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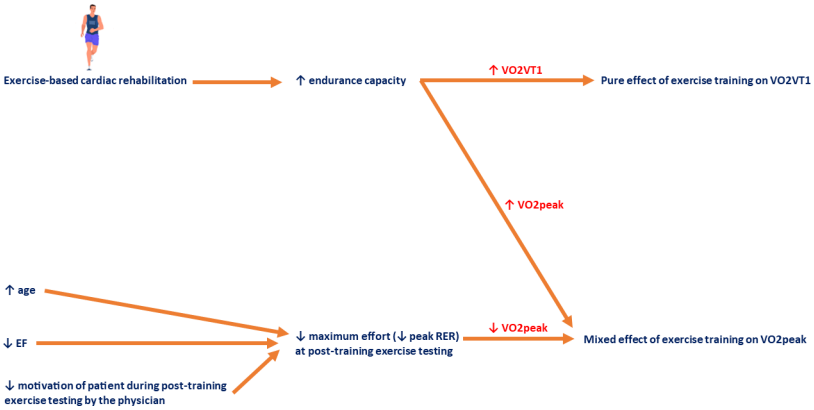

Title: Ergophysiological evaluation of heart failure patients with reduced ejection fraction undergoing exercise-based cardiac rehabilitation: A systematic review and meta-analysis.

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ABSTRACT

Background: This systematic review and meta-analysis aims to explore in heart failure (HF) patients with reduced ejection fraction (EF) undergoing exercise-based cardiac rehabilitation: 1) the comparison of temporal changes between peak oxygen uptake (VO2peak) and first ventilatory threshold (VO2VT1), 2) the association of VO2peak and VO2VT1 changes with physiological factors and 3) the differential effects of continuous aerobic exercise (CAE) and interval training (IT) on VO2peak and VO2VT1.

Methods: A systematic literature search was conducted in PubMed, CENTRAL, and Scopus. Inclusion criteria: 1) original research articles using exercise-based cardiac rehabilitation, 2) stable HF patients with reduced EF, 3) available values of VO2peak and VO2VT1 (in mL/kg/min) for both baseline and after exercise training with comparison between these time points.

Results: Among the 30 eligible trials, 24 used CAE, 5 IT and one CAE and IT. Multivariable meta-regression with duration of exercise training and percentage of males as independent variables and the change in VO2peak as dependent variable showed that the change in VO2peak was negatively associated with duration of exercise training (coefficient= -0.061, p=0.027), implying the possible existence of a waning effect of exercise training on VO2peak in the long term. Multivariable meta-regression demonstrated that both age (coefficient= -0.140, p<0.001) and EF (coefficient=0.149, p<0.001) could predict the change in VO2VT1, whereas only age (coefficient= -0.095, p=0.022), but not EF (coefficient=0.082, p=0.100) could predict the change in VO2peak. The post-training peak respiratory exchange ratio, as an index of maximum effort during exercise testing, correlated positively with the change in VO2peak (coefficient=0.021, p=0.044). The exercise-induced changes of VO2peak (p=0.438) and VO2VT1 (p=0.474) did not differ between CAE and IT.

Conclusions: The improvement of endurance capacity during cardiac rehabilitation may be detected more accurately with the assessment of VO2VT1 rather than VO2peak.

Keywords: heart failure, cardiac rehabilitation, exercise training, ventilatory threshold, cardiopulmonary exercise testing.

1. Introduction

Exercise-based cardiac rehabilitation has a central role in the management of patients with chronic heart failure (HF) aiming at improving functional capacity.[1] The most common types of exercise training used for enhancement of functional capacity in cardiac rehabilitation are continuous aerobic exercise (CAE) and interval training (IT). Among patients with HF, exercise prescription is undoubtfully most challenging in patients with reduced ejection fraction (EF) (i.e. EF<40%), due to the higher risk of exercise-related cardiac events.[2]

The rationale underlying exercise prescription is the maintenance of benefit-risk balance, since functional capacity should be improved to the maximum extent without excess cardiac risk.[1,3]

The benefit of an exercise programme in the context of cardiac rehabilitation can be assessed more accurately through spiroergometric evaluation.[4] Serial measurements of oxygen uptake should be expressed in mL/kg/min to avoid the confounding effect of altered muscular mass.[5] The spiroergometric parameter that is most commonly used for this reason is peak oxygen uptake (VO2peak), whereas oxygen uptake at the first (VO2VT1) or second (VO2VT2) ventilatory threshold has not been widely applied as an end point of efficacy of cardiac rehabilitation in routine clinical practice.[1,3] However, convincing evidence suggests that threshold measurements may be highly useful in the assessment of improvement of endurance capacity as a result of an exercise training programme. Specifically, endurance exercise training in athletes can induce an early increase in VO2peak with subsequent levelling off or even no significant change in VO2peak during a macrocycle, whereas VO2VT1 and VO2VT2 appear to rise continuously from the beginning of exercise training and even when VO2peak has reached a plateau.[6,7] Moreover, peak performance of athletes in endurance events is more strongly related to VO2VT1 or VO2VT2, rather than to VO2peak.[6,8]

On the other hand, the characteristic of exercise programme that mostly influences the risk of exercise-related cardiac events is exercise intensity.[9] This risk may increase considerably at exercise intensities above VT1 and even more above VT2, due to the excessive upregulation

not only of sympathetic nervous system with potential implications for arrhythmogenesis, but also of cardiac output with resultant increased myocardial work.[10] The VT1 is possibly the most traditionally established upper limit of exercise intensity for exercise prescription in patients with HF, especially those with New York Heart Association (NYHA) class 3, whereas VT2 has not been widely applied for this reason yet.[11] Furthermore, VT2 is often not achieved in individuals with decreased functional capacity, as is the case with HF.[11] In this respect, assessment of VT1 in patients with HF attending a cardiac rehabilitation programme may be more relevant than VT2 for clinical decision making.[11,12]

Therefore, this systematic review and meta-analysis aims to explore in HF patients with reduced EF undergoing exercise-based cardiac rehabilitation: 1) the comparison of temporal changes between VO2peak and VO2VT1, 2) the association of VO2peak and VO2VT1 changes with physiological factors and 3) the differential effects of CAE and IT on VO2peak and VO2VT1. To our knowledge, no previous article has addressed these issues so far.

2. Methods

The study protocol has been registered to the international Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020198257). The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were followed.[13]

2.1. Inclusion criteria

Studies were included when all the following criteria were fulfilled:

a) Original research articles published in English.

b) All participants were adults and had stable HF with reduced EF (i.e. < 40%).

c) Studies using treadmill or cycle ergometers.

d) The intervention was exercise-based cardiac rehabilitation, involving CAE or IT.

e) Available values of both VO2peak and VO2VT1 (in mL/kg/min) at baseline and post-intervention.

f) Comparison of both VO2peak and VO2VT1 (in mL/kg/min) between baseline and after exercise training.

2.2. Exclusion criteria

a) Patients with implanted left ventricular assist device.

b) Patients evaluated within one year after acute coronary syndrome, coronary intervention or cardiac surgery.

c) Not the same time duration of cardiac rehabilitation for all participants.

d) Cardiac rehabilitation including inspiratory muscle training.

2.3. Literature search

Eligible studies for inclusion were identified by searching electronic databases and scanning reference lists of included articles and pertinent reviews. The systematic search was applied to MEDLINE (via PubMed), CENTRAL and Scopus (from inception to 1 September 2022). The following algorithm was used to search for all relevant studies: (cardiac rehabilitation OR heart failure) AND (threshold OR peak oxygen). Generic search terms were used in the algorithm to ensure the maximal sensitivity of the search.

