HELLENIC JOURNAL OF CARDIOLOGY VOL. 77, 2024: 106–119

REVIEW ARTICLE

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

Georgios A. Christou,[a,b] Maria A. Christou,[c,d] Constantinos H. Davos,[e] Georgios Markozannes,[d] Konstantinos A. Christou,[d] Stefanos Mantzoukas,[f] Dimitrios K. Christodoulou,[f] Dimitrios N. Kiortsis,[g] Panagiota A. Christou,[c] Stelios Tigas,[c] Dimitra Nikoletou[b]

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 the following: 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 were 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) both at 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 a 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 posttraining peak respiratory exchange ratio, as an index of maximum effort during exercise testing, correlated positively with the change in VO2peak

[a]Laboratory of Physiology, Faculty of Medicine, University of Ioannina, Ioannina, Greece
[b]MSc Sports Cardiology, St George's University of London, London, United Kingdom
[c]Department of Endocrinology, University Hospital of Ioannina, Ioannina, Greece
[d]Department of Hygiene and Epidemiology, School of Medicine, University of Ioannina, Ioannina, Greece
[e]Cardiovascular Research Laboratory, Biomedical Research Foundation, Academy of Athens, Athens, Greece
[f]Research Laboratory of Integrated Care, Health and Well-being, Department of Nursing, School of Health Sciences, University of Ioannina, Ioannina, Greece
[g]Atherothrombosis Research Centre, Faculty of Medicine, University of Ioannina, Ioannina, Greece
Peer review under responsibility of Hellenic Society of Cardiology.

Manuscript received September 18, 2023; revised manuscript received December 23, 2023, accepted January 17, 2024. Available online January 19, 2024

ISSN 1109-9666 https://doi.org/10.1016/j.hjc.2024.01.004

(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 groups.

CONCLUSIONS Improvement of endurance capacity during cardiac rehabilitation may be detected more accurately with the assessment of VO2VT1 rather than VO2peak. (Hellenic Journal of Cardiology 2024;77:106-119)

1. INTRODUCTION

Exercise-based cardiac rehabilitation has a central role in the management of patients with chronic heart failure (HF) aiming to improve 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) (ie, EF <40%) because of 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 program 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 program. Specifically, endurance exercise training in athletes can induce an early increase in VO2peak with subsequent leveling off or even no significant change in VO2peak during a macrocycle. However, 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 VO2peak.[6,8]

Additionally, the characteristic of an exercise program that influences the risk of exercise-related cardiac events the most is exercise intensity.[9] This risk may increase considerably at exercise intensities above the first ventilatory threshold (VT1) and even more above the second ventilatory threshold (VT2) because of the excessive upregulation not only of the 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 commonly used upper limit of exercise intensity for exercise prescription in patients with HF, especially those in New York Heart Association (NYHA) class III, 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 program 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 the following: 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 in the PROSPERO (International Prospective Register of Systematic Reviews) database (CRD42020198257). The guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 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 (ie, <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 after 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 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 September 1, 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, and data extraction from included studies were conducted 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 etiology, NYHA class, EF, HF treatments, comorbidities, rhythm, type of ergometer, phase of cardiac rehabilitation, type of exercise training, study duration, and values at 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 nonrandomized clinical trials, respectively.[14,15]

2.6. STATISTICAL ANALYSIS. Quantitative analysis was conducted to assess the exercise training-induced changes in VO2peak and VO2VT1. When the 95% confidence interval (CI) 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 posttraining and baseline. The overwhelming majority of studies in this systematic review that included a control group did not report the necessary information for comparison of outcomes either within the control group or between the active and control groups (relevant information was only reported in 2 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% CIs. We performed random-effects meta-regression to investigate the exercise training-induced changes in VO2peak and VO2VT1 with other parameters of interest. We used the 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 2-tailed p value <0.05 was considered statistically significant. All statistical analyses were performed using the software IBM SPSS Statistics, Version 29.0.

