International Journal of Cardiology 176 (2014) 94–98

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Minimal important difference for 6-minute walk test distances among patients with chronic heart failure

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ARTICLE INFO

Article history:
Received 29 April 2013
Received in revised form 7 January 2014
Accepted 24 June 2014
Available online 1 July 2014

Keywords:
Heart failure
6-minute walk-test
Minimal important difference
Biovariability

ABSTRACT

Background: The 6-minute walk test (6WT) is an established tool in the assessment of endurance and prognosis in patients with chronic heart failure (CHF). For these patients there is very limited data on biological variation of 6WT distances. We determined the minimal important difference (MID) for the 6WT in patients with stable systolic CHF.

Methods: Two cohorts of patients with stable systolic CHF were included from the outpatients' clinic of the University of Heidelberg. In these cohorts, two 6WT measurements were performed – in cohort 1 (n = 461) 180 days and in cohort 2 (n = 512) 365 days apart. Stability was defined as the absence of clinical events (3 months before the first test, between both tests, and 6 months after the second test) and stability of symptoms (NYHA) between tests. Using a standard error of measurement (SEM)-based approach, we determined the MID for both cohorts.

Results: The intraclass correlation coefficient was 0.89 at 180 days and 0.88 at 365 days. The results were consistent for groups stratified for age, gender, etiology of CHF, and individual NYHA class. The MID for the 6WT in stable CHF patients was 35 m and 37 m between presentation and 180 and 365 days, respectively.

Conclusion: Submaximal exercise capacity as represented by the 6WT varies little in stable CHF patients for up to 1-year intervals. The MID for changes in 6WT values in patients with stable CHF over a period of 6 to 12 months is ~36 m.

1. Introduction

The 6-minute walk test (6WT) was used initially as a measure of reduced exercise endurance in the evaluation of patients with pulmonary disease [1]. Subsequently, this test was rapidly adopted by cardiologists [2] and clinicians in other clinical subspecialties [3,4].

The widespread use of the 6WT in evaluating the degree of heart disease in patients with chronic heart failure (CHF) relates both to its value in the evaluation of therapeutic strategies in the treatment of patients with CHF [5,6] and in predicting the future likelihood of an adverse event (e.g., cardiac decompensation or death) in these patients [5–9]. Consequently, the 6WT is used widely as a non-invasive, easy-to-perform, and inexpensive test for identifying patients with CHF who are the most suitable for inclusion in clinical trials of new therapeutic strategies and as an endpoint for evaluating the long-term efficacy of these strategies in patients with CHF [10–18].

For pulmonary patients biological variation and MID are known [19–26]. In contrast and despite its widespread use in CHF, there is limited to no information on biological variation or its proxies such as minimal important difference (MID) of 6WT distances in CHF patients. So far, studies in CHF patients addressed either correlation of changes in 6WT distances with other clinical variables or endpoint driven cut-offs for change between 6WT measurements [27–32]. Neither of these approaches represents biological variation. Biological variation can be regarded as the random variation around a homeostatic set point of the respective test result. It is inherent to any biological system and can only be measured in strict absence of any change induced by instability or intervention.

Our study sought to close the gap in our knowledge of biological variation and MID for the 6WT in patients with stable systolic CHF. Using a standard error of measurement (SEM)-based approach, we determined the MID for 6WTs from patients with two tests either 180 or 365 days apart.

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http://dx.doi.org/10.1016/j.ijcard.2014.06.035
0167-5273/

2. Materials and methods

2.1. Patients

The clinical registry to the ongoing longitudinal observational study on chronic heart failure formed the basis of this study. Patients presenting to the outpatients' clinic of the University of Heidelberg Hospital (UHH), Germany, for assessment of heart failure and/or evaluation toward cardiac transplantation have been asked to consent to have their data recorded and used for research purposes. The UHH is a 1685-bed tertiary care facility that serves the populace of the Rhein–Neckar region (app. 900,000 persons) in Germany. Recruitment into this longitudinal study has been continuous and prospective.

For the present analysis, we retrospectively selected the clinical data from all patients meeting the following clinical and stability criteria: 1) CHF due to chronic systolic dysfunction; 2) no evidence of cardiac decompensation in the 3 months preceding the inclusion visit (V1) of this study where the initial 6WT was performed; 3) a second measurement of 6WT at a separate visit (V2) – either 180 days or 365 days after V1; 4) no evidence of cardiac decompensation between V1 and V2; 5) no change in perceived symptoms or subjective exercise capacity as evidenced by the NYHA functional class between V1 and V2; and 6) absence of any clinical event defined as evidence of cardiac decompensation or all-cause death or cardiac transplantation in the 6 months following V2.

The timeline and temporal requirements of the present study are displayed in Fig. 1. If a given patient had more than 2 visits with measurement intervals meeting the requirements for both cohorts, inclusion into both cohorts was considered. This was assumed valid since the "learning effect" had been excluded already at the inclusion into this study at V1 (see below) and all the patients were stable between the two walk tests irrespective of cohorts by protocol definition.

The diagnosis of CHF was based on standard clinical criteria, including systolic dysfunction and abnormal echocardiographic findings [33,34]. Systolic dysfunction was defined as a left-ventricular ejection fraction (LVEF) ≤45%. The protocol of the underlying clinical registry to the ongoing longitudinal observational study met the requirements of the Helsinki Declaration and was approved by the UHH Ethics Committee in its original conception in 1996 under the number 198/1996. Consequent modifications due to change in clinical variables/modalities and/or legal requirements have been systematically updated with the UHH Ethics committee ever since.