2.4. Study Selection and Data Extraction

Screening of titles, abstracts, and full texts, as well as data extraction from included studies were performed independently by 2 researchers (GAC, MAC). Disagreements between the researchers were resolved by consensus. If no agreement could be reached, a third researcher (GM) decided. From each study, information was extracted on the first author, publication year, study design, Country, number of patients, age, percentage of males, HF aetiology, NYHA class, EF, HF treatments, comorbidities, rhythm, type of ergometer, phase of cardiac rehabilitation, type of exercise training, study duration and values for baseline and after exercise training for VO2peak, VO2VT1, peak power output and peak respiratory exchange ratio (RER).

2.5. Risk of bias assessment

The Cochrane tools RoB 2 and ROBINS-I were used to assess risk of bias in randomized and non-randomized clinical trials, respectively.[14,15]

2.6. Statistical analysis

Quantitative analysis was carried out to assess the exercise training-induced changes in VO2peak and VO2VT1. When the 95% confidence interval or the respective standard error of the exercise training-induced changes in VO2peak and VO2VT1 were not reported, we calculated them indirectly using the reported p values of the comparisons between post-training and baseline. The overwhelming majority of studies with a control group in this systematic review did not report the necessary information for the comparisons of either within control group or between the active and control groups (relevant information was only reported in two studies on VO2peak and VO2VT1 change, respectively). Hence, a meta-analysis assessing the comparison of outcomes between the active and control groups could not be performed. Instead, we performed inverse-variance random-effects meta-analysis using the DerSimonian and Laird estimator to estimate the overall weighted mean VO2peak and VO2VT1 changes and the corresponding 95% CI. We carried out random-effects meta-regression to investigate the exercise training-induced changes in VO2peak and VO2VT1 with other parameters of interest. We used Wald Chi-Squared Test as a model coefficient test. Residual heterogeneity was assessed with I^2, which is the ratio of true heterogeneity to total observed variation. Values of $I^2 > 75\%$ indicate considerable heterogeneity. A two-tailed p value < 0.05 was considered statistically significant. All statistical analyses were performed using the software IBM SPSS Statistics 29.0.

3. Results

3.1. Study characteristics

The process of study selection is detailed in the flow diagram provided in Figure 1. Thirty studies met the eligibility criteria and were included in the Systematic Review (Table 1).

With regard to study design, 20 randomized clinical trials (67%), 1 cross-over randomized clinical trial (3%), 4 non-randomized clinical trials with a control group (13%) and 5 non-randomized clinical trials without a control group (17%) were considered eligible. ~~The~~

~~publication year of studies included in the analysis extended from 1996 to 2022, with most studies being published in 2012 (n=5, 17%). The majority of studies were conducted in Europe (n=21, 70%).~~

3.1.1. Participants

The total number of HF patients undergoing cardiac rehabilitation was 839. The mean age of the studies ranged from 44 to 72 years. The percentage of participants that completed the cardiac rehabilitation programme ranged from 81 to 100%. The majority of studies included both males and females with predominance of males, except for one study with equal numbers of males and females and one study with slightly greater number of females, whereas 5 studies included only males.[16,19,22,25,29,33,38] Among the 26 studies with available data on HF aetiology, at least 50% of patients had HF of ischaemic aetiology in 16 studies (62%). The aetiology of non-ischaemic HF was dilated cardiomyopathy, apart from two studies that also included hypertensive cardiomyopathy and valvular heart disease.[37,39] With regard to NYHA class, available data were for 26 studies. All of them included HF patients with NYHA class 2. Apart from 3 studies, there were patients with NYHA 3.[16,27,35] Three studies included patients with NYHA 1 and 2 studies patients with NYHA 4.[16,18,22,27,35] Left ventricular EF ranged from 17 to 36%. The proportions of studies with at least 50% of participants taking HF medications were: 100% for angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers, 77% for b-blockers, 17% for aldosterone receptor antagonists, 73% for loop diuretics and 32% for digitalis. No study included participants taking angiotensin receptor neprilysin inhibitor or sodium-glucose cotransporter-2 inhibitors. In all studies the majority of participants were in sinus rhythm, apart from one study that included only individuals with atrial fibrillation.[16]

3.1.2 Type of intervention

Intervention in all eligible studies was endurance exercise training and in 9 studies it was supplemented with resistance exercise training. The most common type of endurance exercise training was CAE (n= 22 moderate intensity, n= 2 low intensity), whereas for 5 studies was IT and for one study a combination of CAE and IT. The median (minimum-maximum)

duration of exercise training was 12 (3-56) weeks. In all studies cardiac rehabilitation was of phase 3 (i.e. outpatient cardiac rehabilitation programme that is intensive and structured), apart from two studies using phase 4 cardiac rehabilitation (i.e. community programme focusing on long-term maintenance of physical activity).[18,40]

3.1.3 Comparator

When the comparator group was available, it usually referred to maintenance of previous activity levels and less commonly CAE (when the active group was subjected to IT).

3.1.4 Outcome Definition and Method of Assessment

The main outcome was effect of exercise training on VO2peak and VO2VT1 in HF patients with reduced EF undergoing cardiac rehabilitation. The most common type of ergometer used in cardiopulmonary exercise testing was cycle, while 9 studies used treadmill.

3.2. Outcomes of included studies

3.2.1. The comparison of temporal changes between VO2peak and VO2VT1

Among the 39 exercise interventions, meta-analysis was feasible in 24 interventions for the change in VO2peak and in 24 interventions for the change in VO2VT1. The change in VO2peak ranged from 0.2 to 5.3 mL/kg/min with a weighted mean change of 2.8 (CI: 2.2, 3.3) mL/kg/min ($p<0.001$) and $I^2 = 76.2\%$ (Figure 2). The change in VO2VT1 ranged from -1.1 to 6.2 mL/kg/min with a weighted mean change of 2.1 (CI: 1.7, 2.6) mL/kg/min ($p<0.001$) and $I^2 = 76.2\%$ (Figure 3). ~~The results did not differ between CAE and IT.~~ The difference between the changes in VO2peak and VO2VT1 ranged from -2.6 to 2.6 mL/kg/min. Regarding the 20 exercise interventions that used cycle ergometer with available data for peak power output, the median (minimum-maximum) exercise training-induced increase in peak power output was 21 (2-38) Watts.

The minimum duration of CAE that was reported to significantly increase VO2peak and VO2VT1 was 4 weeks.[23,36] ~~The maximum duration of CAE-induced increases in VO2peak and VO2VT1 was demonstrated to be 56 weeks.[18]~~ The minimum duration of IT that was reported to significantly increase VO2peak and VO2VT1 was 3 weeks.[32] ~~The maximum~~

~~duration of IT-induced increases in VO2peak was 24 weeks, whereas for VO2VT1 was 16 weeks.~~[42,43]

Five studies reported significant increases in VO2VT1, without significant increases in VO2peak.[19,22,40-42] All these studies used CAE and the duration of exercise training was between 8 and 48 weeks. Five studies reported significant increases in VO2peak, without significant increases in VO2VT1.[24,28,39,43,45] All these studies used CAE and the duration of exercise training was between 8 and 16 weeks, apart from one study that used IT of 24 weeks. The two studies that found no significant changes in both VO2peak and VO2VT1 used CAE.[25,35] Among these studies, one used low intensity CAE with duration of 12 weeks and the other study used moderate intensity CAE for 8 weeks.

