Triangulating Clinically Meaningful Change in the Six-minute Walk Test in Individuals with Chronic Heart Failure: A Systematic Review

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ABSTRACT

Purpose: The purpose of the present review was to use existing, published data to provide an estimate of the amount of change in six-minute walk test distance (Δ6MWT) that represents a clinically meaningful change in individuals with chronic heart failure (CHF). **Methods:** The present review included two separate literature searches of the CINAHL and Medline databases for articles that: (1) reported the intraclass correlation coefficient (ICC) of the 6MWT in individuals with CHF, and (2) used the 6MWT along with either aerobic capacity or health-related quality of life (HRQL) as study endpoints in randomized controlled trials (RCTs) of exercise-based intervention for individuals with CHF. The ICCs were used to calculate the minimum detectable difference (MDD) at the 95% confidence interval for each included study. The Δ6MWT associated with aerobic capacity and HRQL within-group effect sizes for the intervention and control groups in each included RCT was analyzed using receiver operating characteristic (ROC) curves. **Results:** Thirteen articles reported the ICC for the 6MWT. The mean (standard deviation) MDD calculated based on these data was 43.1(16.8) m. Eighteen RCTs measured the 6MWT and either aerobic capacity and/or HRQL. A Δ6MWT of 40-45 m was associated with at least moderate aerobic capacity and HRQL effect sizes in the intervention groups. The Δ6MWT thresholds that discriminated between intervention and control groups using ROC curves revealed the following sensitivity/specificity for the respective thresholds: 19 m, 94.4/83.3%, 32 m, 83.3/94.4%, and 48 m 44.4/100% (AUC = .935, p = .009, $CI_{95\%}$ .855, 1.015). **Conclusions:** A Δ6MWT of approximately 45 m appears to exceed measurement error and be associated with significant changes in either aerobic capacity and/or HRQL.

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Key Words: heart failure, six-minute walk test, clinically meaningful change, minimum detectable difference

INTRODUCTION

Chronic heart failure (CHF) affects nearly 4 million U.S. residents and more than 15 million people worldwide.[1] Symptoms and limitations experienced by individuals with CHF include fatigue, dyspnea on exertion, muscle atrophy, weakness, reduced health-related quality of life (HRQL), and poor exercise tolerance,[2-4] with exercise intolerance reported as the most frequent and debilitating symptom.[5] Rehabilitation interventions are primarily directed at improving exercise tolerance with an anticipated reduction in the other symptoms and limitations associated with CHF.[6] One of the most common instruments for measuring changes in exercise tolerance following exercise-based interventions is the six-minute walk test (6MWT). Interpretation of clinically meaningful change in the 6MWT is important for clinicians for making decisions about the effectiveness of interventions in individual patients, and is important for researchers in estimating required sample sizes and making conclusions regarding magnitude of treatment effect. Unfortunately, the amount of change in 6MWT distance (Δ6MWT) that should be considered to be clinically meaningful has not been well studied.

The first estimate of clinically meaningful Δ6MWT was intially reported by Guyatt et al[7] in 1988 who reported the within-person standard deviation of 22.5 m. Opasich et al[8] and Pinna et al,[9] in two papers reporting on the same data set, calculated the minimum detectable difference (MDD) for the 6MWT in patients with CHF to be between 32 and 55 m depending on the confidence level (95% versus 99%) and number of trials (average vs. single) used, with 45 m representing the 95% confidence interval calculated based on two trials. In attempting to estimate the minimum clinically important difference (MCID) of the 6MWT, O'Keefe et al[10] used a 5-point, patient-rated Global Rating Scale (GRS) and found mean changes of 24 m and 43 m, respectively, for those who reported being "a little worse" or "a little better" over the course of a 4-week follow-up period. Spertus et al[11] used a 15-point, clinician-rated GRS collapsed into either large, moderate, small, and negligible improvement or decline. They found that mean Δ6MWT distances for moderate improvement or decline were 55 m and 90 m, respectively.

The aforementioned studies using the within-person standard deviation, MDD, or MCID suggest a somewhat large range of 22.5 m to 90 m that may represent meaningful Δ6MWT in individuals with CHF.[12] Other methods for determining clinically meaningful change can include systematic review and meta-analysis of Δ6MWT in response to interventions in randomized controlled trials (RCTs). Rees et al[13] and an update by Davies et al,[14] found a weighted mean difference of 41 m for Δ6MWT between control and intervention groups, as well as statistically significant changes in other measures of exercise capacity (eg, maximum oxygen consumption and peak work) and HRQL. However, the weighted mean difference of 41 m only accounts for differences between intervention and control groups, and there was no analysis of concurrent changes between the 6MWT and other measures. Olsson et al[12] examined Δ6MWT concurrent with changes in other study end points in a systematic review of clinical trials investigating pharmacologic and cardiac resynchronization interventions in individuals with CHF. They found that the 6MWT appeared to be a responsive study endpoint for cardiac resynchronization therapy trials, and that changes in symptoms were concordant with Δ6MWT. Unfortunately, Olsson et al[12] did not report sufficient data to suggest a specific threshold or threshold range associated with these concordant changes that might constitute clinically meaningful change.

Because an optimal method for determining clinically meaningful change has not been established, some have recommended triangulation using several approaches to determine a threshold or threshold range.[15-17] In addition to the MDD and MCID, other methods can include the analysis of concordant changes between the measure of interest and other measures.[12] Therefore, the purpose of this review is to use a novel approach for triangulating the Δ6MWT that should be considered to be clinically meaningful.

METHODS

Two literature reviews were conducted to assist in meeting the planned overall objective of triangulating a threshold for clinically meaningful Δ6MWT. First, a literature search for articles that reported intra-class coefficients (ICCs) for the 6MWT in patients with CHF was conducted to allow for the calculation of MDD estimates. A second literature search investigating the effect of exercise interventions in patients with CHF was conducted to allow for an ecological analysis using group-level data from multiple trials. The objectives of this analysis were (1) to examine whether Δ6MWT is associated with concurrent changes in exercise capacity and HRQL, and (2) to determine if there is a Δ6MWT threshold that discriminates between intervention and placebo groups.

