Regression Analysis

<table>
<thead>
<tr>
<th></th>
<th>Systolic HF Only (n=211, 36 Events)</th>
<th>Entire Group (n=253, 43 Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>V̇e/V̇co₂ slope*</td>
<td>1.06 (1.03 to 1.09)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>EOB†‡</td>
<td>4.55 (2.13 to 9.70)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Peak V̇o₂, mL·kg⁻¹·min⁻¹</td>
<td>0.926 (0.858 to 1.003)</td>
<td>0.06</td>
</tr>
<tr>
<td>6MWT distance, m</td>
<td>0.999 (0.995 to 1.003)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*Both V̇e/V̇co₂ slope and EOB were retained in multivariate Cox regression analysis (P<0.05).
†Statistically significant.
‡Dichotomous variable.

Discussion

In this study, we prospectively investigated the 6MWT and CPET-derived variables in the clinical and prognostic assessment of patients with stable chronic HF of both systolic and diastolic origin. Although previous reports have focussed on whether 6MWT may be a reliable substitute of peak V̇o₂ as the only reference CPET variable,13,24–27 the present investigation extends the analysis by including exercise abnormalities in ventilation efficiency (ie, V̇e/V̇co₂ slope) and patterns suggestive of ventilatory control instability (EOB) that, in recent years, have consistently emerged as the most relevant exercise indicators of HF clinical status and outcome.6–9

Major findings are that 6MWT is of proven validity for defining the extent of exercise limitation and physical disability, which correlates with peak V̇o₂ and the V̇e/V̇co₂ slope, both established prognostic indicators. Nonetheless, these findings indicate that 6MWT does not portend any prognostic information when compared with CPET-derived parameters. A number of further considerations require attention.

6MWT Versus CPET: Clinical Information on Functional Limitation

In patients with HF, the 6MWT has become widely applied to screen exercise impairment and to assess the responses to various treatment interventions, especially pharmacological therapies or devices.12,15 A series of advantages of this functional testing approach have been repeatedly advocated, such as simplicity, feasibility, and negligible cost. Furthermore, there is the premise that the 6MWT has a high applicability to everyday activities of daily living even though gas exchange analysis has been performed with combined portable systems, most patients exercised on a predominantly anaerobic metabolism, suggesting that their energy expenditure was close to or even maximal.28,29 This may well explain why in the majority of previous studies and in the present one, peak V̇o₂ and 6MWT distance linearly correlate.13,24–27 The possibility that most patients may exercise on primarily anaerobic demand is further reinforced by the observed correlation with V̇o₂ at anaerobic threshold and with the V̇e/V̇co₂ slope. Notably, an excessive ventilation for a given CO₂ production rate is the result of increased peripheral stimuli because of early acidosis and increased concentration of anaerobic metabolites (ie, lactates and H⁺) as well as of an increased chemoreflex activation because of an altered Paco₂ set point.30,31 When 6MWT distance was assessed according to both Weber and VC classes, averaged walk distance reduced according to class severity. However, no distance differences occurred between survivors and nonsurvivors. In agreement with established evidences, no correlation was found between LVEF and both 6MWT distance and CPET-derived variables. On the other hand, a correlation was found between the examined exercise measures with reliable estimates of LV filling pressures such as E/E’ ratio.

These observations altogether suggest that the 6MWT is a valid exercise testing modality for objectively assessing the degree of clinical status and exertional limitation, and, to this specific end, it may represent a more immediate and advantageous application than CPET.

6MWT Versus CPET: Prognostic Insights

A point that has received considerable attention in the past but that remains uncertain due to conflicting observations is whether and in which type of population with HF the 6MWT affords prognostic insights. This is a critical area of investigation, given the reliance placed on the prognostic information gained from exercise testing in patients with HF.

Initial observations obtained in a subgroup of patients studied in the Studies of Left Ventricular Dysfunction (SOLVD) trials documented that walked distance is an independent prognostic predictor of long-term mortality.32,33 However, findings were obtained in patients with HF who were not receiving β-blocker as standard therapy. Later studies have actually provided opposite results. Ingle et al34 reported a limited
6MWT prognostic utility in patients with mild LV dysfunction, whereas it remained a mortality predictor in patients with severe heart disease. Landmark observations by Lucas et al. demonstrated that 6MWT distance was useless for identification of patients in need of heart transplantation. Furthermore, the test showed no prognostic value in multivariate analysis that included important prognostic markers other than peak VO₂, such as LV volumes, pulmonary capillary wedge pressure, and serum sodium.