The exercise training-induced change in VO2peak tended to be negatively associated with the duration of exercise training (coefficient= -0.047, p=0.070, I^2=71.8%). This association was stronger for studies using CAE (coefficient= -0.055, p=0.054, I^2=74.6%). Further adjustment for sex was deemed appropriate, since the change in VO2peak was higher in studies with percentage of males below the median (i.e. 81%) (coefficient= 1.260, p=0.004, I^2=71.8%), indicating superior adaptations from endurance exercise training in females, as previously reported.[46] Thus, aiming to adjust for sex, we performed multivariable meta-regression with duration of exercise training (coefficient= -0.061, p=0.027) and percentage of males (coefficient= -0.014, p=0.245) as independent variables and the change in VO2peak as dependent variable (Wald Chi-Squared Test: p=0.036, I^2=62.6%). Thus, only duration of exercise training could significantly predict the change in VO2peak, implying the possible existence of a waning effect of exercise training on VO2peak. However, the exercise training-induced change in VO2VT1 was not associated with the duration of exercise training (coefficient= -0.015, p=0.524, I^2=74.4%).

3.2.2. Association of the changes in VO2peak and VO2VT1 with physiological factors

We investigated whether the exercise training-induced changes in spiroergometric parameters could be predicted by the well-known modifiers of functional capacity in HF, the age and EF. Multivariable meta-regression demonstrated that both age (coefficient= -0.140, p<0.001) and EF (coefficient=0.149, p<0.001) could significantly predict the change in VO2VT1 (Wald Chi-Squared Test: p<0.001, I^2=53.6%) (Supplementary Figure 1A,B). However, multivariable meta-regression showed that only age (coefficient= -0.095, p=0.022), but not EF (coefficient=0.082, p=0.100) could predict the change in VO2peak (Wald Chi-Squared Test: p=0.026, I^2=65.5%) (Supplementary Figure 1C,D). After performing multivariable meta-regression to predict the changes in VO2VT1 or VO2peak, when we chose as independent variables the corresponding categorical variables of age and EF (i.e. above or below the median), similar results were obtained with the above-mentioned analyses.

We attempted to elucidate whether the normally expected positive association between the exercise-induced change in VO2peak and change in VO2VT1 weakened in individuals that were older or with lower EF, since these frail patients were less likely to achieve maximal effort during exercise testing resulting in lower post-training VO2peak than would be expected from exercise training. Thus, when we investigated only the studies with mean age below the median age of all studies (i.e. 55 years), the change in VO2peak correlated positively with the change in VO2VT1 (coefficient=0.646, p<0.001, I^2=45.9%) (Figure 4A). Among the studies with mean age above the median age of all studies, the change in VO2peak was not significantly associated with the change in VO2VT1 (coefficient=0.178, p=0.707, I^2=21.4%) (Figure 4B). Moreover, when we investigated only the studies with mean EF above the median EF of all studies (i.e. 29%), the change in VO2peak correlated positively with the change in VO2VT1 (coefficient=0.892, p<0.001, I^2=39.1%) (Figure 4C), whereas among the studies with mean EF below the median EF of all studies, the change in VO2peak was not significantly associated with the change in VO2VT1 (coefficient=0.118, p=0.633, I^2=16.4%) (Figure 4D).

The post-training peak RER, as an index of maximum effort during exercise testing, correlated positively with the change in VO2peak (coefficient=0.021, p=0.044, I^2=85.4%) (Figure 5).

3.2.3 The differential effects of CAE and IT on VO2peak and VO2VT1

Among the CAE exercise interventions, the change in VO2peak ranged from 0.2 to 5.3 mL/kg/min with a weighted mean change of 2.8 (CI: 2.2, 3.5) mL/kg/min (p<0.001) (Figure 2). The change in VO2VT1 ranged from -1.1 to 6.2 mL/kg/min with a weighted mean change of 2.2 (CI: 1.7, 2.8) mL/kg/min (p<0.001) (Figure 3). The difference between the changes in VO2peak and VO2VT1 ranged from -2.6 to 2.6 mL/kg/min.

Among the IT exercise interventions, the change in VO2peak ranged from 1.9 to 2.9 mL/kg/min with a weighted mean change of 2.2 (CI: 1.5, 2.9) mL/kg/min (p<0.001) (Figure 2). The change in VO2VT1 ranged from 1.1 to 2.9 mL/kg/min with a weighted mean change of 1.7 (CI: 1.2, 2.3) mL/kg/min (p<0.001) (Figure 3). The difference between the changes in VO2peak and VO2VT1 was ranged from -0.4 to 1.7 mL/kg/min.

Results of meta-regression indicated that exercise-induced changes of VO2peak (p=0.438, I^2=74.8%) and VO2VT1 (p=0.474, I^2=74.4%) did not differ between CAE and IT.

Among the two studies comparing the responses of VO2peak and VO2VT1 between IT and CAE, nonsignificant differences were reported.[25,42] ~~These two studies reported significant increases in both VO2peak and VO2VT1 after IT.[25,42] However, both studies found non-significant changes in VO2peak with CAE.[25,42] With regard to VO2VT1, only the one study using CAE of 16-week duration demonstrated an increase in VO2VT1, whereas the other study using CAE of 8-week duration did not show any significant change of VO2VT1.[25,42]~~

3.3. Risk of bias assessment

Based on the risk of bias assessment, the majority of the randomized clinical trials had low overall risk of bias, whereas the remainder had some concerns due to bias caused by deviations from the intended interventions (Supplementary Table 1). Additionally, the majority

of the non-randomized clinical trials had low overall risk of bias, apart from 3 studies that were characterized by moderate risk of bias due to deviations from the intended interventions (Supplementary Table 2).

4. Discussion

The key findings of the present study are: 1) the improvement of endurance capacity of HF patients with reduced EF undergoing exercise-based cardiac rehabilitation may be detected more accurately through the assessment of VO2VT1, rather than VO2peak, since the exercise training-induced change in VO2peak was greatly influenced by the level of maximum effort at post-training exercise testing and slightly waned in the long term of cardiac rehabilitation, as opposed to a more sustained or even gradually augmented improvement of VO2VT1 during the whole process of cardiac rehabilitation. 2) the changes in VO2peak and VO2VT1 did not differ between CAE and IT.

4.1. Temporal changes in VO2peak and VO2VT1

The available data suggest that the minimum duration of exercise-based cardiac rehabilitation that has been shown to increase both VO2peak and VO2VT1 in HF patients with reduced EF appears to be 4 weeks for CAE and 3 weeks for IT.[23,32,36] Therefore, the earliest spiroergometric reassessment of HF patients with reduced EF could be reasonably performed after approximately 4 weeks of endurance training to confirm any improvement of functional capacity.

The present study demonstrated that the improvement in endurance capacity of HF patients at 12-24 weeks of CAE was mainly accompanied by an increase in VO2VT1, rather than VO2peak. Therefore, the improvement in endurance capacity of HF patients subjected to CAE, which represents the most common type of exercise training during cardiac rehabilitation of HF patients, can be assessed more accurately through the measurement of VO2VT1 at the end of phase 3, which is the classic stage of cardiac rehabilitation, or during the maintenance phase 4. Although VO2peak can increase early in HF patients undergoing exercise training, it

has been previously found to level off after the first 12-16 weeks, as opposed to the continuing increase in VO2VT1 during a period of 26 weeks of exercise training.[47,48] Consistently, the results of the present study imply for the first time that the exercise training-induced improvement of VO2peak in HF patients with reduced EF may slightly wane in the long term of cardiac rehabilitation, as opposed to the accompanied improvement of VO2VT1, that could be more sustained or even gradually augmented during the whole process of cardiac rehabilitation, including phase 4. In this respect, VO2VT1 may reflect more accurately than VO2peak the continuing improvement of endurance capacity of HF patients during the whole process of cardiac rehabilitation, especially in the case of CAE.