Literature Search for Intraclass Correlation Coefficients

The literature was searched on April 14, 2011, for English-language articles using Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus with Full-Text (EBSCO) and MEDLINE (via PubMed) databases using "heart failure" and the following key words: "walk test," "walking test," "reproducibility," and "reliability." Articles were included if they reported the ICC for the 6MWT in patients with CHF. Reference lists from articles found during the search were also used for discovering potentially relevant articles.

Calculation of the MDD

The $MDD_{95\%}$ was calculated as follows:[18] $MDD_{95\%} = z * SEM * \sqrt{2}$ where z = 1.96 and SEM (standard error of measurement) = $\sigma_{baseline}\sqrt{(1\text{-}ICC)}$.

Analysis of Findings

In anticipation of a range of values, the $MDD_{95\%}$ was plotted as a function of several variables including mean age, baseline 6MWT distance, mean left ventricular ejection fraction, mean New York Heart Association Functional Class, sample size, and test-retest interval to determine the potential influence of these variables on MDD.

Literature Search for Concurrent Changes in Exercise-based Controlled Trial Outcomes

The literature was also searched on April 15, 2011, for English-language articles using CINAHL Plus with Full-Text (EBSCO) and MEDLINE (via PubMed) databases using "heart failure" and the following key words: "exercise," "training," and "rehabilitation." All years of publication were included, and randomized controlled trial (RCT) filters were applied when available. Reference lists from articles found during the search were also used for discovering potentially relevant articles

Study Selection Criteria

For inclusion into the present review, studies met the following criteria: (1) participants included adults diagnosed with HF, (2) randomized study design, (3) exercise-related intervention, and (4) use of the 6MWT as a study endpoint in addition to cardiopulmonary exercise testing or HRQL measures. Studies were excluded if the language was anything other than English, or if they were not RCTs.

Methodological Quality of Reviewed Studies

The methodological quality and rigor of each article was evaluated using a 10-point scale adopted from Medlicott and Harris.[19] Item 7 of the original scale, "blinding of the patient, treatment provider, and assessor," was modified to "blinding of the assessor" to account for exercise studies where it is difficult to blind patients to exercise-based interventions.[20]

Articles were scored based on the number of "yes" answers for each of the 10 items[21] and were rated as "strong" for scores of 80% or higher, "moderate" for scores of 60% to 79%, or "weak" for scores of 59% or less.

Analysis of Findings

An ecological approach using group-level data included both visual and quantitative analysis. Visual analysis was conducted using scatterplots of the mean Δ6MWT for intervention and placebo groups plotted against the exercise capacity and HRQL within-group effect sizes (conservatively assuming a pre/post measure correlation of 0.5) to account for variability in samples and the instruments used for measuring these variables. Quantitative analysis included comparison of Δ6MWT, aerobic capacity effect size, and HRQL effect size between intervention and control groups using the appropriate independent groups comparison strategy (independent t-tests or Mann Whitney U), as well as receiver operating characteristic (ROC) curves to determine the optimal threshold for Δ6MWT that discriminates between intervention and control groups.

RESULTS

Literature Search for Intra-class Correlation Coefficients

Eight-hundred twenty-five unique articles were found using the aforementioned search strategy, yielding 13 articles[8-10, 20-29] that reported the ICC for the 6MWT in patients with CHF. The results of the search strategy are outlined in Figure 1. A summary of each included study is presented in Table 1. Of the 13 articles,[8-10,20-29] one reported on two different samples,[26] and two different articles[8,9] reported on the same sample. Five studies[20-23, 27] did not report the standard deviation of the 6MWT for the subgroup of subjects in whom the ICC was calculated. Therefore, the standard deviation from the entire sample was used.

Overall, the search permitted calculation of 13 estimates of the $MDD_{95\%}$ for the 6MWT, which ranged from 20 to 151 m with a mean (standard deviation) of 57.9 (37.5) m and a 95% confidence interval of 34.0 to 81.7 m (Figure 2). Given the wide range of calculated MDDs and two apparent outliers, potential explanatory factors were explored using scatterplots of the $MDD_{95\%}$ plotted against test-retest interval, disease severity as measured by left ventricular ejection fraction, New York Heart Association Functional Class, baseline distance walked, sample size, and age. Additionally, several factors known to influence 6MWT distance,[22] including instruction to walk as far as possible in 6 minutes, use of a practice trial, use of a course longer than 33 m, and providing encouragement were also explored using scatterplots. No relationships among the calculated $MDD_{95\%}$ and any of the aforementioned variables emerged. It should be noted that Ingle et al 2005[28] used a one year test-retest interval that likely introduced other sources of variability, and although there were no discernable factors that contributed to the high $MDD_{95\%}$ calculated based on the Roul et al[21] data, it appeared to be an outlier. Therefore, these two outliers were removed for additional analysis. The mean (standard deviation) $MDD_{95\%}$ was 43.1(16.8) m with a 95% confidence interval of 31.8 to 54.4 m in the revised sample.

Literature Search for Concurrent Changes in Exercise-based Controlled Trial Outcomes

Four-hundred seventy-two unique articles were found using the aforementioned search strategy, yielding 18 RCTs[6,27,30-45] investigating exercise-based interventions for patients with CHF using the 6MWT as a study endpoint. The results of the search strategy are outlined in Figure 3. A summary of each included study is presented in Table 2.

Eleven studies[6,27,30-33,36,38,41,42,44] measured both the 6MWT and aerobic capacity. Visual analysis of the scatterplots depicting Δ6MWT versus the within-group effect size for aerobic capacity in both the treatment and intervention groups revealed that Δ6MWT for the intervention groups were all greater than 20 m compared to only one placebo group exceeding 20 m. However, most aerobic capacity effect sizes in the intervention groups were small (0.2-0.5), with some having no effect or a small effect in the opposite direction. In further exploring these results, only 5[6,27,30,31,44] of the 11 studies that measured aerobic capacity used an intervention that was of sufficient frequency (≥ 3 days per week), intensity (> 65% of predicted or measured maximal capacity), duration (≥ 25 minutes per session) and type (large muscle groups, rhythmic motion) to be reasonably expected to produce a change in aerobic capacity. Therefore, in plotting the data from only these 5 studies, moderate aerobic capacity effect sizes for the intervention group only appeared to be associated with a Δ6MWT greater than 40 m (Figure 4).

