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The influence of training characteristics on the effect of exercise training in patients with coronary artery disease: Systematic review and meta-regression analysis

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ABSTRACT

Background: Although exercise-based cardiac rehabilitation improves exercise capacity of coronary artery disease patients, it is unclear which training characteristic determines this improvement. Total energy expenditure and its constituent training characteristics (training intensity, session frequency, session duration and programme length) vary considerably among clinical trials, making it hard to compare studies directly. Therefore, we performed a systematic review and meta-regression analysis to assess the effect of total energy expenditure and its constituent training characteristics on exercise capacity.

Methods: We identified randomised controlled trials comparing continuous aerobic exercise training with usual care for patients with coronary artery disease. Studies were included when training intensity, session frequency, session duration and programme length was described, and exercise capacity was reported in peakVO_2. Energy expenditure was calculated from the four training characteristics. The effect of training characteristics on exercise capacity was determined using mixed effects linear regression analyses. The analyses were performed with and without total energy expenditure as covariate.

Results: Twenty studies were included in the analyses. The mean difference in peakVO_2 between the intervention group and control group was 3.97 $ml \cdot min^{-1} \cdot kg^{-1}$ ($p < 0.01$, 95% CI 2.86 to 5.07). Total energy expenditure was significantly related to improvement of exercise capacity (effect size 0.91 $ml \cdot min^{-1} \cdot kg^{-1}$ per 100 J·kg, $p < 0.01$, 95% CI 0.77 to 1.06), no effect was found for its constituent training characteristics after adjustment for total energy expenditure.

Conclusions: We conclude that the design of an exercise programme should primarily be aimed at optimising total energy expenditure rather than on one specific training characteristic.

1. Introduction

Exercise-based cardiac rehabilitation (ECR) improves exercise capacity and quality of life, and decreases cardiovascular mortality and morbidity in patients with coronary artery disease (CAD) [1–3]. Exercise training is therefore considered a crucial component of cardiac rehabilitation and is highly recommended in both European and American clinical guidelines [4,5]. Furthermore, ECR is widely implemented in daily practice for CAD patients. Because exercise capacity is strongly associated with morbidity and mortality in CAD patients [6], it is important to understand which factors determine the beneficial effects of exercise. Moreover, if we understand which training characteristics are the strongest determinants of improvement in exercise capacity after exercise training, the most effective exercise programme can be prescribed [7].

Studies with healthy adults showed that the effects of exercise training improve when total energy expenditure of an exercise programme increases [8]. Recently, two systematic reviews confirmed that total energy expenditure was the strongest predictor of improvement in exercise capacity in chronic heart failure patients [9,10]. Total energy expenditure of an exercise programme is determined by session frequency, session duration, training intensity and programme length. Although practice guidelines describe the content of an exercise programme, the individual characteristics of an exercise programme vary considerably in practice and between training studies [1,11,12]. Therefore, the individual effect of the training characteristics remains under debate.

Vanhees et al. showed in a retrospective cohort study that session frequency and training intensity were strong predictors for the

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improvement in exercise capacity [13]. Other studies indicated that although a minimum energy expenditure was required to achieve improvement in exercise capacity, adjustments to individual characteristics above a certain cut-off value (e.g. session duration of 30 min, session frequency of twice a week) did not influence the improvement in exercise capacity [14,15]. However, those studies did not adjust for total energy expenditure of the exercise programmes. Since energy expenditure is comprised by the four training characteristics, a correction for energy expenditure is necessary to identify the individual effect of the training characteristics. Therefore, studies comparing training protocols to determine the effect of a training characteristic should perform an isocaloric comparison (i.e. a comparison in which energy expenditure of both exercise programmes are matched). Besides, other training characteristics such as type (strength or aerobic training), and modality (interval or continuous training) should be similar between studies for a fair comparison as well.