Notably, the few studies using CAE that reported significant increases only in VO2peak, but not in VO2VT1, were characterized by considerable dropout rates.[28,39,45] Taking into account that completers of a cardiac rehabilitation programme appear to be more motivated to engage in exercise and possibly can achieve higher levels of maximum effort during exercise testing than non-completers, the high dropout rates of the studies that reported significant increases only in VO2peak, but not in VO2VT1, may lead to analysis of a highly selected subgroup of patients with increased levels of maximum effort during follow up exercise testing and thus increased probability to experience an improvement in VO2peak.[49] Therefore, the reported increase in VO2peak of these studies may represent a serial increase in maximum effort during follow up exercise tests, rather than a true improvement in maximum aerobic capacity.

4.2. Association of changes in VO2peak and VO2VT1 with physiological factors

The current study demonstrated that the exercise training-induced change in VO2VT1 of HF patients with reduced EF could be more evidently predicted by the well-known modifiers of functional capacity in HF, the age and EF, compared to the change in VO2peak. Even more, the normally expected positive association between the changes in VO2peak and VO2VT1 disappeared in studies including individuals that were older and with lower EF. These frail patients were less likely to achieve maximal effort during exercise testing leading to lower post-

training VO2peak than would be expected from exercise training. Indeed, the exercise training-induced change in VO2peak was demonstrated to correlate positively with the level of maximum effort at post-training exercise testing, as estimated by post-training peak RER. In this regard, the change in VO2VT1 appears to reflect more accurately the exercise training-induced physiological responses and as submaximal spiroergometric parameter may not be influenced by the magnitude of effort during exercise testing, provided that VT1 is achieved, which is almost always the case on serial exercise testing during cardiac rehabilitation. The latter issue could be more relevant in HF patients with reduced EF, in whom the ability to achieve maximum effort during exercise testing is profoundly attenuated. Notably, serial reassessment of VO2VT1 is possibly more feasible and accurate compared to VO2peak, since VO2VT1 is almost always achieved on serial exercise testing, even on submaximal testing, as opposed to VO2peak, the measurement of which greatly depends on patient motivation and could be prone to investigator bias.

4.3. Ergophysiological basis of the changes in VO2peak and VO2VT1

The lower ability of the change in VO2peak compared to the change in VO2VT1 to reflect the exercise training-induced improvement in endurance capacity of HF patients could be attributed not only to the great reliance of VO2peak on the magnitude of effort during exercise testing, but also to the dependence of VO2VT1 on more physiological components of functional capacity than VO2peak. Specifically, taking into account that the main limiting factor of VO2peak is central, rather than peripheral, the improvement in VO2peak of HF patients in the early stages of cardiac rehabilitation is possibly caused more by the augmentation of maximum cardiac output, rather than any considerable improvement of mitochondria's ability to consume oxygen.[6] On the other hand, VO2VT1 equates to the product of VO2peak with the percent of VO2peak that can be maintained during prolonged exercise, the latter of which is linked primarily to muscular adaptations resulting from prolonged training.[6] Thus, the continuing increase in VO2VT1 of HF patients during the whole process of cardiac rehabilitation may be attributed to the improvement of both central and peripheral factors,

indicating that changes in VO2VT1 can reflect more thoroughly the underlying ergophysiological mechanisms of the cardiac rehabilitation-induced improvement in endurance capacity.[6]

4.4. Utility of VO2VT1 in exercise prescription

Importantly, the detection of any increase in VO2VT1 is expected to be more closely associated with the accompanied improvement of patients' functional status in everyday life compared to any increase in VO2peak.[3,4] Indeed, upregulation of VO2VT1 is linked with an increased upper limit of exercise intensity that can be performed in the aerobic zone without undue dyspnoea.[3,4] On the other hand, VO2peak represents the maximum aerobic capacity that is classically reproduced only experimentally and is not actually reached in everyday activities of patients with HF.[3,4] In this context, future studies can confirm these considerations evaluating the association of the improvement of indices of quality of life in HF patients with reduced EF undergoing cardiac rehabilitation with the changes in VO2peak and VO2VT1.

With regard to reassessment of VO2VT1 in HF patients during cardiac rehabilitation, the documentation of no increase in VO2VT1 after a period of exercise training compared to baseline can reasonably indicate that training programme is ineffective or the existence of overtraining. Even more, the detection of any upregulation of VT1 has an additional clinical significance, as it can guide exercise prescription in CAE to revise the recommended intensity of exercise to a higher level equal to the new VT1.[3,4] Therefore, the continuing reassessment of VO2VT1 in HF patients during cardiac rehabilitation not only can detect any improvement in endurance capacity more accurately, but also can influence the prescribed intensity of CAE in a dynamic manner making exercise prescription more efficient.[3,4]

4.5. The differential effects of CAE and IT on VO2peak and VO2VT1

The current study showed that the exercise training-induced changes in VO2peak and VO2VT1 did not differ between CAE and IT in HF patients with reduced EF undergoing cardiac rehabilitation. Consistently, previous studies have shown that IT can induce greater

increases in VO2peak in healthy individuals and patients with coronary artery disease, but not in HF patients with EF < 45%.[50,51] In this respect, the potential of high intensity exercise training in the context of IT to result in superior improvements of endurance capacity may be diminished in HF patients with reduced EF. A plausible explanation may be the fact these frail individuals possibly could not attain adequately high exercise intensities during IT to elicit advantageous responses of endurance capacity compared to CAE.

It should be acknowledged that although studies using only IT in HF patients with reduced EF could be informative from a pathophysiological point of view, the applicability of their results in real clinical practice may be questionable. Specifically, IT is destined only for low-risk patients with HF, due to the inherent higher risk of this type of exercise training for cardiac events.[2] Additionally, IT is classically included as a complementary element of CAE in cardiac rehabilitation programmes of HF patients, with CAE representing the main volume of exercise training, and not as the sole type of exercise training.[3,4] Furthermore, IT is more difficult to be maintained in the long term, especially for the phase 4 of cardiac rehabilitation, which is largely unsupervised.

4.6. Study strengths and limitations

Strengths of the current study include the fact that we assessed for the first time through meta-analysis the change in VO2VT1 as an end point of efficacy of cardiac rehabilitation. Secondly, considering that the overwhelming majority of the analysed studies did not report the standard errors of the exercise training-induced changes in VO2peak and VO2VT1, we managed to calculate them indirectly based on the p values of the comparisons between post-training and baseline in order to perform meta-analysis. Moreover, we focused our investigation to HF patients with reduced EF, that constitute the most challenging population of cardiac rehabilitation, since the risk of cardiac events is higher and the potential of exercise training-related improvement of functional capacity may be limited with possibly different pathophysiological regulation of this fitness improvement compared to less fragile populations.

Fourthly, most included randomized and non-randomized clinical trials were characterized by low overall risk of bias.