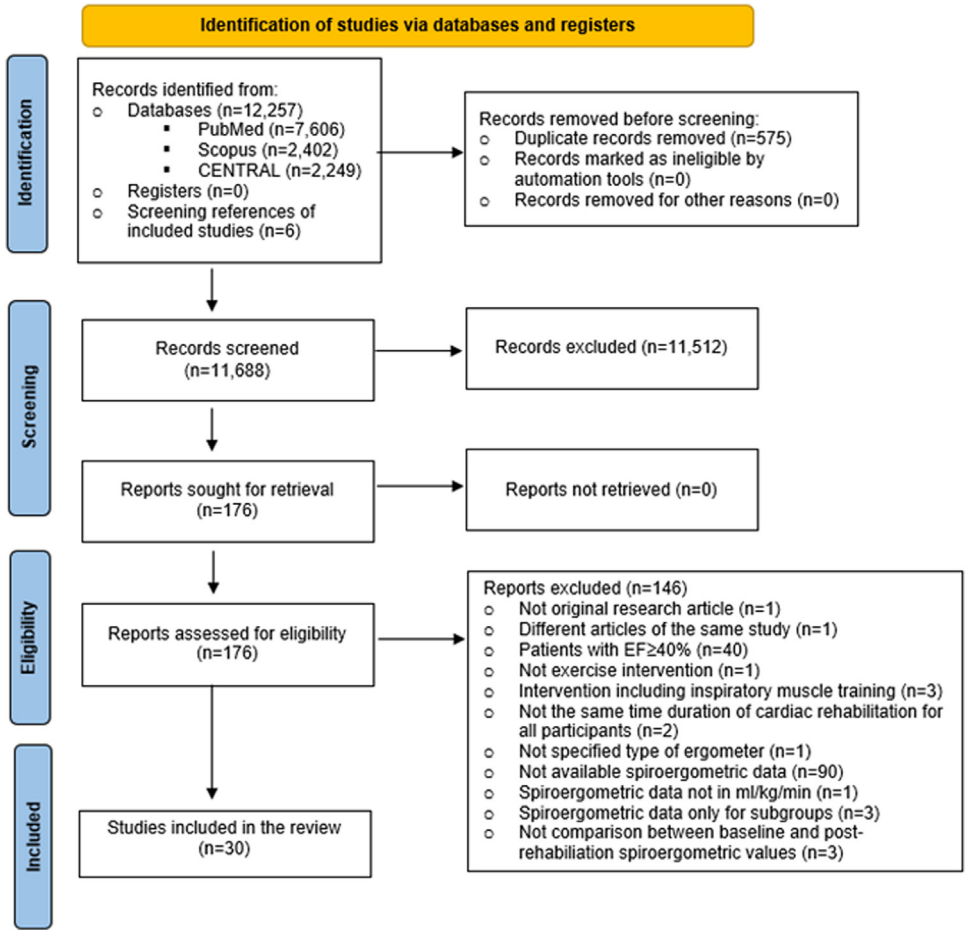
3. RESULTS

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 crossover randomized clinical trial (3%), 4 nonrandomized clinical trials with a control group (13%), and 5 nonrandomized clinical trials without a control group (17%) were considered eligible.

3.1.1. Participants. The total number of HF patients undergoing cardiac rehabilitation was 839. The mean age of participants in the studies ranged from 44 to 72 years. The percentage of participants who completed the cardiac rehabilitation program ranged from 81% to 100%. Most studies included both males and females, with a predominance of male participants. The exceptions to this included 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

FIGURE 1 **PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. On the basis of electronic database 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 texts of the remaining 176 citations were examined in more detail. Finally, 30 studies met the eligibility criteria and were included in the systematic review**



EF: ejection fraction.

the 26 studies with available data on HF etiology, at least 50% of patients had HF of ischemic etiology in 16 studies (62%). The etiology of nonischemic HF was dilated cardiomyopathy, except in 2 studies that also included hypertensive cardiomyopathy and valvular heart disease.[37,39] With regard to NYHA class, data were available for 26 studies. All of them included HF patients with NYHA class II, and all except 3 studies included HF patients with NYHA class III.[16,27,35] Three studies included patients with NYHA class I, and 2 studies included patients with NYHA class IV.[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 the following: 100% for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, 77% for beta-blockers, 17% for aldosterone receptor antagonists, 73% for loop diuretics, and 32% for digitalis. No study included participants taking angiotensin receptor neprilysin inhibitors or sodium-glucose cotransporter-2 inhibitors. In all studies, most participants were in sinus rhythm, except in one study that included only individuals with atrial fibrillation.[16]

3.1.2. Type of intervention. The 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 5 studies

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 (%)	Ischemic etiology 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]	Crossover 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

Continued on the next page

TABLE 1 Continued

First author (year of publication)	Study design	Number of participants (analyzed)	Percentage of males (%)	Age (years)	EF (%)	Ischemic etiology 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
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: Nonrandomized clinical trial with a control group, nRCT-C: Nonrandomized clinical trial without a control group, NR: Not reported, NS: Nonsignificant ($p \geq 0.05$), 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.

involved IT and one study a combination of CAE and IT. The median (minimum-maximum) duration of exercise training was 12 (3-56) weeks. All studies involved phase 3 cardiac rehabilitation (ie, outpatient cardiac rehabilitation program that is intensive and structured), apart from 2 studies using phase 4 cardiac rehabilitation (ie, community program focusing on long-term maintenance of physical activity).[18,40]