Previous studies with isocaloric comparisons but dissimilar session frequency and/or programme length in the exercise programmes showed that the improvement in exercise capacity was similar [16,17]. In addition, the exact role of training intensity appears unclear. Whereas two systematic reviews showed a superior effect on exercise capacity after high intensity training compared to moderate intensity training [18,19], other studies comparing isocaloric programmes showed no differences between the exercise programmes [20–22]. However interpretation of the results of these studies is hampered, as exercise programmes in those studies did not only differ in training intensity but also in modality. High intensity training is performed using an interval protocol, whereas moderate intensity training is performed as continuous training. Interval training, which has a large anaerobic metabolic component, results in different physical adaptations compared to continuous aerobic training. Whereas, anaerobic training attenuates hypertrophy and improves buffers to lactate, continuous aerobic training results in adaptations such as endothelial improvement and the development of coronary collateral vessels [23,24]. Although both training responses are beneficial for the patient, the different training responses between aerobic continuous training and anaerobic interval training impedes a fair analysis on the individual effect of the training characteristics that compose the total energy expenditure of a training programme.

With large sets of exercise data, regression analyses can be used to explore the individual effect of the training characteristics on the improvement of exercise capacity. In addition, a correction for energy expenditure can be performed in the analyses. Therefore, the objective of this systematic review and meta-regression analysis was to investigate which training characteristics determine the improvement of exercise capacity after ECR in CAD patients, correcting for total energy expenditure of the exercise programme.

2. Methods

2.1. Literature search strategy

We conducted a systematic literature search in the database of EMBASE and MEDLINE to find papers published between 1st of April 2007 and 1st of April 2015, addressing aerobic exercise training after cardiac rehabilitation for CAD patients. In the search strategy, which involved a mix of MeSH-terms and free text terms, we combined synonyms on three topics: population and diagnosis (i.e. coronary artery disease, cardiac patients, myocardial infarction), therapy (i.e. cardiac rehabilitation, secondary prevention, exercise training, physical training) and outcome (i.e. physical function, exercise capacity, exercise tolerance). The search was limited to randomised controlled trials published between 01-04-2007 and 01-04-2015 and written in English. The complete search strategy is described in Appendix A. The protocol of this systematic review and meta-regression analysis is published in the Prospero database (http://www.crd.york.ac.uk/prospero) with registration number CRD42014014846 [10].

2.2. Study selection

We included randomised controlled trials comparing continuous aerobic exercise programmes with usual care in CAD patients. Only studies reporting change in peakVO_2 to evaluate training effects were included. Studies evaluating interval training, resistance training or cardiac rehabilitation modalities not affecting exercise capacity (e.g. cognitive therapy, stress-management) were excluded. Studies that reported the results of a combination of aerobic exercise with strength training were excluded as well. All included studies were required to describe the aerobic exercise programme in detail, with at least information concerning session frequency, session duration, programme length and training intensity (% of peak heart rate, peakVO_2 or maximum workload). The authors of 12 studies were contacted for missing data concerning the exercise programme or outcome parameter, and we received feedback from seven authors.

2.3. Data collection process

Four couples of researchers screened the titles and abstracts using the abovementioned in- and exclusion criteria. Both researchers in each couple performed the screening independently using a screening form. Afterwards, they compared the results and reached consensus. The full papers of the selected articles were screened by three couples of researchers using a second screening form, to make a final decision on inclusion in a similar procedure. When no consensus was reached between the two researchers, a third researcher decided whether the article was included. Used data from the full texts was stored in a Microsoft Access database.

2.4. Energy expenditure

We calculated energy expenditure ($J \cdot kg^{-1}$) for all interventions by multiplying total training time (i.e. session frequency ∗ session duration ∗ programme length) with training intensity. First, training intensity was converted to a percentage of peakVO_2 using a conversion table from the American College of Sports Medicine [25]. Second, the oxygen consumption (VO_2 $ml \cdot kg^{-1}$) per intervention was calculated using pre-training exercise capacity (peakVO_2) multiplied with training intensity (% of peakVO_2), and total programme length in minutes. Finally, total oxygen uptake per kg (in $ml \cdot kg^{-1}$) was converted to Joules per kg under the assumption that consumption of 1 l oxygen equals 20.93 J [25].