One important limitation of all studies was that neither of them used angiotensin receptor neprilysin inhibitor and sodium-glucose transport protein 2 inhibitors, while very few of them used aldosterone receptor antagonist. Thus, the results of these studies may have been suboptimal regarding the current standard of care, since the participants may have not reaped the full benefits of an optimized medical treatment for HF. Moreover, the use of different ergometers between studies may have influenced not only the magnitude of VO2peak and VO2VT1, but the level of intensity corresponding to VT1 as well.[5] Furthermore, taking into account that the overwhelming majority of studies with a control group in this systematic review did not report specific p values for the comparisons of either within control group or between active and control group, the comparison between active and control group was feasible only in two studies for the change in VO2peak and also two studies for the change in VO2VT1. Hence, a meta-analysis assessing the comparison of outcomes between the active and control groups was not performed. Another limitation was the different duration of intervention among the studies.

4.7. Knowledge gaps and future avenues for research

- The clinical significance of VO2VT1 in the serial evaluation of HF patients with reduced EF undergoing cardiac rehabilitation has not been investigated. It remains to be elucidated whether a VO2VT1-guided cardiac rehabilitation of HF patients with reduced EF can lead to superior cardiovascular outcomes compared to strategies using VO2peak. Moreover, the association of the exercise training-induced improvements in VO2VT1 with the changes in exercise testing-derived markers with established prognostic significance, such as heart rate recovery, should be explored as well.
- Further studies are needed to evaluate the association of the improvement of indices of quality of life in HF patients with reduced EF undergoing cardiac rehabilitation with the changes in VO2VT1.

5. Conclusions

In conclusion, the continuing improvement of endurance capacity of HF patients with reduced EF during the whole process of exercise-based cardiac rehabilitation may be detected more accurately with the assessment of VO2VT1, rather than VO2peak. Importantly, the serial reassessment of VO2VT1 in this setting, achieved even on submaximal testing, can influence the prescribed intensity of exercise training in a dynamic manner making exercise prescription more efficient. Further well-designed studies are needed to investigate whether reliance of exercise prescription on VO2VT1 can improve the management of HF patients with reduced EF undergoing cardiac rehabilitation in terms of reduction of cardiovascular events.

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Competing interests

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Author contributions

All authors contributed to the study conception and design, literature search, data analysis and drafted and/or critically revised the work.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

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Table 1. Characteristics of studies that investigated patients with heart failure and reduced ejection fraction subjected to cardiac rehabilitation.

First author (year of publication)	Study design	Number of participants (analyzed)	Percentage of males (%)	Age (years)	EF (%)	Ischaemic aetiology of HF (%)	NYHA class	Type of exercise training	Duration (weeks)	Ergometer	Change in VO2peak (mL/kg/min)	Statistical significance of change in VO2peak	Change in VO2VT1 (mL/kg/min)	Statistical significance of change in VO2VT1	Change in peak power output (Watts) for cycle ergometer	Statistical significance of change in peak power output
Alves L (2022) [16]	RCT	13 (13)	100	58±3	31±1	100	1,2	CAE + R	12	Cycle	15.2±2.4 → 19.0±2.2	S	8.1±1.2 → 12.2±1.1	S	75±9 → 85±9	S
Belardinelli R (1996) [17]	RCT	29 (29)	93	55±7	26±7	100	NR	CAE	8	Cycle	15.6±1.2 → 17.9±1.3	S	10.7±2.0 → 11.8±1.5	S	96±19 → 110±17	S
Belardinelli R (1999) [18]	RCT	50 (48)	90	56±7	28±6	86	2,3,4	CAE	56	Cycle	15.7±2.0 → 19.9±1.0	S	10.2±2.0 → 13.4±2.0	S	NR	NR
Belardinelli R (2006) [19]	RCT	30 (30)	100	55±14	30±7	100	2,3	CAE	8	Cycle	14.8±2.5 → 18.9±2.7	S	9.3±1.8 → 13.5±1.9	S	81±21 → 110±25	S
Beniaminovitz A (2002) [20]	RCT	20 (17)	71	50±12	20±4	47	NR	CAE + R	12	Cycle	12.0±0.5 → 14.0±0.5	S	10.2±0.5 → 11.9±0.5	S	NR	NR
Conraads V (2004) [21]	nRCT+C	27 (27)	78	59±2	26±5	70	2,3	CAE + R	16	Treadmill	18.4±0.9 → 20.4±1.1	S	13.5±0.6 → 15.3±0.8	S		
Corvera-Tindel T (2004) [22]	RCT	42 (42)	100	64±10	29±9	57	2,3,4	CAE	12	Cycle	14.3±3.7 → 15.3±3.8	NS	12.1±2.8 → 13.2±2.8	S	83±29 → 85±27	NS
Curnier D (2001) [23]	nRCT+C	16 (16)	NR	51±9	34±8	94	2,3	CAE	4	Cycle	20.3±6.1 → 23.9±6.4	S	15.6±4.8 → 19.0±5.7	S	113±44 → 139±50	S
		18 (18)	NR	55±13	29±7	44	2,3	CAE	4	Cycle	17.9±3.8 → 20±4.4	S	13.8±3.1 → 16.2±2.8	S	93±29 → 116±42	S
Degache F (2007) [24]	nRCT+C	12 (11)	73	55±10	32±5	46	2,3	CAE	8	Cycle	17.8±4.5 → 22.3±4.9	S	10.9±3.6 → 13.7±4.1	S	112±14 → 123±15	S
		12 (12)	92	50±13	32±5	42	2,3	CAE + R	8	Cycle	18.6±3.7 → 20.5±2.8	S	11.6±1.9 → 12.1±2.8	NS	111±22 → 135±25	S
Freyssin C (2012) [25]	RCT	12 (12)	50	54±9	28±5	83	NR	IT	8	Treadmill	10.7±2.9 → 13.6±3.2	S	7.7±2.3 → 9.4±2.4	S		
		14 (14)	50	55±12	31±8	86	NR	CAE	8	Treadmill	10.6±4.1 → 10.8±4.1	NS	7.3±2.4 → 7.5±3.4	NS		
Huang S (2014) [26]	nRCT+C	33 (33)	79	60±17	33±9	76	NR	CAE + IT	12	Cycle	16.4±0.6 → 18.6±0.9	S	11.3±0.5 → 12.5±0.5	S	86±29 → 107±46	S
Jakovljevic D (2010) [27]	RCT	11 (11)	73	65±12	36±6	36	1,2	CAE	12	Treadmill	23.3±6.5 → 25.1±6.7	S	14.2±3.9 → 15.5±4.5	S		
Karapolat H (2009) [28]	RCT	37 (32)	66	45±14	27±7	NR	2,3	CAE	8	Treadmill	17.9±4.4 → 19.4±4.6	S	16.1±3.2 → 15.1±3.7	NS		
		37 (36)	62	44±12	29±11	NR	2,3	CAE	8	Treadmill	17.5±6.1 → 18.1±6.0	S	16.7±6.2 → 15.7±5.4	NS		
Kiilavuori K (1996) [29]	RCT	12 (12)	100	52±7	24±5	33	2,3	CAE	12	Cycle	19.3±1.6 → 21.7±2.3	NS	10.5±0.8 → 12.7±1.0	S	118±35 → 140±45	S
		12 (12)	100	52±7	24±5	33	2,3	CAE	24	Cycle	19.3±1.6 → 21.7±2.5	NS	10.5±0.8 → 12.3±1.2	S	118±35 → 137±42	S
Klecha A (2007) [30]	RCT	25 (25)	80	60±10	27±6	100	2,3	CAE	24	Treadmill	14.6±2.9 → 19.2±3.8	S	10.4±2.5 → 12.9±3.2	S		
Laoutaris I (2013) [31]	RCT	14 (14)	86	59±8	31±5	36	2,3	CAE	12	Treadmill	17.6±3.6 → 19.5±4.1	S	13.7±2.1 → 15.1±2.4	S		
Meyer K (1996) [32]	Cross-over RCT	9 (9)	NR	51±6	21±3	44	2,3	IT	3	Cycle	12.6±0.7 → 14.5±1.0	S	10.2±0.5 → 12.1±0.7	S	68±15 → 82±12	S
Mezzani A (2013) [33]	RCT	15 (14)	100	65±7	28±7	NR	NR	CAE	12	Cycle	15.7±2.4 → 17.1±2.7	S	9.0±1.5 → 10.3±1.5	S	105±20 → 116±22	S
Myers J (2002) [34]	RCT	12 (12)	83	53±12	29±10	0	2,3	CAE	8	Cycle	21.7±3.8 → 25.3±5.2	S	12.8±4.0 → 19.0±5.1	S	134±36 → 164±49	NS
Okwose N (2019) [35]	nRCT-C	20 (17)	90	68±7	31±8	50	1,2	CAE	12	Cycle	16.8±3.8 → 17.6±4.2	NS	11.5±2.9 → 12.8±2.2	NS	82±10 → 91±19	NS
Sandri M (2012) [36]	RCT	15 (15)	80	50±19	27±23	53	2,3	CAE	4	Cycle	13.3±1.6 → 18.1±1.5	S	10.3±1.4 → 13.2±1.6	S	66±12 → 86±8	S
		15 (15)	80	72±16	29±23	67	2,3	CAE	4	Cycle	12.9±1.4 → 17.1±1.1	S	10.3±2.0 → 13.5±1.4	S	60±2 → 82±2	S
Sarullo F (2006) [37]	RCT	30 (30)	77	53±6	29±5	50	2,3	CAE	12	Cycle	14.5±1.4 → 17.7±2.6	S	12.9±1.0 → 15.5±1.7	S	85±15 → 110±12	S
Servantes D (2012) [38]	RCT	18 (17)	47	52±10	30±7	NR	NR	CAE	12	Treadmill	15.4±2.7 → 20.6±4.4	S	11.6±2.1 → 15.3±2.9	S		
		18 (17)	47	51±10	31±5	NR	NR	CAE + R	12	Treadmill	15.6±2.7 → 20.9±4.2	S	11.6±1.9 → 15.1±2.9	S		
Shephard R (1998) [39]	nRCT-C	21 (17)	81	62±6	22±7	71	2,3	CAE	16	Cycle	15.6±3.5 → 18.2±4.1	S	12.1±2.8 → 13.2±3.6	NS	104±35 → 117±35	S
Smart N (2005) [40]	nRCT-C	30 (30)	93	64±11	28±9	67	2,3	CAE + R	48	Cycle	12.2±4.8 → 13.2±3.8	NS	7.8±1.6 → 9.6±3.1	S	NR	NR
Smart N (2006) [41]	nRCT-C	37 (37)	95	63±9	29±6	68	2,3	CAE	8	Cycle	12.4±4.5 → 13.5±4.1	NS	7.8±1.6 → 9.0±2.9	S	NR	NR
		37 (33)	95	63±9	29±6	68	2,3	CAE + R	16	Cycle	12.4±4.5 → 15.0±4.9	S	7.8±1.6 → 10.3±2.8	S	NR	NR
Smart N (2012) [42]	RCT	13 (13)	0	63±9	30±7	54	2,3	CAE	16	Cycle	12.4±5.5 → 14.0±4.0	NS	7.4±1.4 → 9.2±2.0	S	NR	NR

