International Journal of Cardiology 212 (2016) 265–273

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Six-minute walk test in systemic sclerosis: A systematic review and meta-analysis

Els Vandecasteele [a,*,1,2], Michel De Pauw [a,1,2], Filip De Keyser [b,c,1,2], Saskia Decuman [b,2], Ellen Deschepper [d,2], Yves Piette [c,2], Guy Brusselle [e,2], Vanessa Smith [b,c,2]

[a] Department of Cardiology, Ghent University Hospital, Ghent, Belgium
[b] Department of Internal Medicine, Ghent University, Ghent, Belgium
[c] Department of Rheumatology, Ghent University Hospital, Ghent, Belgium
[d] Biostatistics Unit, Department of Public Health, Ghent University, Ghent, Belgium
[e] Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium

ARTICLE INFO

Article history:
Received 2 February 2016
Accepted 19 March 2016
Available online 25 March 2016

Keywords:
Six-minute walk test
Pulmonary arterial hypertension
Interstitial lung disease
Systemic sclerosis
Exercise testing

ABSTRACT

Background: Pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) are the leading causes of death in systemic sclerosis (SSc). Although the six-minute walk test (6MWT) is generally used for evaluating PAH and ILD, utility in SSc is undetermined. This study evaluates the role of 6MWT in SSc by systematic review and meta-analysis.

Methods: A systematic literature search on PubMed, Web of Science and Cochrane Library Online was performed using the medical subject heading search terms for "systemic sclerosis", "CREST" and "six minute walk test", "six minute walk distance (6MWD)", "(cardiopulmonary) exercise test", "treadmill test" or "step test".

Results: Meta-analysis of 43 included studies (3185 SSc-all patients) revealed that the mean 6MWD was comparable between the SSc–PAH and SSc–ILD–PH subgroups (288 m [95% CI: 259–317 m] vs 286 m [95% CI: 259–314 m], $p = 0.93$). The pooled mean of 725 SSc-PAH patients was significantly lower than the pooled mean of 413 SSc–noPAH patients (430 m [95% CI: 402–458 m], $p < 0.001$). 95 SSc–ILD–PH patients walked significantly less than 328 SSc–ILD patients (388 m [95% CI: 362–415 m], $p < 0.001$) and significantly less than 86 SSc-noILD patients (420 m [95% CI: 325–515 m], $p = 0.008$). 81–98% of the SSc–PAH/ILD/ILD–PH patients performed a 6MWT.

Conclusions: During a 6MWT, SSc–PAH patients walk less than SSc–noPAH patients and SSc–ILD–PH patients walk less than SSc–ILD and SSc–noILD patients.

1. Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by (micro)vascular, inflammatory and fibrotic components. SSc is a heterogeneous disease with skin and/or visceral organ (gastrointestinal tract, lungs, heart and kidneys) manifestations. Mortality remains high (30–35% at 10 years) and in recent era pulmonary (interstitial lung disease [ILD] and pulmonary arterial hypertension [PAH]) and cardiac manifestations are the leading causes of disease related mortality (up to 85%) [1,2]. PH is defined as mean pulmonary arterial pressure (PAP) ≥25 mm Hg by right heart catheterization (RHC) and can be precapillary (pulmonary capillary wedge pressure [PCWP] ≤15 mm Hg) or postcapillary (PCWP >15 mm Hg). In SSc, PH can be precapillary (pulmonary arterial hypertension [PAH] [WHO group I], PH secondary to lung disease and/or hypoxia [WHO group III], chronic thromboembolic PH [CTEPH] [WHO group IV]), postcapillary (due to left heart disease [World Health Organization [WHO] group II]), or a combination [3] (Supplementary file 1). PAH occurs in approximately 8–13% of the SSc patients [4,5]. Screening programs identify SSc–PAH earlier than without screening programs and earlier diagnosis leads to earlier treatment and better prognosis [4,6].

The six-minute walk test (6MWT) is a submaximal, aerobic exercise test which correlates with the daily physical activity. It's a simple, safe, non-invasive, reproducible test [7,8].