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

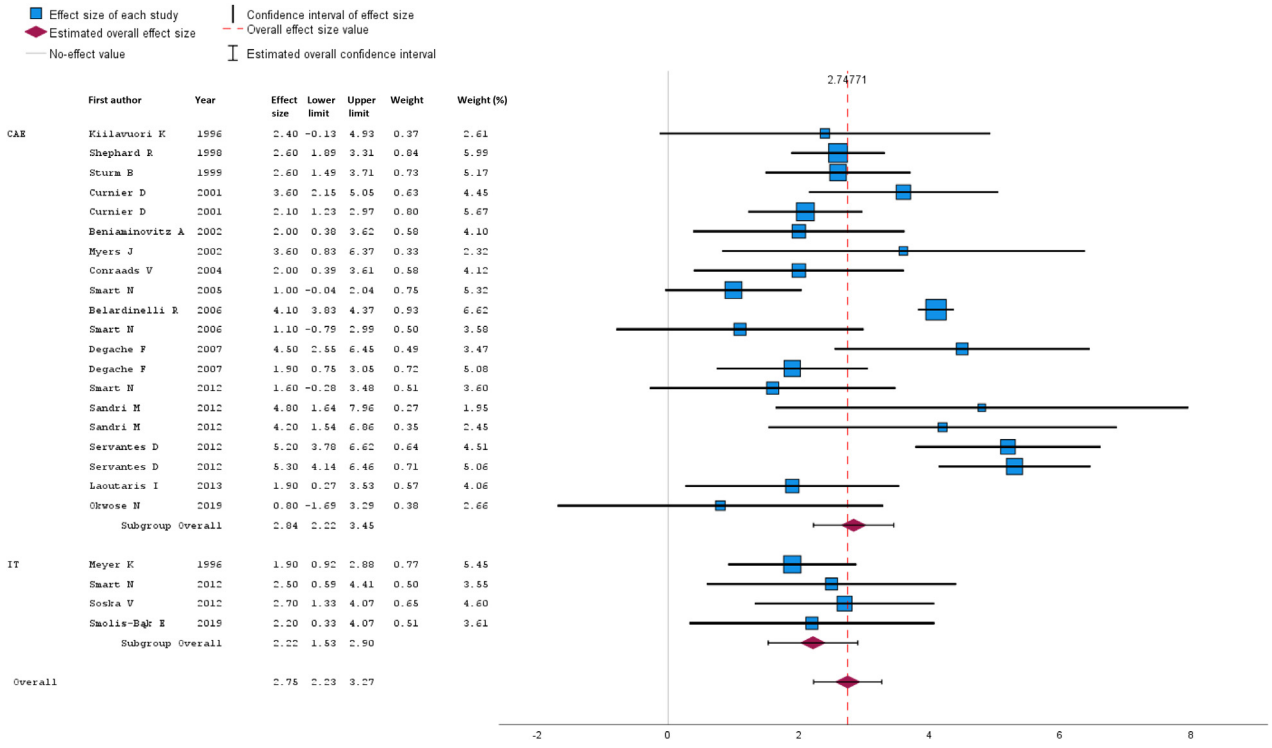
3.1.4. Outcome definition and method of assessment. The main outcome was the effect of exercise training on VO2peak and VO2VT1 in HF patients with reduced EF undergoing cardiac rehabilitation. The most common type of ergometer used in cardiopulmonary exercise testing was the cycle, while 9 studies used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

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 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 minimum duration of IT that was reported to significantly increase VO2peak and VO2VT1 was 3 weeks.[32]

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, except in one study that used IT of 24 weeks. The 2 studies that found no significant changes in both VO2peak and VO2VT1 used CAE.[25,35] Among these studies, one used low-intensity CAE for 12 weeks and the other study used moderate-intensity CAE for 8 weeks.