		10 (10)	80	59±11	27±8	50	2,3	IT	16	Cycle	12.2±6.5 → 14.7±4.5	S	7.3±1.6 → 10.2±3.9	S	NR	NR
Smolis-Bąk E (2019) [43]	nRCT-C	33 (33)	88	62±9	24±NR	NR	3	IT + R	24	Cycle	12.6±3.9 → 14.8±5.6	S	12.1±3.3 → 13.5±5.6	NS	NR	NR
Soska V (2012) [44]	RCT	29 (26)	92	64±5	35±7	81	2,3	IT + R	12	Cycle	17.8±0.9 → 20.6±0.9	S	11.4±0.5 → 12.5±0.7	S	NR	NR
Sturm B (1999) [45]	RCT	13 (11)	NR	55±9	17±7	0	2,3	CAE	12	Cycle	15.9±3.4 → 18.5±2.9	S	9.1±2.1 → 9.7±1.3	NS	77±26 → 99±31	S

Abbreviations. CAE: Continuous aerobic exercise, EF: Ejection fraction, HF: Heart failure, IT: Interval training, nRCT+C: Non-randomized clinical trial with a control group, nRCT-C: Non-randomized clinical trial without a control group, NR: Not reported, NS: Non-significant ($p \geq 0.05$), NYHA: New York Heart Association, R: Resistance exercise, RCT: Randomized clinical trial, S: Significant ($p < 0.05$) VO2peak: Peak oxygen uptake, VO2VT1: Oxygen uptake at first ventilatory threshold.

Notes: Age, VO2peak and VO2VT1 are expressed as mean±standard deviation.

Figure legends

Graphical Abstract. The causes of the changes in peak oxygen uptake (VO2peak) and first ventilatory threshold (VO2VT1) during exercise-based cardiac rehabilitation in heart failure patients with reduced ejection fraction (EF).

RER: respiratory exchange ratio.

Figure 1. Preferred reporting items for systematic reviews flow diagram. Based on electronic databases search, 12,257 potentially eligible citations were identified. Six additional eligible studies were found through other sources. Of these 12,263 citations, 12,087 did not meet the inclusion criteria after reviewing the titles and abstracts. The full text of the remaining 176 citations was examined in more detail. Finally, 30 studies met the eligibility criteria and were included in the systematic review.

EF: ejection fraction.

Figure 2. Forest plot showing the changes in peak oxygen uptake (VO2peak) during continuous aerobic exercise (CAE) exercise interventions, interval training (IT) exercise interventions and in overall.