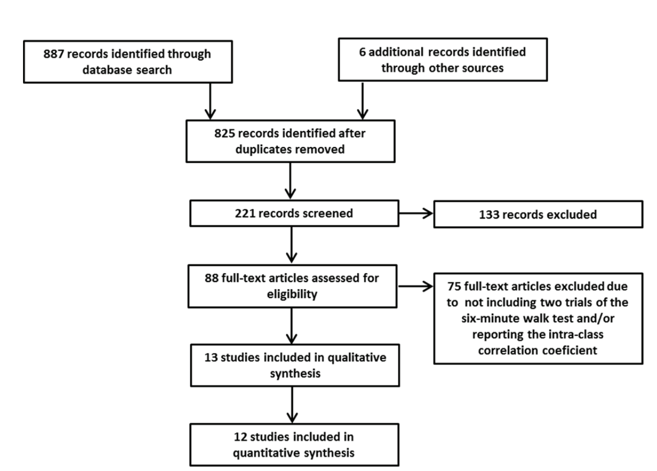
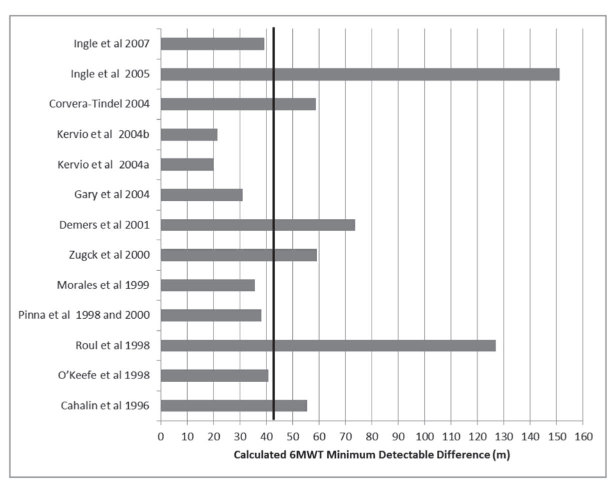


Figure 1. Results of search strategy for Intraclass Correlation Coefficients.



Bold line indicates mean minimum detectable difference with outlliers removed; 6MWT, six-minute walk test

Figure 2. Calculated minimum detectable difference values.

Table 1. Summary of Literature Search for Intraclass Correlation Coefficients

AUTHOR YEAR	PURPOSE OF STUDY	STUDY POPULATION	TEST-RETEST INTERVAL	BASELINE 6MWT ICC CALCULATED MDD	NOTES
Cahalin et al 1996[20]	62 week longitudinal study to determine if 6MWT predicts peak VO_2 and survival	N=45 Age: 49(8) years LVEF: 20(6)% NYHA-FC: 3.3(.6)	"Later" on same day	6MWT: 310(100)m ICC: 0.96 MDD: 55.4	Used subgroup of 20 subjects used for ICC Selection method NR Baseline data from entire sample Standard procedure except: no encouragement provided
O'Keefe et al 1998[10]	Cross-sectional study with 3-8 week f/u to determine reproducibility and responsiveness of the 6MWT	N=60 Age: median 81 years LVEF: NR NYHA-FC: 2.5(.85)	Median 4 weeks (range 3-8)	6MWT: 237(49)m ICC: 0.91 MDD: 40.7	Used subgroup of 24 subjects who reported "No change" in status at follow-up Standard procedure except: no practice trial, 25 m course
Roul et al 1998[21]	Up to 3 year longitudinal study to determine if 6MWT predicts peak VO_2 and survival	N=121 Age: 59(11) years LVEF: 29.6(13)% NYHA-FC: 2.5(.5)	Same day	6MWT: 433(108)m ICC: 0.82 MDD: 127.0	Used subgroup of 40 subjects used for ICC Selection method NR Baseline data from entire sample Standard procedures except: course length unspecified, no practice trial
Pinna et al 1998[8] and Opasich et al 2000[9]	Cross sectional study to determine reproducibility of the 6MWT	N=233 Age: 54(9) years LVEF: 26(7)% NYHA-FC: 2.2(.7)	30 min for 202 subjects Next day for 31 subjects	6MWT: 400(69)m ICC: 0.96 MDD:38.3	2nd test was 20 m and 15 m farther for the 30 min and next day test-retest interval groups, respectively Standard procedure except: no encouragement provided, no practice trial
Morales et al 1999[22]	Cross-sectional study comparing the 6MWT to the Shuttle Walk test	N=46 Age: 53(10) years LVEF: 28(8)% NYHA-FC: 2.8(.7)	Not well described; no more than 2 tests were given on the same day, and all tests were completed in ≤ 2 weeks	6MWT: 496(91)m r: 0.98 MDD: 35.7	Used the first 17 subjects who did 3 trials with the Pearson correlation coefficient calculated based on trials 2 and 3 3rd test was 9m farther than the 2nd test Baseline standard deviation from entire sample Standard procedure except: 20 m course
Zugck et al 2000[23]	Cross-sectional study to compare the 6MWT to peak VO_2 with regard to prognosis	N=113 Age: 54(12) years LVEF: 19(7)% NYHA-FC: 2.2(.8)	3 consecutive days	6MWT: 466(107)m ICC: 0.96 MDD: 59.3	Used subgroup of 10 subjects who performed 3 trials Selection method NR Baseline data from entire sample Standard procedure except: no encouragement provided
Demers et al 2001[24]	43 week longitudinal subanalysis of the RESOLVD trial to assess reliability, validity, and responsiveness of 6MWT	N=768 Age: 63(11) years LVEF: 27(10)% NYHA-FC: 2.35(.5)	Within 5 days	6MWT: 381(84)m ICC: 0.90 MDD: 73.6	Distances at 18 and 43 weeks were within 6 m of each other with ICCs of .88 and .91, respectively Standard procedure except: 20 m course, no practice trial
Gary et al 2004[25]	Interventional study assessing the effect of medical intervention in patients with diastolic heart failure	N=32 Age: 68(11) years LVEF: 55(8)% NYHA-FC: 2.6(.5)	2 hours	6MWT: 254(112)m ICC: 0.99 MDD: 31.0	Follow-up ICC for control and intervention groups were .97 and .93, respectively Standard procedure except: 18 m course, no practice trial
Kervio et al 2004[26]	Cross-sectional study to determine reproducibility of the 6MWT in patients with and without cardiac pacing	N=24 Age: 65(6) years LVEF: 27(8.6)% NYHA-FC: 2.3(.5)	Within 24 - 48 hours	6MWT: 445(73)m and 407(55)m, non-paced/paced, respectively ICC: 0.99 and 0.98 for non-paced/paced, respectively MDD: 20.2, 21.6, respectively	2nd test was 3 m farther in the non-paced group and 1 m farther in the paced group Standard procedure except: 18 m course no practice trial
Corvera-Tindel et al 2004[27]	12 week home-based walking RCT	N=79 Age: 63(10) LVEF: 28(10) NYHA-FC: 2.2(.4)	Not specified	6MWT: 379(75)m ICC: 0.92 MDD: 58.8 m	Used 10% of the sample to assess test-retest reliability Selection method NR Baseline data from entire sample Standard procedure except: course length not specified, no encouragement provided, no practice trial
Ingle et al 2005[28]	Longitudinal 1 year f/u to determine reproducibility and sensitivity of the 6MWT over time	N=1013 Age: 72(7) years LVEF: 33(8)% NYHA-FC: 2.25(.6)	1 year	6MWT: 285(122)m ICC: 0.80 MDD: 124.0	Used subgroup of 74 subjects who reported no change in symptoms as defined by a pre-to-post change in the Euro Heart Failure Survey of ≤ 3 points at 1 year follow-up Standard procedure except: 15 m course, no practice trial
Ingle et al 2007[29]	Cross-sectional study of VO_2 during the 6MWT and to compare to peak VO_2	N=24 Age: 76(5) years LVEF: 36(5)% NYHA-FC: 78% III or IV	Next day	6MWT: 340(100)m ICC: 0.98 MDD: 47.8	2nd test was 4 meters farther on average Standard procedure except: 15 m course, no practice trial