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



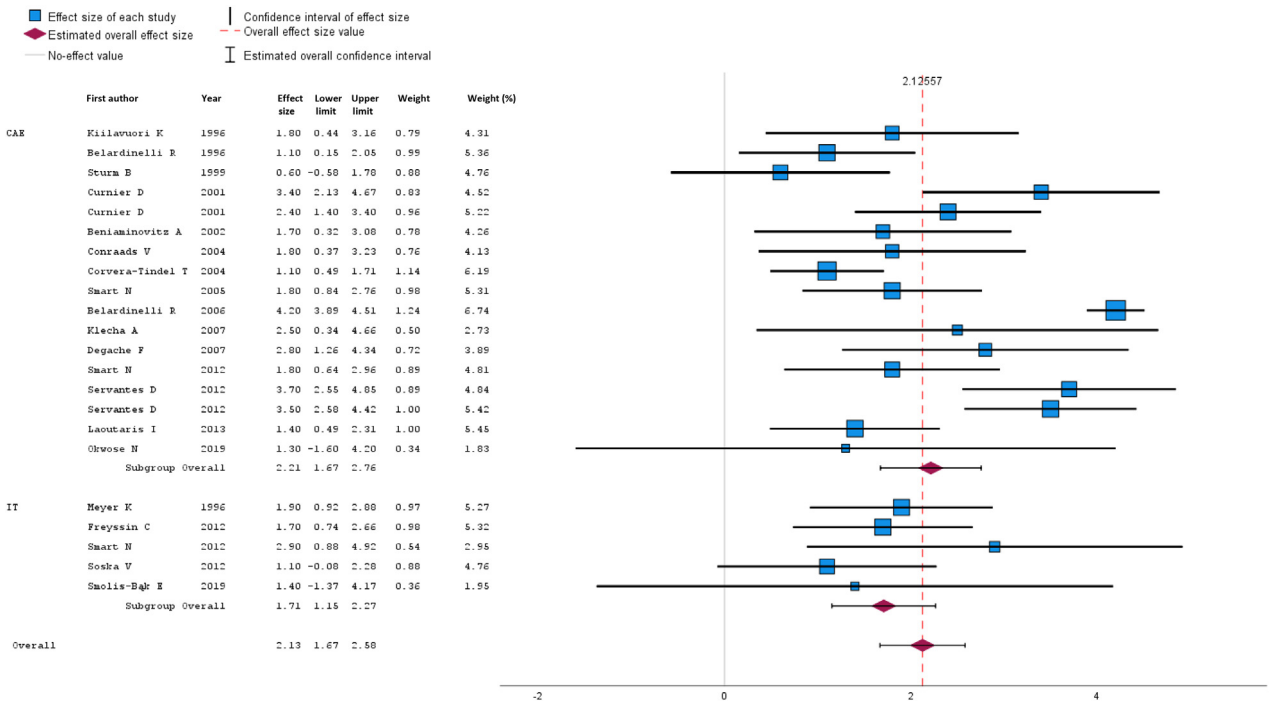
	First author	Year	Effect size	Lower limit	Upper limit	Weight	Weight (%)
CAE	Kiilavuori K	1996	2.40	-0.13	4.93	0.37	2.61
	Shephard R	1998	2.60	1.89	3.31	0.84	5.99
	Sturm B	1999	2.60	1.49	3.71	0.73	5.17
	Curnier D	2001	3.60	2.15	5.05	0.63	4.45
	Curnier D	2001	2.10	1.23	2.97	0.80	5.67
	Beniaminovitz A	2002	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		

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 (ie, 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 a 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, we chose the corresponding categorical variables of age and EF (ie, above or below the median) as independent variables. The results obtained were similar to those of the above-mentioned analyses.

We attempted to elucidate whether the normally expected positive association between the exercise training-induced change in VO2peak and change in VO2VT1 weakened in individuals who were older or had lower EF, since these frail patients were less likely to achieve maximal effort during exercise testing, resulting in lower posttraining VO2peak than would be expected from exercise training. Thus, when we investigated only the

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



	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		

studies with mean age below the median age of all studies (ie, 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 (ie, 29%), the change in VO2peak correlated positively with the change in VO2VT1 (coefficient = 0.892, p<0.001, I^2 = 39.1%) (Figure 4C). Conversely, 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 posttraining 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.