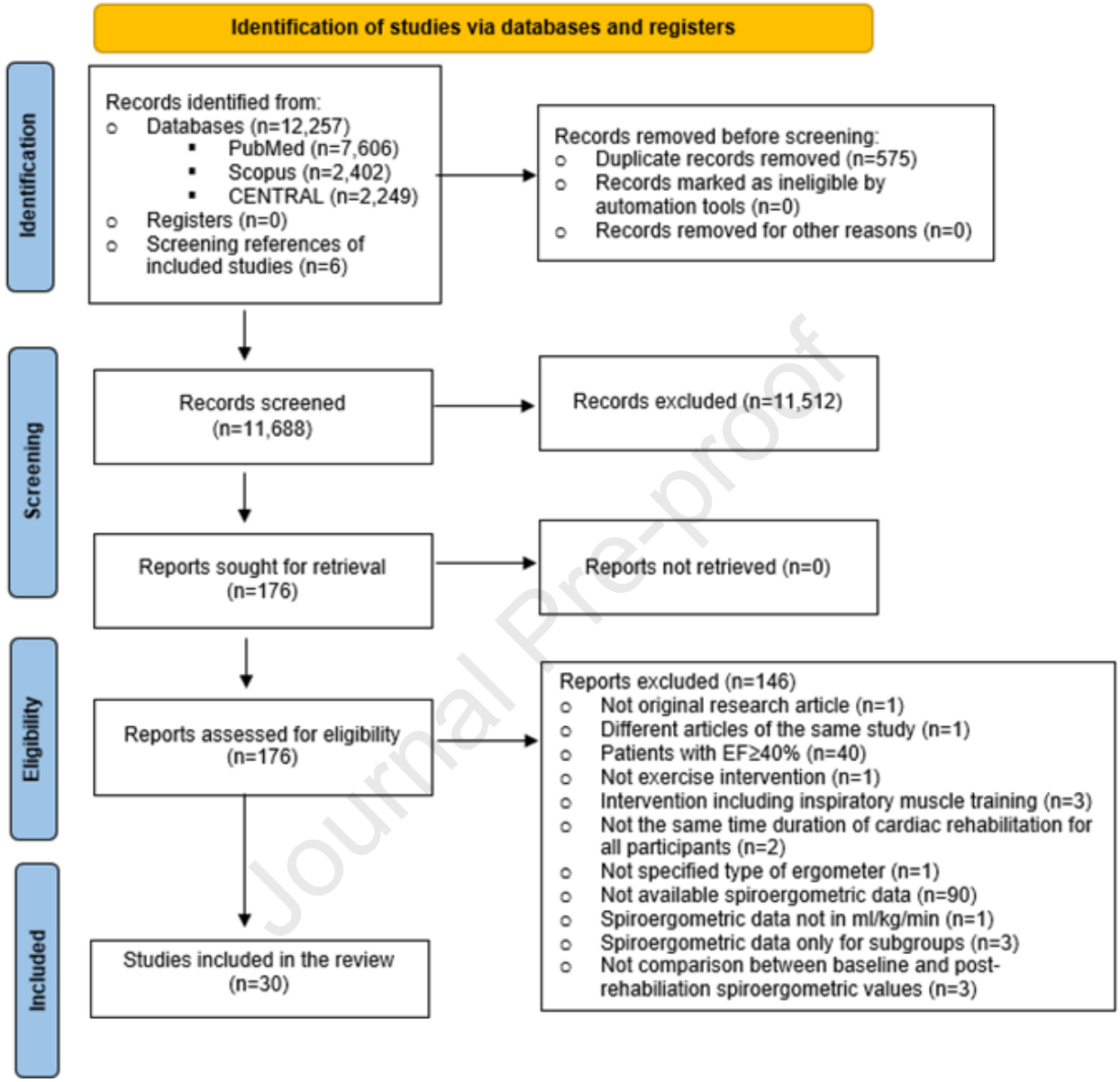
Figure 3. Forest plot showing the changes in oxygen uptake at the first ventilatory threshold (VO2VT1) during continuous aerobic exercise (CAE) exercise interventions, interval training (IT) exercise interventions and in overall.

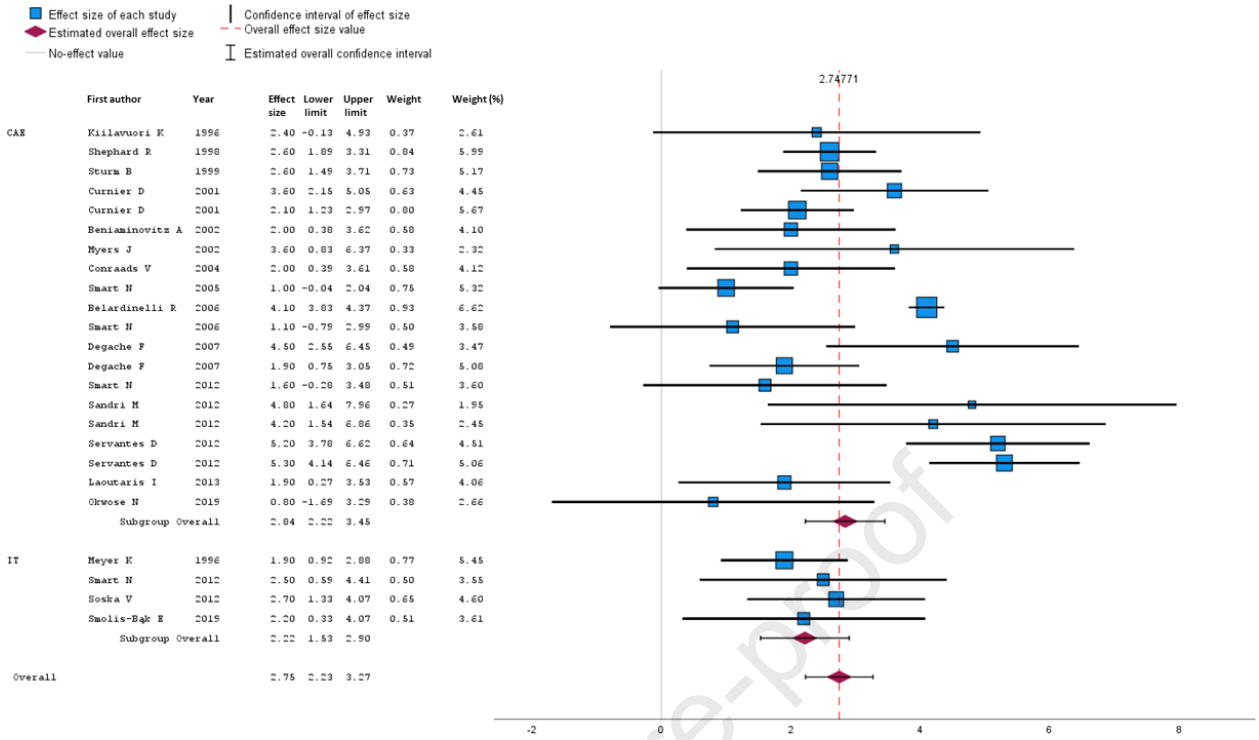
Figure 4. Bubble plots with fitted meta-regression lines with 95% confidence intervals showing the association between the exercise training-induced change in peak oxygen uptake (VO2peak) and the change in oxygen uptake at the first ventilatory threshold (VO2VT1) in (A) studies with mean age below the median age of all studies (i.e. 55 years), (B) studies with mean age above the median age of all studies, (C) studies with mean ejection fraction (EF) above the median EF of all studies (i.e. 29%) and (D) studies with mean EF below the median EF of all studies.

Figure 5. Bubble plot with fitted meta-regression line with 95% confidence intervals depicting the association between the post-training peak respiratory exchange ratio (RER) and the exercise training-induced change in peak oxygen uptake (VO2peak).