Abbreviations: LVEF, left ventricular ejection fraction; NHYA-FC, New York Heart Association Functional Class; 6MWT, six-minute walk test; ICC, Intraclass Correlation Coefficient; MDD, minimum detectable difference; NR, not sufficiently reported; standard procedure = (1) subject encouraged to walk as far as possible, (2) course length is ≥ 33 m, (3) a practice trial is provided, (4) standardized encouragement is provided as regular intervals

Fourteen studies[6,27,31,34-40,42-45] measured and sufficiently reported both 6MWT and HRQL. Visual analysis of the scatterplots depicting Δ6MWT versus the within-group effect size for HRQL in both the treatment and intervention groups revealed that Δ6MWT for the intervention groups were all greater than 20 m compared to only one placebo group exceeding 20 m (Figure 5). Reported Δ6MWT distance for the intervention groups were all more than 20 m compared to only one placebo group exceeding 20 m; however, moderate HRQL effect sizes for the intervention group only appeared to be associated with a Δ6MWT greater than 45 m. There appears to be a linear association between the magnitude of Δ6MWT and the magnitude of within-group effect size for HRQL, with an apparent threshold of 35 m discriminating between intervention and placebo groups. It should be noted that the intervention group in the Brubaker et al[43] study had a HRQL effect size indicating decline. Brubaker et al[42] also demonstrated statistically insignificant changes in 6MWT distances of 56 and 47 m for the intervention and placebo groups, respectively, and had near-zero between-subject effect sizes in all measures (6MWT, VO_2, and HRQL).

With regard to the quantitative analysis of the differences in Δ6MWT, aerobic capacity effect size, and HRQL, intervention and control groups were significantly different for Δ6MWT (Mdn = -1 vs 45.5, U=21.0 , p=.000, r=.74), aerobic capacity (Mdn = .04 vs .85, U=0.0, p=.008, r=.83), and HRQL (Mdn = .08 vs .32, U=28.5, p=.001, r=.60). The coordinates of the median for each variable are plotted in Figures 4 and 5 to provide quantitative support for the visual analysis.

Quantitative analysis of the Δ6MWT threshold that discriminated between intervention and control groups using ROC curves revealed the following sensitivity/specificity for the respective thresholds: 19 m, 94.4/83.3%, 32 m, 83.3/94.4%, and 48 m 44.4/100% (AUC = .935, p = .009, $CI_{95\%}$ .855, 1.015).

DISCUSSION

Few studies have investigated the Δ6MWT that is necessary to be considered clinically meaningful. There are numerous methods for determining this threshold, and because no single method is considered to be optimal,

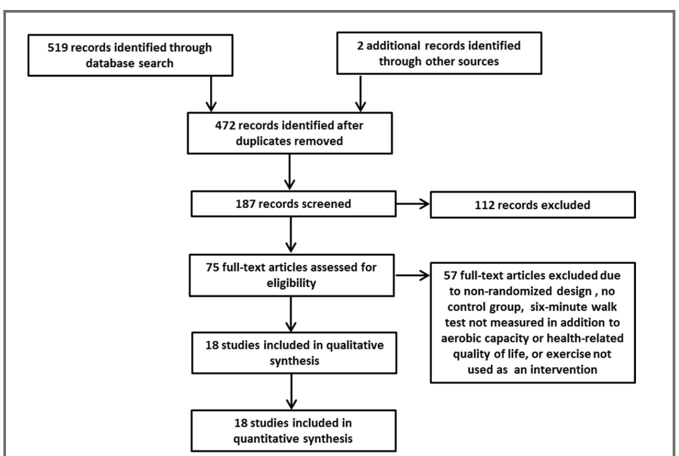
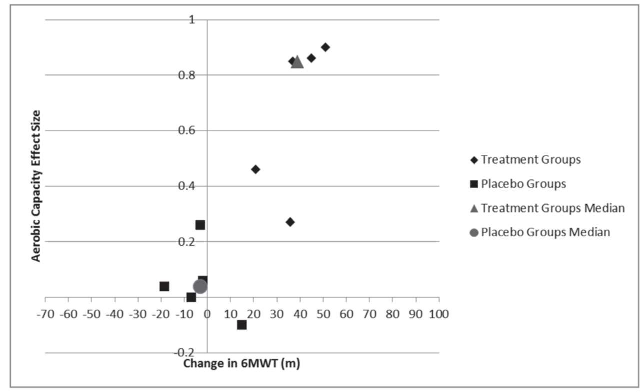


Figure 3. Search results for concurrent changes in exercise-based controlled trial.