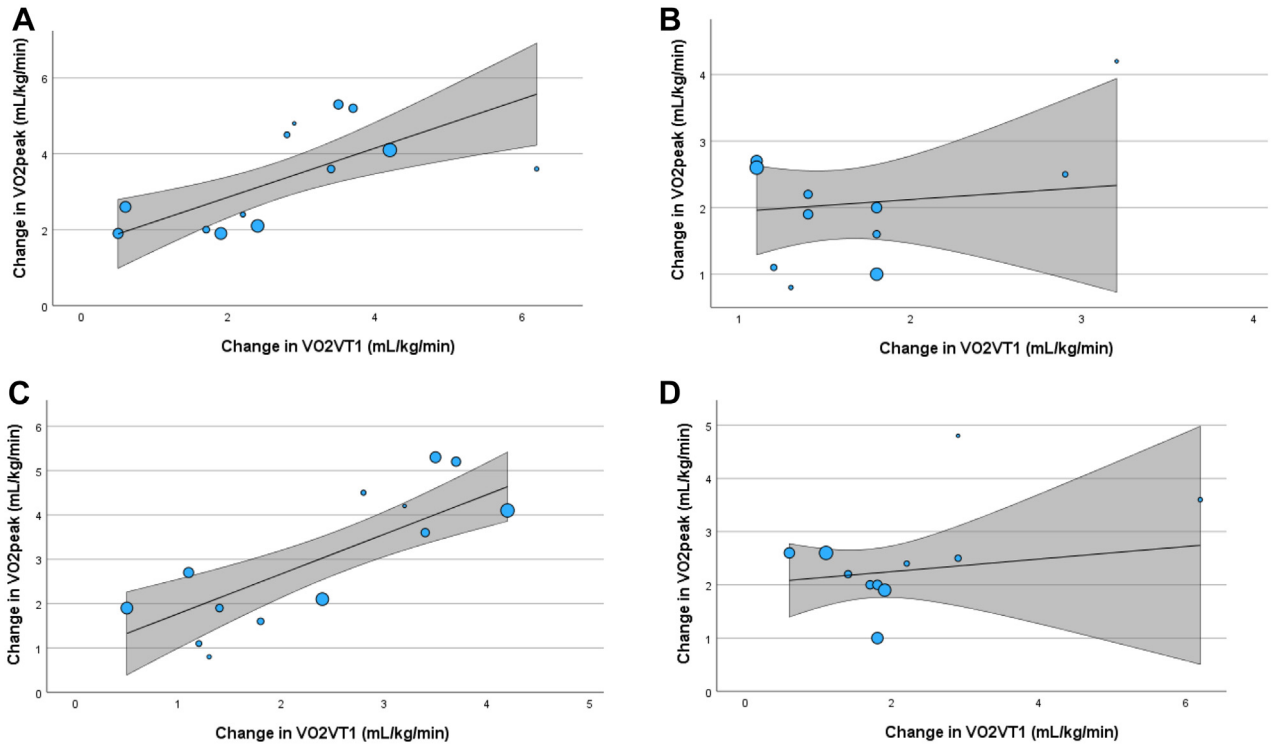
Among the IT exercise interventions, the change in VO2peak ranged from 1.9 to 2.9 mL/kg/min with a weighted mean change of 2.2 (CI: 1.5, 2.9) mL/kg/min (p<0.001) (Figure 2). The change in VO2VT1 ranged from 1.1 to 2.9 mL/kg/min with a weighted mean change of 1.7 (CI: 1.2, 2.3) mL/kg/min (p<0.001) (Figure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

In the 2 studies comparing the responses of VO2peak and VO2VT1 between IT and CAE, nonsignificant differences were reported.[25,42]

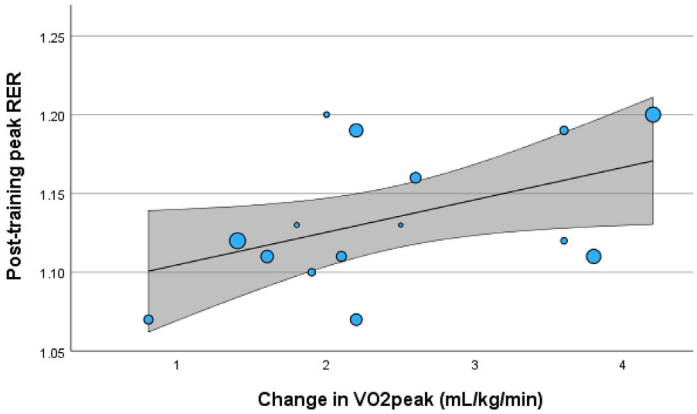
3.3. RISK OF BIAS ASSESSMENT. According to the risk of bias assessment, most of the randomized clinical trials had low overall risk of bias, whereas the remainder had some concerns due to bias caused by deviations from the intended interventions (Supplementary Table 1). Additionally, most of the nonrandomized clinical trials had low overall risk of

FIGURE 4 **Bubble plots with fitted meta-regression lines and 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 (ie, 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 (ie, 29%), and (D) studies with mean EF below the median EF of all studies**



bias, apart from 3 studies that were characterized by moderate risk of bias due to deviations from the intended interventions (Supplementary Table 2).

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



4. DISCUSSION

The key findings of the present study are the following: 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; this is because the exercise training-induced change in VO2peak was greatly influenced by the level of maximum effort at posttraining exercise testing and slightly waned in the long term of cardiac rehabilitation, whereas the improvement of VO2VT1 was more sustained or even gradually augmented during the entire process of cardiac rehabilitation; 2) the changes in VO2peak and VO2VT1 did not differ between CAE and IT groups.

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 to 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 to 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 concurrent improvement of VO2VT1, which 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 program appear to be more motivated to engage in exercise and possibly can achieve higher levels of maximum effort during exercise testing than noncompleters, 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 of experiencing 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 with the change in VO2peak. Furthermore, the normally expected positive association between the changes in VO2peak and VO2VT1 disappeared in studies including individuals who were older and had lower EF. These frail patients were less likely to achieve maximal effort during exercise testing, leading to lower posttraining 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 posttraining exercise testing, as estimated by posttraining peak RER. In this regard, the change in VO2VT1 appears to reflect more accurately the physiological responses induced by exercise training. As a submaximal spiroergometric parameter, VO2VT1 may not be influenced by the magnitude of effort during exercise testing, provided that VT1 is achieved, which is almost always the case during serial exercise testing in 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 with VO2peak. This is because 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 with 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] Conversely, VO2VT1 equates to the product of VO2peak with the percentage 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 with 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 dyspnea.[3,4] Conversely, 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 changes in VO2peak and VO2VT1 with the improvement of indices of quality of life in HF patients with reduced EF undergoing cardiac rehabilitation.