Although 6MWT is generally used for evaluating functional exercise capacity, assessing prognosis, determining outcome of clinical trials and evaluating response to treatment in heart and lung diseases like PAH, ILD, chronic obstructive pulmonary disease (COPD) and congestive heart failure [9–11], evidence for 6MWT testing in SSc–PAH/ILD is conflicted. In this way, in some studies,

* Corresponding author at: Department of Cardiology, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium.
E-mail address: els.vandecasteele@ugent.be (E. Vandecasteele).
[1] E Vandecasteele, M De Pauw and F De Keyser equally contributed to this study.
[2] The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2016.03.084
0167-5273/

data on the six-minute walk distance (6MWD) were missing in up to 30% of the included SSc–PAH/ILD/ILD–PH patients, without explanation why the data are not reported [12–14]. In contrast to the diseases the 6MWT was originally designed for, SSc is a heterogeneous disease. Unfortunately, SSc patients often do not suffer from a solitary heart or lung disease but combinations of heart, lung and/or multiple other manifestations (skin fibrosis, musculoskeletal involvement, renal involvement). This may confound the 6MWT. In SSc–PAH, according to the OMERACT filter, 6MWT is only partially validated (face validity, feasibility and discriminant capacity in response to therapy) [15]. A meta-analysis on the effect of oral treatment with endothelin receptor antagonist (ERA) or phosphodiesterase-5 inhibitor (PDE5-I) on exercise capacity in SSc–PAH suggested no improvement of 6MWD. However, in the randomized controlled trials (RCTs) used for the latter meta-analysis, results of connective tissue disease (CTD) related PAH were extrapolated to SSc–PAH whilst no subgroup analysis of SSc–PAH was made [16].

In a Delphi-consensus on outcome measures in SSc–PAH, 6MWT was one of the core set measures judged by experts as most appropriate and comprehensive to use in RCTs in SSc–PAH [17]. In 2014, another Delphi-consensus on performing RHC for suspected PAH in SSc, excluded 6MWT as core set criterion [18].

Since the 6MWT is only partially validated in SSc–PAH and not generally used as a stratification/prognostification/treatment response tool for PAH or ILD in SSc, we wanted to evaluate the role of 6MWT in SSc by systematic review. A meta-analysis was performed to assess the 6MWD walked in SSc–PH, SSc–PAH, SSc–ILD–PH, SSc–ILD, SSc–noILD, SSc–noPAH, SSc–noPAH–noILD and SSc–other patients. Moreover, in the SSc–ILD/PAH/ILD–PH studies included in the systematic review, the percentage performing a 6MWT and the reason not to perform a 6MWT were evaluated.

2. Methods

2.1. Search strategy

A literature search of PubMed, Web of Science and Cochrane Library Online was conducted on articles published from 1966 until January 2016 using the medical subject heading (MeSH) search terms for “systemic sclerosis” (systemic sclerosis, systemic sclerosis limited, systemic sclerosis diffuse, scleroderma systemic, scleroderma diffuse and scleroderma limited) or “CREST” and “six minute walk test”, “six minute walk distance”, “(cardiopulmonary) exercise test”, “treadmill test” or “step test”. The search was limited to studies in human adults and only studies published in English were retained. Reference lists of the included articles were scrutinized for additional articles.

2.2. Selection process

Two investigators (E.V., S.D.) independently evaluated the eligibility of the articles. Articles identified by the database search were selected first according to their titles and abstracts. At both steps, articles considered eligible by one or both of the investigators were included in the next stage. Finally, the articles were selected based on their full texts. Articles were included if they were original studies, systematic reviews or meta-analysis, if data on 6MWT of SSc patients could be analyzed separately and if there was a minimum sample size of 5 SSc patients. SSc should be defined by the preliminary classification criteria of the American College of Rheumatology (ACR) [19], the LeRoy/Medsger criteria for early SSc [20] or the recently published ACR/European League Against Rheumatism (EULAR) classification criteria [21]. If classification criteria were not clearly described the study was excluded.