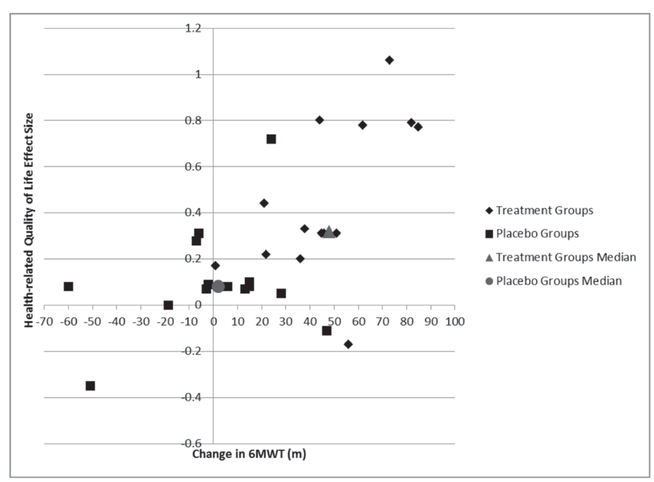


Abbreviation: 6MWT, six-minute walk test

Figure 4. Scatterplot of change in six-minute walk test distance and aerobic capacity within-group effect size.

triangulation of the threshold for clinically meaningful change is recommended.[15-17] Therefore, the purpose of the present review was to use several different methods for analysis of existing data, including the calculation of the range of MDD values based on reported ICCs, as well as using an ecologic analysis of RCT group-level data to determine what amount of change discriminates between exercise intervention and control groups. Each method used in the present review resulted in similar estimates of a threshold for clinically meaningful Δ6MWT and were consistent with those already reported in the literature.

The initial range of calculated $MDD_{95\%}$ values was quite large; however, the majority of $MDD_{95\%}$ values were between 20 m and 40 m. Two outliers were apparent, with one (Ingle et al)[28] likely due to the lengthy test-retest interval of one year that allows for innumerable confounding factors. With regard to the second outlier (Roul et al),[21] numerous variables were examined to determine their association with the calculated $MDD_{95\%}$ which is based on the ICC and sample standard deviation. Although there appeared to be no study or sample characteristic that may



Abbreviation: 6MWT, six-minute walk test

Figure 5. Scatterplot of change in six-minute walk test distance and health-related quality of life.

Table 2. Summary of Concurrent Changes in Exercise-based Controlled Trial Outcomes

Author, Year, Design, and Rigor	Subjects at Baseline	Intervention	Outcomes		
			6MWT (m)	Peak VO_2 (mL/kg/min)	MLHFQ/Other*
Tyni-Lenne et al 1996[6] M&HR =60%	Treatment 1: N=7 Age: 60(10) LVEF(%): 26(13) Treatment 2: N=7 Age: 57(10) LVEF(%): 29(9) Control: N=7 Age: 63(6) LVEF(%): 28(10)	3x/week for 8 weeks Treatment 1: 15 min of continuous one-legged knee extensor training using one leg at a time at 35% of absolute peak two-legged work load using a modified ergometer cycle Treatment 2: 15 min of continuous two-legged knee extensor training performed simultaneously at 65-75% of absolute peak two-legged work load using a modified ergometer cycle Control: habitual physical activity	Treatment 1: Pre: 469(39) Post: 525(38) Δ: 56 Treatment 2: Pre: 484(72) Post: 505(80) Δ: 21 Control: Pre: 467(58) Post: 460(65) Δ: -7 ES: 1.27 ES: 0.43	Treatment 1: Pre: 13.8(1.1) Post: 14.2(1.1) Δ: 0.4 ES_{w-g} 0.36 Treatment 2: Pre: 12.6(1.2) Post: 13.1(0.9) Δ: 0.5 ES_{w-g} 0.46 Control: NR	Treatment 1: Pre: 10(6) Post: 8(6) Δ: -2 ES_{w-g} 0.33 Treatment 2: Pre: 13(13) Post: 8(8) Δ: -5 ES_{w-g} 0.44 Control: Pre: 10(6) Post: 12(8) Δ: 2 ES_{w-g} 0.28 ES: 0.67 ES: 0.69 *Sickness Impact Profile
Tyni-Lenne et al 1997[30] M&HR=80%	Treatment N=8 Age: 62(10) LVEF(%): 30(5) NYHA-FC: 2.5(.5) Control N=8 Age: 63(10) LVEF(%): 28(10) NYHA-FC: 2.4(.5)	Treatment: 3x/week for ~25 min (warm-up, exercise, cool down) for 8 weeks for endurance training of leg muscles at 65-75% of absolute baseline peak work rate. Control: ordinary daily activities	Treatment: Pre: 466(85) Post: 503(72) Δ: 37 Control: Pre: 465(67) Post: 463(61) Δ: -2 ES: 0.51	Treatment: Pre: 10.0(2.4) Post: 12.0(2.3) Δ: 2.0 ES_{w-g} 0.85 Control: Pre: 8.9(1.8) Post: 8.8(1.8) Δ: -0.1 ES_{w-g} 0.06 ES: 1.41	Sickness Impact Profile NSR
Gottlieb et al 1999[31] M&HR =80%	Treatment: N=11 Age: 67(7) LVEF(%): 22(8) NYHA-FC: 2.7(.5) Control: N=14 Ages=64(10) LVEF(%)=25(10) NYHA-FC: 2.5(.5)	Treatment: 3x/week for 6 months supervised graded aerobic exercise program using Schwinn Airdyne bike and treadmill, following a Borg scale of 12-13 Control: usual care	Treatment: Pre: 408.4(38.7) Post: NR Δ: 44.8(59.1) Control: Pre: 393.5(48.8) Post: NR Δ:-18.6(40.8) . ES: 1.44	Treatment: Pre: 14.1(1.9) Post: NR Δ: 2.4(2.8) ES_{w-g} 0.86 Control: Pre: 14.0(2.9) Post: NR Δ: 0.1(2.6) ES_{w-g} 0.04 ES: 0.94	Treatment: Pre: 29(25) Post: 22(20) Δ: -7 ES_{w-g} 0.31 Control: Pre: 47(24) Post: NR Δ: NR
Tyni-Lenne et al 2001[32] M&HR=60%	Treatment: N=16 Ages= 63(9) M:F =1:1 LVEF(%)= 30(9) NYHA-FC: 2.3(.5) Control: N=8 Ages= 62(11) M:F = 5:3 LVEF(%)= 30(10) NYHA-FC: 2.3(.4)	Treatment: 3x/week for 60 min (warm-up, training, cool down) for 8 weeks for continuous repetitive muscle contraction using a thera-band for 2 x 25 repetitions in arm, leg and trunk muscles at a 70 bpm frequency using a Borg scale of 13-16 Control: ordinary daily activities	Treatment: Pre: 500(64) Post:555(59) Δ: 55 Control: Pre: 504(30) Post:504(27) Δ: 0 ES: 1.1	Treatment: Pre: 14.8(4.2) Post: 15.9(4.3) Δ: 1.1 ES_{w-g} 0.26 Control: Pre: 16.4(4.0) Post: 14.4(2.8) Δ: -2.0 ES_{w-g} -0.56 ES: 0.76	NSR