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 relative to baseline can reasonably indicate that the training program is ineffective or that overtraining has occurred. Furthermore, 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 can not only detect any improvement in endurance capacity more accurately, but also influence the prescribed intensity of CAE in a dynamic manner, improving the efficiency of exercise prescription.[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 that these frail individuals possibly cannot attain adequately high exercise intensities during IT to elicit advantageous responses of endurance capacity compared with 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 intended only for low-risk patients with HF because of 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 programs 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 maintain in the long term, especially in 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 analyzed studies did not report the standard errors of the exercise training-induced changes in VO2peak and VO2VT1, we managed to calculate them indirectly on the basis of the p values of the comparisons between posttraining and baseline in order to perform meta-analysis. Moreover, we focused our investigation on HF patients with reduced EF, who constitute the most challenging population for cardiac rehabilitation. This is because 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 with less fragile populations. Fourthly, most included randomized and nonrandomized clinical trials were characterized by low overall risk of bias.

One important limitation of all studies was that none used angiotensin receptor neprilysin inhibitors and sodium-glucose transport protein 2 inhibitors, while very few used aldosterone receptor antagonists. 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 among the studies may have influenced not only the magnitude of VO2peak and VO2VT1, but also the level of intensity corresponding to VT1.[5] Furthermore, the overwhelming majority of studies that included a control group in this systematic review did not report specific p values for comparisons either within the control group or between the active and control groups. Thus, the comparison between the active and control groups was feasible only in 2 studies for the change in VO2peak and in 2 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 difference in 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 with 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 also be explored.
- Further studies are needed to evaluate the association of changes in VO2VT1 with the improvement of indices of quality of life in HF patients with reduced EF undergoing cardiac rehabilitation.

5. CONCLUSIONS

The continuing improvement of endurance capacity of HF patients with reduced EF during the entire 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, improving the efficiency of exercise prescription. 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.

FUNDING

There was no funding source.

AUTHOR CONTRIBUTIONS

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

DATA AVAILABILITY STATEMENT

The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

DECLARATION OF COMPETING INTEREST

Declarations of interest: none.

CORRESPONDING AUTHOR. Georgios A. Christou, MD, MSc, PhD, Cardiologist, Laboratory of Physiology, Faculty of Medicine, University of Ioannina, Ioannina, Greece, MSc Sports Cardiology, St George's University of London, London, United Kingdom Ioannina, PC: 45332, Greece. Tel: +306936276936 E-mail: georgios.christou@yahoo.gr.

REFERENCES

1. Hansen D, Dendale P, Coninx K, et al. The European Association of Preventive Cardiology Exercise Prescription in Everyday Practice and Rehabilitative Training (EXPERT) tool: A digital training and decision support system for optimized exercise prescription in cardiovascular disease. Concept, definitions and construction methodology. *Eur J Prev Cardiol*. 2017;24(10):1017-1031.

2. Silva AK, Barbosa MP, Bernardo AF, et al. Cardiac risk stratification in cardiac rehabilitation programs: a review of protocols. *Rev Bras Cir Cardiovasc*. 2014;29(2):255-265.

3. Myers J. Principles of exercise prescription for patients with chronic heart failure. *Heart Fail Rev*. 2008;13(1):61-68.

4. Carvalho VO, Mezzani A. Aerobic exercise training intensity in patients with chronic heart failure: principles of assessment and prescription. *Eur J Cardiovasc Prev Rehabil*. 2011;18(1):5-14.

5. Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122(2):191-225.

6. Bassett DR Jr, Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med Sci Sports Exerc*. 2000;32(1):70-84.

7. Martin DE, Vroon DH, May DF, et al. Physiological Changes in Elite Male Distance Runners Training for Olympic Competition. *Phys Sportsmed*. 1986;14(1):152-206.

8. Coyle EF, Coggan AR, Hopper MK, et al. Determinants of endurance in well-trained cyclists. *J Appl Physiol (1985)*. 1988;64(6):2622-2630.

9. Borjesson M, Urhausen A, Kouidi E, et al. Cardiovascular evaluation of middle-aged/ senior individuals engaged in leisure-time sport activities: position stand from the sections of exercise physiology and sports cardiology of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil*. 2011;18(3):446-458.