2.3. Data extraction and analysis

For the systematic review, the following data were extracted: study design, number of patients, subgroup classification (SSc–PH, SSc–PAH, SSc–ILD–PH, SSc–ILD, SSc–noPAH, SSc–noILD, SSc–noILD–noPAH and SSc–other), diagnostic criteria used for the different subgroups, number of patients performing a 6MWT, reason not performing a 6MWT, sex, age, disease duration (since diagnosis, first Raynaud's or non-Raynaud's symptom), New York Heart Association (NYHA) functional class, modified Rodnan skin score, Scleroderma Health Assessment Questionnaire (SHAQ), Health Assessment Questionnaire Disability Index (HAQ-DI), percentage of each subset (diffuse cutaneous systemic sclerosis [DcSSc], limited cutaneous systemic sclerosis [LcSSc]), 6MWD, delta oxygen saturation (SpO_2) during the 6MWT, SpO_2 and Borg dyspnoea score at the beginning and the end and heart rate before the test. These data were extracted by the first author and the data used for the meta-analysis were independently checked by S.D.

Studies or subgroups of studies were classified as SSc–PH when all included patients were diagnosed with SSc–PH by RHC [3]. The group SSc–PH was subdivided in a SSc–ILD–PH, a SSc–PAH and a SSc–PH-not-specified subgroup. Precapillary SSc–PH studies where all patients had ILD (defined as *interstitial lung involvement on high resolution computed tomography scan of the chest [HRCT]-scan and total lung capacity [TLC] <70% of the predicted value [pred] or functional vital capacity [FVC] <70% pred on pulmonary function test [PFT] [22] or *HRCT total disease extent >30% or HRCT total disease extent 10–30% and FVC <70% pred [13]) were classified in the SSc–ILD–PH subgroup. The subgroup SSc–PAH was restricted to precapillary SSc–PH studies without patients with ILD. The studies containing both SSc–PAH and SSc–ILD–PH patients or where it was unclear whether patients had SSc–PAH or SSc–ILD–PH, were classified as SSc–PH-not-specified.

Studies or subgroups of studies were classified as SSc–ILD, when all included patients had ILD (defined as *the presence of characteristic multifocal or diffuse abnormalities on HRCT [subpleural opacities, parenchymal bands, thickened interlobular septae, an irregular pleural interface, honeycomb lung) [23]; *reticular changes or ground-glass appearances extending to the venous confluence on HRCT [24]; *ground-glass or reticular opacity on HRCT [14] or *FVC < 80% [25]).

Studies or subgroups of studies with exclusion of patients with ILD (defined as *FVC, TLC or forced expiratory volume in one second [FEV1] <60% pred or more than patchy fibrosis on HRCT [26]; *more than minimal lung fibrosis on HRCT or TLC <70% pred [27] or *ground-glass or reticular opacity on HRCT [14]) were classified as SSc–noILD and studies or subgroups of studies where all patients had mean PAP <25 mm Hg on RHC were classified as SSc–noPAH. Studies excluding patients with ILD and PAH (on RHC) were classified as SSc–noILD–noPAH. All other studies were classified as SSc–other.

For all patients, data from the baseline 6MWT were used. Studies were evaluated whether the 6MWT was performed following the description of Guyatt or the guidelines of the American Thoracic Society (ATS) [7,8].

2.4. Statistical analysis

The pooled mean 6MWD was calculated in a meta-analysis for SSc–PH (with subgroup analysis of SSc–PAH, SSc–ILD–PH and SSc–PH-not-specified), SSc–ILD, SSc–noILD, SSc–noPAH, SSc–noILD–noPAH and SSc–other groups. A DerSimonian–Laird random-effects model and weighted estimation with inverse variance weights were used to incorporate the means and standard deviations of the 6MWD and the sample sizes of the included studies. Forest plots showed graphical representation of the results. Heterogeneity was assessed to examine the null hypothesis that all measurements are evaluating the same effect. Test results of the Cochran's Q test and the quantity I^2 were reported to measure the inconsistencies in 6MWD recordings in the individual studies [28]. Differences in pooled mean 6MWD between two groups/