Pu et al 2001[33] M&HR=70%	Treatment: N=9 Age: 76.6(2.0) LVEF(%): 36.3(2.7) NYHA-FC: 2.2(.1) Control: N=7 Age: 76.6(2.4) LVEF(%): 36(2.9) NYHA-FC: 2.3(.2)	Treatment: 3x/week for 60 min (warm-up, exercise, stretching) for 10 weeks for progressive resistive training at 80% 1RM for 3 sets of 8 repetitions for upper and lower extremities Control: 2x/week for 60 min (stretching) for 10 weeks for "sham exercise"	Treatment: Pre: 372(42) Post:421(50) Δ: 49 Control: Pre: 365(42) Post:362(31) Δ: -3 ES: 1.22	Treatment: Pre: 15.46(1.04) Post: 15.08(1.6) Δ: -0.42 ES_{w-g} -0.27 Control: Pre: 14.40(1.13) Post: 14.75(0.9) Δ: 0.35 ES_{w-g} 0.34 ES: 0.71 (decline)	Not measured
McKelvie et al 2002[34] M&HR=90%	Treatment: N=90 Age: 64.8(10) LVEF(%): 28.2(8) NYHA-FC: 2.3(.4) Control: N=91 Age: 66.1(9.4) LVEF(%): 27.7(9) NYHA-FC: 2.3(.4)	Treatment: 2x/week for 3 months supervised 30 min aerobic exercise at 60-70% max HR using cycling, treadmill, and arm ergometry, and resistance training at 40-60% of 1RM for arm curls, knee extension, and leg press with a 1x/week walk at home. This was followed by a 3x/week for 9 months home-based training program of cycling, and free weights. Control: usual level of physical activity	Treatment: Pre: 434(66) Δ at 3 mos: 22(47) Control: Pre: 421(76) Δ at 3 mos: 15(48) ES: 0.10	NSR	Treatment: Pre: 32.5(23.7) Δ at 3 mos: -3.9(18.1) ES_{w-g} 0.22 Control: Pre: 28.6(20) Δ at 3 mos: -1.2(14.3) ES_{w-g} 0.08 ES: 0.12
Parnell et al 2002[35] M&HR=40%	Treatment: N=11 Age: 57(15) LVEF(%): 25(7) NYHA-FC: 2.4(.5) Control: N=10 Age: 53(11) LVEF(%)= 24(10) NYHA-FC: 2.3(.5)	Treatment: 3x/week for 30 min to 5-7x/week for 60 min for 8 weeks at 50-60% max HR while walking, using light hand weights and stationary cycling Control: continue with usual lifestyle	Treatment: Pre: 474(90) Post:547(113) Δ: 73 Control: Pre: 517(66) Post:515(92) Δ: -2 ES: 0.95	Not measured	Treatment: Pre: 46(23) Post: 24(17) Δ: -22 ES_{w-g} 1.06 Control: Pre: 30(23) Post: 28(23) Δ: -2 ES_{w-g} 0.09 ES: 0.87
Van den Berg-Emons et al 2004[36] M&HR=50%	Treatment: N=18 Age: 59(12) LVEF(%): 24(9) NYHA-FC: 2.4(.5) Control: N=16 Age: 59(11) LVEF(%)= 28(6) NYHA-FC: 2.4(.5)	Treatment: 2x/week for 60 min at 60% HRR aerobic walking and cycling for 3 months Control: Usual care	Treatment: Pre: 455(71) Post:501(96) Δ: 46 Control: Pre: 435(77) Post:448(84) Δ: 13 ES: 0.53	Treatment: Pre: 16.6(4.2) Post:17.8(4.0) Δ: 1.2 ES_{w-g} 0.29 Control: Pre: 16.1(3.8) Post:15.8(2.9) Δ: -0.3 ES_{w-g} -0.09 ES: 0.37	Treatment: Pre: 24.1(19.7) Post:18.1(18.5) Δ: -6 ES_{w-g} 0.31 Control: Pre: 27.5(13.9) Post: 26.5(12.7) Δ: -1 ES_{w-g} 0.07 ES: 0.29
Corvera-Tindel et al 2004[27] M&HR=70%	Treatment: N=42 Age: 64(10) LVEF(%): 29(9) NYHA-FC: 2.2(.4) Control: N=37 Age: 61(11) LVEF(%)= 25(9) NYHA-FC: 2.2(.4)	Treatment: 5x/week for 60 min at 65% max home walking program for 12 weeks Control: Usual care	Treatment: Pre: 372(74) Post:408(83) Δ: 36 Control: Pre: 388(76) Post:385(78) Δ: -3 ES: 0.52	Treatment: Pre: 14.3(3.7) Post:15.3(3.8) Δ: 1.0 ES_{w-g} 0.27 Control: Pre: 14.2(3.4) Post:15.2(4.1) Δ: 1.0 ES_{w-g} 0.26 ES: 0	Treatment: Pre: 6.4(1.4) Post:6.1(1.6) Δ: -0.3 ES_{w-g} 0.20 Control: Pre: 6.2(1.4) Post: 6.3(1.5) Δ: 0.1 ES_{w-g} 0.07 ES: 0.29 *HFSSI