10. Peinado AB, Rojo JJ, Calderón FJ, et al. Responses to increasing exercise upon reaching the

anaerobic threshold, and their control by the central nervous system. *BMC Sports Sci Med Rehabil*. 2014;6:17.

11. Meyer T, Lucía A, Earnest CP, et al. A conceptual framework for performance diagnosis and training prescription from submaximal gas exchange parameters-theory and application. *Int J Sports Med*. 2005;26(Suppl 1):S38-S48.

12. Meyer T, Görge G, Schwaab B, et al. An alternative approach for exercise prescription and efficacy testing in patients with chronic heart failure: a randomized controlled training study. *Am Heart J*. 2005;149(5):e1-e7.

13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.

14. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.

15. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.

16. Alves LS, Bocchi EA, Chizzola PR, et al. Exercise training in heart failure with reduced ejection fraction and permanent atrial fibrillation: A randomized clinical trial. *Heart Rhythm*. 2022;19(7):1058-1066.

17. Belardinelli R, Georgiou D, Cianci G, et al. Effects of exercise training on left ventricular filling at rest and during exercise in patients with ischemic cardiomyopathy and severe left ventricular systolic dysfunction. *Am Heart J*. 1996;132(1 Pt 1):61-70.

18. Belardinelli R, Georgiou D, Cianci G, et al. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation*. 1999;99(9):1173-1182.

19. Belardinelli R, Capestro F, Misiani A, et al. Moderate exercise training improves functional capacity, quality of life, and endothelium-dependent vasodilation in chronic heart failure patients with implantable cardioverter defibrillators and cardiac resynchronization therapy. *Eur J Cardiovasc Prev Rehabil*. 2006;13(5):818-825.

20. Beniaminovitz A, Lang CC, LaManca J, et al. Selective low-level leg muscle training alleviates dyspnea in patients with heart failure. *J Am Coll Cardiol*. 2002;40(9):1602-1608.

21. Conraads VM, Beckers P, Vaes J, et al. Combined endurance/resistance training reduces NT-proBNP levels in patients with chronic heart failure. *Eur Heart J*. 2004;25(20):1797-1805.

22. Corvera-Tindel T, Doering LV, Woo MA, et al. Effects of a home walking exercise program on functional status and symptoms in heart failure. *Am Heart J*. 2004;147(2):339-346.

23. Curnier D, Galinier M, Pathak A, et al. Rehabilitation of patients with congestive heart failure with or without beta-blockade therapy. *J Card Fail*. 2001;7(3):241-248.

24. Degache F, Garet M, Calmels P, et al. Enhancement of isokinetic muscle strength with a combined training programme in chronic heart failure. *Clin Physiol Funct Imaging*. 2007;27(4):225-230.

25. Freyssin C, Verkindt C, Prieur F, et al. Cardiac rehabilitation in chronic heart failure: effect of an 8-week, high-intensity interval training versus continuous training. *Arch Phys Med Rehabil*. 2012;93(8):1359-1364.

26. Huang SC, Wong MK, Lin PJ, et al. Modified high-intensity interval training increases peak cardiac power output in patients with heart failure. *Eur J Appl Physiol*. 2014;114(9):1853-1862.

27. Jakovljevic DG, Donovan G, Nunan D, et al. The effect of aerobic versus resistance exercise training on peak cardiac power output and physical functional capacity in patients with chronic heart failure. *Int J Cardiol*. 2010;145(3):526-528.

28. Karapolat H, Demir E, Bozkaya YT, et al. Comparison of hospital-based versus home-based exercise training in patients with heart failure: effects on functional capacity, quality of life, psychological symptoms, and hemodynamic parameters. *Clin Res Cardiol*. 2009;98(10):635-642.

29. Kiilavuori K, Sovijärvi A, Näveri H, et al. Effect of physical training on exercise capacity and gas exchange in patients with chronic heart failure. *Chest*. 1996;110(4):985-991.

30. Klecha A, Kawecka-Jaszcz K, Bacior B, et al. Physical training in patients with chronic heart failure of ischemic origin: effect on exercise capacity and left ventricular remodeling. *Eur J Cardiovasc Prev Rehabil*. 2007;14(1):85-91.

31. Laoutaris ID, Adamopoulos S, Manginas A, et al. Benefits of combined aerobic/resistance/inspiratory training in patients with chronic heart failure. A complete exercise model? A prospective randomised study. *Int J Cardiol*. 2013;167(5):1967-1972.

32. Meyer K, Schwaibold M, Westbrook S, et al. Effects of short-term exercise training and activity restriction on functional capacity in patients with severe chronic congestive heart failure. *Am J Cardiol*. 1996;78(9):1017-1022.