2.2. 6WT

The 6WT was performed according to a published protocol [7]. To avoid the "learning effect" that occurs when patients have not previously undergone a 6WT [35,36], only patients with a minimum of one 6WT value prior to the 6WT at V1 were included in our study. In general, patients had performed a median of two 6WTs prior to V1 – the first of these prior 6WT dating a median of 352 days before V1.

2.3. Determination of endpoints

Endpoints were part of the definition of stability as outlined above. Cardiac decompensation, all-cause mortality, and cardiac transplantation were the predefined endpoints for the purpose of this analysis. They were determined from the patients' clinical records, phone calls to the patient's home or physician, or review of hospital in-patient records.

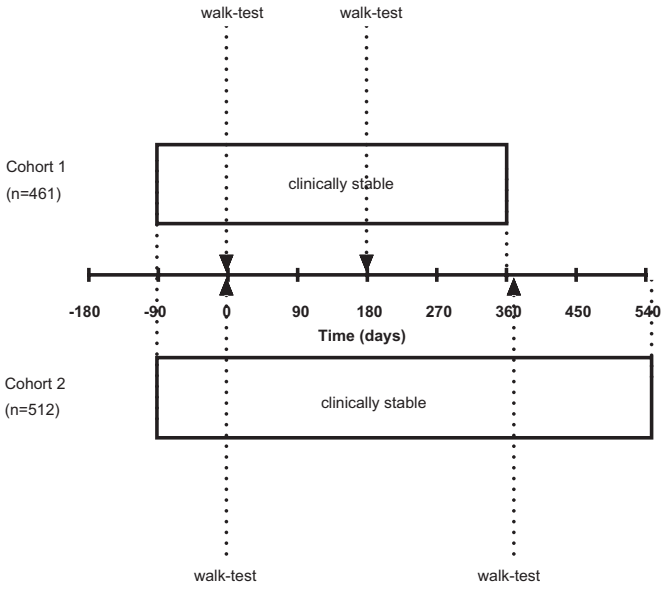

Fig. 1. Study outline regarding timeline with respect to stability criteria and measurement intervals.

2.4. MID

Within-subject biological variation refers to all biological (nondisease-related) sources of variation that can alter any individual's test results, including, but not limited to: seasonal and geographic variation, gender, and pulsatile and circadian biorhythms [37]. MID represents one way of approaching biological variation and the merits and pitfalls of this approach have been discussed previously [38].

MID can be assessed by either anchor-based methods – requiring reliable endpoints as "anchor" for definition – and distribution-based methods – requiring stable cohorts for derivation of the respective descriptive (distribution) statistics of the cohort. The one-standard error of measurement (one-SEM) value is a proxy for MID [39]. It is both valid and simpler than most other approaches [38,40,41] for the determination of MID. In our study, MID was determined using the one-SEM-based approach developed by Wyrwich et al. [41,42] using the formula:

$$\mathrm{MID} = \mathrm{SD} \times \mathit{SQRT}(1-\mathrm{r}),$$

where SD is the population standard deviation and r is the intraclass correlation coefficient (i.e., the degree of absolute agreement among measurements).

Descriptive statistics, the population SD, intra-class correlation coefficient, and paired samples *t*-test values were obtained using MedCalc software version 12.7 (Ostend, Belgium) and the results were displayed using GraphPad Prism version 6.02 for Windows (La Jolla, California, USA). An arbitrary p-value of 0.05 was used to assume statistical significance.

2.5. Ethics and authorship

The authors of this manuscript certify that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [43].

3. Results

3.1. Patient characteristics

The clinical characteristics for all patients in cohorts 1 (180-day-interval) and 2 (365-day-interval) are shown in Table 1. Ischemic heart disease was the underlying etiology in the majority of patients. The mean ejection fraction was relatively low, indicating more advanced heart failure. The distribution of patients was balanced across NYHA functional Classes I–III. The selection of stable cohorts was evidenced by the low event rate. Among the Cohort 1 patients, 40 (8.7%) died during overall follow-up and 35 (7.6%) presented with cardiac decompensation after V2. Among the Cohort 2 patients, 48 (9.4%) died during overall follow-up and 47 (9.2%) presented with cardiac decompensation after V2. For the complete results on endpoints at 1-year, 2-year, and 3-year follow-up see Table 2.

Table 1
Patient demographics and 6WT data at approximately 180- and 365-day intervals[a].

Chacteristic		Cohort 1	Cohort 2
N		461	512
Age, y		57 ± 12	57 ± 12
Sex:	M	360 (78.1)	391 (76.4)
	F	101 (21.9)	121 (23.6)
BMI, kg/m^2		27.9 ± 5.0	27.9 ± 5.2
NYHA Class:	I	101 (21.9)	178 (34.8)
	II	222 (48.2)	211 (41.2)
	III	137 (29.7)	123 (24.0)
	IV	0 (0.0)	0 (0.0)
LVEF, %		30 ± 11	33 ± 12
IHD, n (%)		280 (60.7)	285 (55.7)
No. of days between 6WTs		185 ± 16	366 ± 17
6WT, m		472 ± 106	488 ± 107
Betablocker		414 (89.8)	466 (91.4)
ACE-I/AT1-B		395 (93.5)	418 (93.7)
No. of days of follow-up[b]		665 (320–1844)	734 (371–1364)

[a] All patients had stable CHF; values shown are mean ± SD or mean (% of total) or median (IQR) were appropriate.

[b] After second 6WT measurement. N, number; y, years; M, males; F, females; BMI, body mass index; NYHA, New York Heart Association; LVEF, left-ventricular ejection fraction; IHD, ischemic heart disease.