In a population of 315 patients with chronic heart failure and an average NYHA functional class and peak VO₂ comparable with our population, Opasich et al. demonstrated that the 6MWT was not an independent predictor of survival. Interestingly, prediction was not significant even when using a ≤300-m distance cutoff, a limit emerged as discriminatory in most investigations.

In our study, the 6MWT was not prognostically viable, supporting the findings of Opasich et al. When 6MWT distance was entered into a univariate and multivariate Cox model with peak VO₂, V̇E/V̇CO₂ slope, and EOB, it lost any significant association with survival. Again, the results were consistent when using the dichotomous cutoff of ≤300-m distance. Conversely, CPET-derived ventilatory variables emerged as prognosticator, with EOB (systolic HF) and V̇E/V̇CO₂ slope (entire population with HF) showing the highest prognostic power. Thus, an accurate outcome definition may be provided only by performing a maximal effort with ventilatory gas exchange analysis.

**Study Limitations**

The population of patients with advanced HF was not represented. As observed in studies including severe HF, the predictive power of the 6MWT would likely portend additional clinical insights and some degree of prognostic value in this subset of patients. Thus, our findings do not apply to patients with advanced HF.

Remarkably, the use and applicability of 6MWT in the clinical management of patients with HF have been primarily investigated in population diagnosed with systolic HF, and previous experiences in diastolic HF are, without doubt, scarce. However, findings from the SOLVD trials argue for a similar test accuracy and prediction in both systolic and diastolic HF.

Nonetheless, some special considerations and caution need to be pointed out when interpreting our findings. Seventeen percent of patients included in this study presented with diastolic HF, and this does not actually reflect the proportion reported in epidemiological studies. However, it is well recognized that patients with diastolic HF, especially elderly and female population, are less likely referred for a CPET evaluation, thus increasing the likelihood that the whole spectrum of the preserved EF population with HF is not represented. It follows that, despite the mortality rate of both systolic and diastolic HF being similar, the number of events in the population with diastolic HF was insufficient to perform a meaningful prognostic analysis focusing on the subset of patients with isolated diastolic HF, information that remains challenging for future specifically designed investigations. However, we deemed it important to study a "real-life" population of outpatients with HF to ascertain exercise intolerance and clinical risk prediction.

The 6MWT day-by-day reproducibility was not tested in the entire population. However, in the subgroup of patients in which reproducibility was tested, an acceptable correlation coefficient was observed.

We did not include clinical status and echo-derived variables (ie, NYHA functional classes, LVEF, and E/E') in the univariate and multivariate analyses to adhere to the relationship between number of cardiac events and variables assessed in the Cox proportional hazard model (=10 events per predicting variable). Nonetheless, the trial was specifically designed for assessing 6MWT and CPET-derived variables.

**Conclusions**

In conclusion, the 6MWT is confirmed to be a simple and reliable first-line test for quantification of exercise intolerance in patients with HF. However, there is no supportive evidence for its use as a prognostic marker in alternative to or in conjunction with CPET-derived variables.

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**Disclosures**

None.

**References**

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**CLINICAL PERSPECTIVE**

We performed an head-to-head comparison on the clinical and prognostic validity of the 6-minute walk test (6MWT) and cardiopulmonary exercise testing to identify their most appropriate respective roles in the clinical follow-up of patients with heart failure (HF) of both systolic and diastolic origin. In contrast to previous studies that primarily compared 6MWT distance with peak oxygen consumption (VO2peak), we extended the analysis by including exercise ventilatory gas exchange–derived measures of ventilation efficiency (ie, slope of ventilation to carbon dioxide production, VE/VCO2) and abnormalities in the ventilatory pattern (ie, exercise oscillatory breathing, EOB) that, in recent years, have consistently emerged as powerful indicators of HF clinical status and outcome. We found that 6MWT distance was significantly decreased in proportion with lower peak VO2peak, higher VE/VCO2 slope classes, and EOB presence, suggesting its use for assessing the severity of exercise impairment. However, nonsignificant differences in distance covered were observed between survivors and nonsurvivors. The prognostic use of 6MWT distance was not significant either way when walked distance was analyzed as continuous or dichotomized variable (≥300 m) considering both the population with systolic HF or the entire population. Conversely, cardiopulmonary exercise testing–derived variables emerged as robust prognosticators with the strongest association found for EOB (systolic HF) and VE/VCO2 slope (entire population with HF and patients with a 6MWT≥300 m). Our findings confirm 6MWT as a simple and reliable first-line test for quantification of exercise intolerance and daily life disability in population with HF. However, clinicians running exercise laboratories should refer to cardiopulmonary exercise testing–derived ventilatory variables to collect the most powerful and independent prognostic markers of cardiac outcome.
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