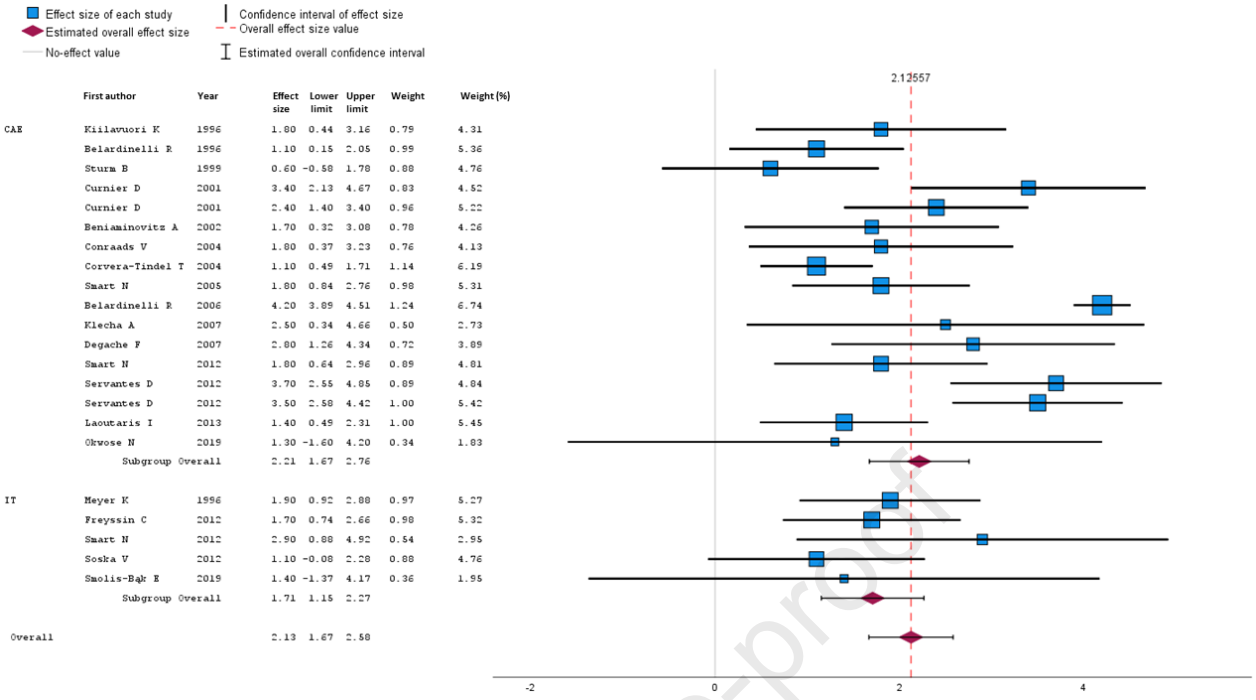
Supplementary Figure 1. Bubble plots with fitted meta-regression lines with 95% confidence intervals displaying the association between (A) the change in oxygen uptake at the first ventilatory threshold (VO2VT1) and age, (B) the change in VO2VT1 and ejection fraction (EF), (C) the change in peak oxygen uptake (VO2peak) and age and (D) the change in VO2peak and EF.

Figure 1. Flow diagram of the literature search and study selection.



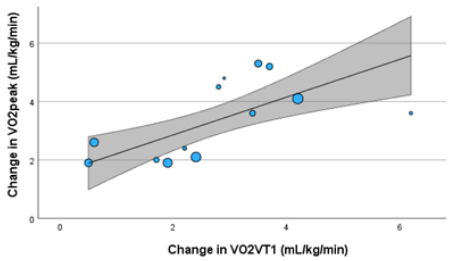


	First author	Year	Effect size	Lower limit	Upper limit	Weight	Weight (%)
CAE	Kiilavuori K	1996	2.40	-0.13	4.93	0.37	2.61
	Shephard R	1998	2.60	1.89	3.31	0.84	5.99
	Sturm B	1999	2.60	1.49	3.71	0.73	5.17
	Curnier D	2001	3.60	2.15	5.05	0.63	4.45
	Curnier D	2001	2.10	1.23	2.97	0.80	5.67
	Beniaminovitz A	2002	2.00	0.38	3.62	0.58	4.10
	Myers J	2002	3.60	0.83	6.37	0.33	2.32
	Conraads V	2004	2.00	0.39	3.61	0.58	4.12
	Smart N	2005	1.00	-0.04	2.04	0.75	5.32
	Belardinelli R	2006	4.10	3.83	4.37	0.93	6.62
	Smart N	2006	1.10	-0.79	2.99	0.50	3.58
	Degache F	2007	4.50	2.55	6.45	0.49	3.47
	Degache F	2007	1.90	0.75	3.05	0.72	5.08
	Smart N	2012	1.60	-0.28	3.48	0.51	3.60
	Sandri M	2012	4.80	1.64	7.96	0.27	1.95
	Sandri M	2012	4.20	1.54	6.86	0.35	2.45
	Servantes D	2012	5.20	3.78	6.62	0.64	4.51
	Servantes D	2012	5.30	4.14	6.46	0.71	5.06
	Laoutaris I	2013	1.90	0.27	3.53	0.57	4.06
	Okwose N	2019	0.80	-1.69	3.29	0.38	2.66
	Subgroup Overall		2.84	2.22	3.45		
IT	Meyer K	1996	1.90	0.92	2.88	0.77	5.45
	Smart N	2012	2.50	0.59	4.41	0.50	3.55
	Soska V	2012	2.70	1.33	4.07	0.65	4.60
	Smolis-Bąk E	2019	2.20	0.33	4.07	0.51	3.61
	Subgroup Overall		2.22	1.53	2.90		
Overall			2.75	2.23	3.27		

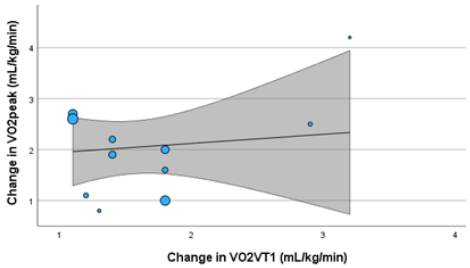


	First author	Year	Effect size	Lower limit	Upper limit	Weight	Weight (%)
CAE	Kiilavuori K	1996	1.80	0.44	3.16	0.79	4.31
	Belardinelli R	1996	1.10	0.15	2.05	0.99	5.36
	Sturm B	1999	0.60	-0.58	1.78	0.88	4.76
	Curnier D	2001	3.40	2.13	4.67	0.83	4.52
	Curnier D	2001	2.40	1.40	3.40	0.96	5.22
	Beniaminovitz A	2002	1.70	0.32	3.08	0.78	4.26
	Conraads V	2004	1.80	0.37	3.23	0.76	4.13
	Corvera-Tindel T	2004	1.10	0.49	1.71	1.14	6.19
	Smart N	2005	1.80	0.84	2.76	0.98	5.31
	Belardinelli R	2006	4.20	3.89	4.51	1.24	6.74
	Klecha A	2007	2.50	0.34	4.66	0.50	2.73
	Degache F	2007	2.80	1.26	4.34	0.72	3.89
	Smart N	2012	1.80	0.64	2.96	0.89	4.81
	Servantes D	2012	3.70	2.55	4.85	0.89	4.84
	Servantes D	2012	3.50	2.58	4.42	1.00	5.42
	Laoutaris I	2013	1.40	0.49	2.31	1.00	5.45
	Okwose N	2019	1.30	-1.60	4.20	0.34	1.83
	Subgroup Overall		2.21	1.67	2.76		
IT	Meyer K	1996	1.90	0.92	2.88	0.97	5.27
	Freyssin C	2012	1.70	0.74	2.66	0.98	5.32
	Smart N	2012	2.90	0.88	4.92	0.54	2.95
	Soska V	2012	1.10	-0.08	2.28	0.88	4.76
	Smolis-Bąk E	2019	1.40	-1.37	4.17	0.36	1.95
	Subgroup Overall		1.71	1.15	2.27		
Overall			2.13	1.67	2.58		

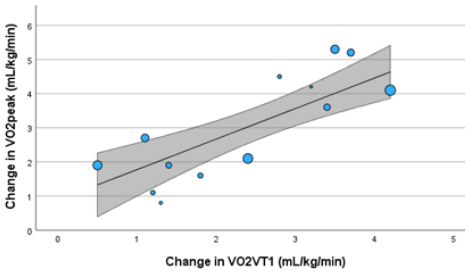
A



B



C



D