Gary et al 2004[37] M&HR=50%	<u>Treatment:</u> N=32 Age: 67(11) LVEF(%): 54(7) NYHA-FC: 2.6(.5) <u>Control:</u> N=32 Age: 69(11) LVEF(%)= 57(9) NYHA-FC: 2.6(.5)	<u>Treatment:</u> 3x/week for 30 min at 60% max home walking program for 12 weeks with weekly supervision <u>Control:</u> 12 home-based education visits	<u>Treatment:</u> Pre: 256(112) Post: 318(97) Δ: 62 <u>Control:</u> Pre: 251(112) Post:223(124) Δ: 28 ES: 0.30	Not Measured	<u>Treatment:</u> Pre: 41(26) Post: 24(18) Δ: -17 ES_{w-g} 0.78 <u>Control:</u> Pre: 27(18) Post: 28(22) Δ: 1 ES_{w-g} 0.05 ES: 0.81
Yeh et al 2004[38] M&HR=70%	<u>Treatment:</u> N=15 Age: 6(12) LVEF(%): 24(7) NYHA-FC: 2.2(1) <u>Control:</u> N=15 Age: 61(14) LVEF(%)= 22(8) NYHA-FC: 2.3(.6)	<u>Treatment:</u> 2x/week for 60 min group-based Tai Chi <u>Control:</u> Usual care	<u>Treatment:</u> Pre: 327(106) Post:412(116) Δ: 85 <u>Control:</u> Pre: 340(117) Post:289(165) Δ: -51 ES: 1.22	<u>Treatment:</u> Pre: 10.5(3) Post:11.4(3) Δ: 0.9 ES_{w-g} 0.30 <u>Control:</u> Pre: 11.1(6) Post:10.4(6) Δ: -0.7 ES_{w-g} -0.12 ES: 0.34	<u>Treatment:</u> Pre: 43(21) Post: 26(23) Δ: -17 ES_{w-g} 0.77 <u>Control:</u> Pre: 44(20) Post: 52(25) Δ: 8 ES_{w-g} -0.35 ES: 1.22
Witham et al 2005[39] M&HR=70%	<u>Treatment:</u> N=41 Age: 80(6) LVEF(%): NSR NYHA-FC: 2.4(.5) <u>Control:</u> N=41 Ages: 81(4) LVEF(%): NSR NYHA-FC: 2.4(.5)	<u>Treatment:</u> 2x/week for 3 months supervised moderate intensity aerobic exercise and strengthening followed 2-3x/week for 3 months home-based exercise <u>Control:</u> usual care	<u>Treatment:</u> Pre: 261(117) Post: 262(110) Δ: 1 <u>Control:</u> Pre: 240(93) Post: 246(111) Δ: 6 ES: 0.05	Not measured	<u>Treatment:</u> Pre: 67(13) Post: 65(10) Δ: -2 ES_{w-g} 0.17 <u>Control:</u> Pre: 70(12) Post: 69(13) Δ: -1 ES_{w-g} 0.08 ES: 0.08 *CHQ
Austin et al 2005[40] M&HR=70%	<u>Treatment:</u> N=100 Age: 72(6) LVEF(%): NSR NYHA-FC: 2.5(.5) <u>Control:</u> N=100 Ages: 72(7) LVEF(%): NSR NYHA-FC: 2.5(.5)	<u>Treatment:</u> 2x/week for 8 weeks cardiac rehab program <u>Control:</u> standard care	<u>Treatment:</u> Pre: 276(119) Post: 320(112) Δ: 44 <u>Control:</u> Pre: 259(118) Post: 253(132) Δ: -6 ES: 0.42	Not measured	<u>Treatment:</u> Pre: 41(25.5) Post: 22.9(17.9) Δ: -18.1 ES_{w-g} 0.80 <u>Control:</u> Pre: 44.3(24.5) Post: 36.9(24) Δ: -7.4 ES_{w-g} 0.31 ES: 0.43
Jonsdottir et al 2006[41] M&HR=60%	<u>Treatment:</u> N=21 Age: 68(7) LVEF(%): 42(14) NYHA-FC: NR <u>Control:</u> N=22 Ages: 69(5) LVEF(%): 41(14) NYHA-FC: NR	<u>Treatment:</u> 2x/week for 5 months of 15 min moderate intensity aerobic exercise and 20 min low intensity resistance exercise <u>Control:</u> Usual care	<u>Treatment:</u> Pre: 489(75) Post:526(72) Δ: 37 <u>Control:</u> Pre: 489(66) Post:495(66) Δ: 6 ES: 0.44	<u>Treatment:</u> Pre: 14.9(3) Post: 14.8(3) Δ: -0.1 ES_{w-g} -0.03 <u>Control:</u> Pre: 16.3(3) Post:16.9(4) Δ: 0.6 ES_{w-g} 0.17 ES: 0.23 (decline)	NSR