33. Mezzani A, Grassi B, Jones AM, et al. Speeding of pulmonary VO2 on-kinetics by light-to-moderate-intensity aerobic exercise training in chronic heart failure: clinical and pathophysiological correlates. *Int J Cardiol*. 2013;167(5):2189-2195.

34. Myers J, Wagner D, Schertler T, et al. Effects of exercise training on left ventricular volumes and function in patients with nonischemic cardiomyopathy: application of magnetic resonance myocardial tagging. *Am Heart J*. 2002;144(4):719-725.

35. Okwose NC, Avery L, O'Brien N, et al. Acceptability, Feasibility and Preliminary Evaluation of a Novel, Personalised, Home-Based Physical Activity Intervention for Chronic Heart Failure (Active-at-Home-HF): a Pilot Study. *Sports Med Open*. 2019;5(1):45.

36. Sandri M, Kozarez I, Adams V, et al. Age-related effects of exercise training on diastolic function in heart failure with reduced ejection fraction: the Leipzig Exercise Intervention in Chronic Heart Failure and Aging (LEICA) Diastolic Dysfunction Study. *Eur Heart J*. 2012;33(14):1758-1768.

37. Sarullo F, Gristina T, Brusca I, et al. Effect of physical training on exercise capacity, gas exchange and N-terminal pro-brain natriuretic peptide levels in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil*. 2006;13(5):812-817.

38. Servantes DM, Pelcerman A, Salvetti XM, et al. Effects of home-based exercise training for patients with chronic heart failure and sleep apnoea: a randomized comparison of two different programmes. *Clin Rehabil*. 2012;26(1):45-57.

39. Shephard RJ, Kavanagh T, Mertens DJ. On the prediction of physiological and psychological responses to aerobic training in patients with stable congestive heart failure. *J Cardiopulm Rehabil*. 1998;18(1):45-51.

40. Smart N, Haluska B, Jeffriess L, et al. Predictors of a sustained response to exercise training in patients with chronic heart failure: a telemonitoring study. *Am Heart J*. 2005;150(6):1240-1247.

41. Smart N, Haluska B, Jeffriess L, et al. Cardiac contributions to exercise training responses in patients with chronic heart failure: a strain imaging study. *Echocardiography*. 2006;23(5):376-382.

42. Smart NA, Steele M. A comparison of 16 weeks of continuous vs intermittent exercise training in chronic heart failure patients. *Congest Heart Fail*. 2012;18(4):205-211.

43. Smolis-Bąk E, Chwyczko T, Kowalik I, et al. Exercise training program in patients with NYHA III class systolic heart failure - Parallel comparison to the effects of resynchronization therapy. *Adv Med Sci*. 2019;64(2):241-245.

44. Soska V, Dobsak P, Pohanka M, et al. Exercise training combined with electromyostimulation in the rehabilitation of patients with chronic heart failure: A randomized trial. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2014;158(1):98-106.

45. Sturm B, Quittan M, Wiesinger GF, et al. Moderate-intensity exercise training with elements of step aerobics in patients with severe chronic heart failure. *Arch Phys Med Rehabil*. 1999;80(7):746-750.

46. Carter SL, Rennie CD, Hamilton SJ, et al. Changes in skeletal muscle in males and females following endurance training. *Can J Physiol Pharmacol*. 2001;79(5):386-392.

47. Van Laethem C, Van De Veire N, De Backer G, et al. Response of the oxygen uptake efficiency slope to exercise training in patients with chronic heart failure. *Eur J Heart Fail*. 2007;9(6-7):625-629.

48. Kavanagh T, Myers MG, Baigrie RS, et al. Quality of life and cardiorespiratory function in chronic heart failure: effects of 12 months' aerobic training. *Heart*. 1996;76(1):42-49.

49. Resurrección DM, Moreno-Peral P, Gómez-Herranz M, et al. Factors associated with non-participation in and dropout from cardiac rehabilitation programmes: a systematic review of prospective cohort studies. *Eur J Cardiovasc Nurs*. 2019;18(1):38-47.

50. Milanović Z, Sporiš G, Weston M. Effectiveness of High-Intensity Interval Training (HIT) and Continuous Endurance Training for VO2max Improvements: A Systematic Review and Meta-Analysis of Controlled Trials. *Sports Med*. 2015;45(10):1469-1481.

51. Wang C, Xing J, Zhao B, et al. The Effects of High-Intensity Interval Training on Exercise Capacity and Prognosis in Heart Failure and Coronary Artery Disease: A Systematic Review and Meta-Analysis. *Cardiovasc Ther*. 2022;2022:4273809.

KEYWORDS heart failure, cardiac rehabilitation, exercise training, ventilatory threshold, cardiopulmonary exercise testing

APPENDIX A. SUPPLEMENTARY DATA Supplementary data to this article can be found online at https://doi.org/10.1016/j.hjc.2024.01.004.