Brubaker et al 2009[42] M&HR=70%	Treatment: N=30 Age: 70(5) LVEF(%): 32(9) NYHA-FC: 2.5(.5) Control: N=29 Ages: 70(6) LVEF(%): 30(9) NYHA-FC: 2.5(.5)	Treatment: 3x/week for 16 weeks of 60 min moderate intensity aerobic exercise Control: Attention control	Treatment: Pre: 406(166) Post:462(164) Δ: 56 Control: Pre: 376(214) Post:423(128) Δ: 47 ES: 0.05	Treatment: Pre: 14.1(3.3) Post: 13.9(4.4) Δ: -0.2 ES_{w-g} -0.05 Control: Pre: 13.5(3.2) Post:13.6(3.8) Δ: 0.1 ES_{w-g} 0.03 ES: 0.09 (decline)	Treatment: Pre: 39.9(23) Post: 44.1(26) Δ: 4.2 ES_{w-g} -0.17 Control: Pre: 35.3(23) Post: 37.9(23) Δ: 2.6 ES_{w-g} -0.11 ES: 0.07
Davidson et al 2010[43] M&HR=70%	Treatment: N=53 Age: 72(NR) LVEF(%): NR NYHA-FC: 2.6(.5) Control: N=52 Ages: 74(NR) LVEF(%): NR NYHA-FC: 2.7(.5)	Treatment: 1x/week for 12 weeks of 30 min endurance exercise Control: Usual care	Treatment: Pre: 279(111) Post:361(132) Δ: 82 Control: Pre: 251(113) Post: 275(107) Δ: 24 ES: 0.52	Not Measured	Treatment: Pre: 44.1(23.7) Post: 27.9(12.5) Δ: -16.2 ES_{w-g} 0.79 Control: Pre: 53.4(26.4) Post: 36.9(16.2) Δ: -16.5 ES_{w-g} 0.72 ES: 0.01
Kitzman et al 2010[44] M&HR=70%	Treatment: N=26 Age: 70(5) LVEF(%): NR NYHA-FC: 2.2(.4) Control: N=27 Ages: 70(6) LVEF(%): NR NYHA-FC: 2.4(.5)	Treatment: 3x/week for 16 weeks of 60 min moderate intensity aerobic exercise Control: Attention control	Treatment: Pre: 455(68) Post:506(53) Δ: 51 Control: Pre: 430(116) Post:445(125) Δ: 15 ES: 0.38	Treatment: Pre: 13.8(2.5) Post: 16.1(2.6) Δ: 2.3 ES_{w-g} 0.90 Control: Pre: 12.8(2.6) Post:12.5(3.4) Δ: -0.3 ES_{w-g} -0.10 ES: 1.02	Treatment: Pre: 32(20) Post: 25(24) Δ: -7 ES_{w-g} 0.31 Control: Pre: 25(22) Post: 27(19) Δ: 2 ES_{w-g} 0.10 ES: 0.43
Gary et al 2010[45] M&HR=100%	Treatment: N=17 Age: NSR LVEF(%):NSR NYHA-FC: NSR Control: N=18 Ages: NSR LVEF(%):NSR NYHA-FC: NSR	Treatment: 3x/week for 12 weeks of 30-60 min home-based walking program and 3 sessions of Cognitive Behavioral Therapy Control: Usual care	Treatment: Pre: 363(100) Post:401(103) Δ: 38 Control: Pre: 347(166) Post: 287(125) Δ: -60 ES: 0.72	Not Measured	Treatment: Pre: 34.3(23.7) Post: 27.3(16) Δ: -7 ES_{w-g} 0.33 Control: Pre: 28.1(17.3) Post: 26.4(23.7) Δ: -1.7 ES_{w-g} 0.08 ES: 0.26

Abbreviations: M&HR, Medlicott and Harris rating scale of methodological rigor; LVEF, left ventricular ejection fraction; HF, heart failure; NR, not reported; 6MWT, six-minute walk test; VO_2, oxygen consumption; HRQL, health-related quality of life; ES_{w-g}, within-group effect size assuming correlation of 0.5; ES, between-group effect size; NYHA-FC, New York Heart Association functional class

have been responsible for the relatively low ICC reported by Roul et al,[21] this was considered to be an outlier given that the $MDD_{95\%}$ was nearly 3 times greater than the others. With these outliers removed, the mean $MDD_{95\%}$ was 43 m. This suggests that in order to have a reasonable degree of confidence that a Δ6MWT was not due to test-retest variability or measurement error, the amount of change must exceed 43 m. This is consistent with the $MDD_{95\%}$ calculation by Pinna et al[8] and with the MCID of 40 m for those subjects who reported clinical improvement over a 4-week period in the study by O'Keefe et al.[10]

With regard to the ecologic analysis of group-level data for subjects enrolled in exercise-based RCTs, the median change in 6MWT for intervention groups was 45.5 m compared to -1 m for the placebo groups. In plotting the individual group data points against the effect sizes for the concurrent changes in aerobic capacity and HRQL, visual analysis of the scatterplots suggest that only the intervention groups had a Δ6MWT of greater than 20 m. However, moderate effect sizes in aerobic capacity and HRQL did not emerge until 40 m. Additionally, the use of ROC curves to quantify the optimal Δ6MWT threshold to discriminate between exercise-based intervention and control groups revealed that, when biasing the threshold toward 100% specificity (and therefore ensuring that true clinical change has occurred), the optimal threshold was

48 m. This value aligns very well with the mean $MDD_{95\%}$ (an index of measurement error) of 43 m calculated in the first analysis. Therefore, a threshold of approximately 45 m should be used for determining clinically meaningful change.

This proposed clinically meaningful threshold of 45 m based on the present review is consistent with Pinna et al[8] and O'Keefe et al,[10] and because of the good alignment of the thresholds determined by multiple methods used in the present review and those of two other studies, confidence in this threshold can be fairly high. However, no study to date has prospectively evaluated and reported different methods of determining clinically meaningful change in individuals with CHF, which would further reveal how these different methods relate to one another. Therefore, future studies should incorporate several different methods for determining clinically meaningful change in the same sample to help further elucidate advantages and disadvantages of different methods for determining clinically meaningful changes, and whether good alignment of meaningful change threshold estimates are consistently observed.

There are several limitations to the present analyses. Calculation of the $MDD_{95\%}$ values for several studies required use of the baseline standard deviation for the entire sample because it was not reported for the subsample in whom the ICC was calculated. However, doing so did not reveal any consistent effect because the range of calculated $MDD_{95\%}$ values from those 4 studies were similar to the others.

A potential limitation of the analysis based on the literature search for concurrent changes in exercise-based RCT outcomes is the underlying assumption that the 6MWT is in fact associated with these variables and that these variables are responsive to exercise interventions. However, previous research supports this assumption,[13,14,20,48-50] and changes in exercise capacity and/or HRQL likely represent meaningful changes resulting from an individual's participation in exercise interventions.

CONCLUSIONS

The present review used two different literature searches based on two different constructs for determining a clinically meaningful change threshold for the 6MWT. A change of 45 m in the 6MWT exceeds measurement error and is associated with moderate aerobic capacity and HRQL within-group effect sizes reported by exercise-based RCTs.

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