2.5. Study and reporting quality

The methodological quality of the included articles was assessed using the TESTEX tool for the assessment of quality and reporting in exercise training studies [26]. The tool provides a 15-point scale, in focuses on study quality (5 points) and reporting (10 points). The TESTEX scale was developed to review exercise training studies, because traditional scales often include criteria that are redundant for these type of studies (such as blinding of participants). Two independent researchers evaluated the quality and reporting of the included studies using the TESTEX scale. When no consensus was reached between the researchers, a third researcher decided the score.

2.6. Synthesis of results

The relationship between training characteristics and exercise-related changes in exercise capacity (peakVO_2) was determined using mixed-effects linear regression analyses. First, a linear regression analysis was used to assess differences in exercise capacity between exercise training and usual care. Second, the effect of energy expenditure and the four training characteristics was assessed separately by five univariate analyses. Subsequently, the effect of the four training characteristics (i.e. session frequency, session duration, training intensity and programme length) was assessed by four multivariate regression analyses with total energy expenditure as a covariate. Model fit was assessed using residual deviance and I^2, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. Large values of I^2 (>75%) indicate inconsistency in the result of the underlying studies. The effect of training characteristics was assessed by their Z-score. Because of the large number of statistical comparisons we considered p-values below 0.01 as significant. When heterogeneity (i.e. I^2) was high and sufficient data were available, the analysis was repeated without outliers. Baseline differences between groups were tested using an independent Student t-test with a significance level of 0.05.

3. Results

3.1. Study selection

We identified 1303 unique studies from the EMBASE and MEDLINE databases. Fig. 1 provides an overview of the search and election studies records. Through screening of titles and abstract we excluded 1047 studies, and 219 studies were excluded after full-paper review. From the remaining 37 studies, 17 were included in an analysis for chronic heart failure patients published elsewhere [10] and 20 were included in this review. One study randomised their participants in two intervention groups (i.e. high intensity training and moderate intensity training) and one control group [27]. Therefore, we included this study as two separate comparisons with the same control group.

3.2. Study and programme characteristics

The programme characteristics are described in Table 1, the baseline characteristics of the studies are provided in Appendix A, Table 1. Median sample size of the included studies was 46 patients, ranging from 19 to 118 included patients. A total of 585 patients were randomised to aerobic exercise training (median age 58.8, 87% male), and 533 patients received usual care (median age 58.6, 87% male). There were no significant differences between groups at baseline for the aggregated data. Median programme length was 12 weeks (range 2 to 28) with a median of 3 sessions per week (range 2 to 42). Session duration varied from 10 to 45 min, with a median of 30 min. Median training intensity was 65% of peakVO_2 (range 45% to 79% of peakVO_2). Total energy expenditure of the training programmes varied from 74 to 1300 $J \cdot kg^{-1}$ with a median of 324 $J \cdot kg^{-1}$.

3.3. Effect of training characteristics

The mean difference in improvement peakVO_2 between the intervention group and control group was 3.97 $ml \cdot min^{-1} \cdot kg^{-1}$ ($p < 0.01$, 95% CI 2.86 to 5.07, Fig. 2). Table 2 presents the results from univariate regression and multivariate regression analyses. Total energy expenditure was significantly associated with improvement of exercise capacity, showing that an increase of energy expenditure of 100 $J \cdot kg^{-1}$ was associated with a peakVO_2 improvement of 0.91 $ml \cdot min^{-1} \cdot kg^{-1}$ ($p < 0.01$, 95% CI 0.77 to 1.06). Programme duration, intensity and length were significantly associated with improvement of peakVO_2 in the univariate analyses. Although heterogeneity for energy expenditure was low ($I^2 = 33\%$), it was high for all individual training characteristics (I^2 ranging from 70% to 91%). When adjusting for total energy expenditure, none of the individual training characteristics was significantly associated with improvement of peakVO_2. After the adjustment, heterogeneity was low for all characteristics (I^2 ranging from 30% to 34%). Detailed results of the regression analyses are provided in Appendix B.

As appears from Fig. 2, the study by Benetti et al. found a much larger effect on peakVO_2 than the other studies, and was probably causing high heterogeneity in the meta-regression. A sensitivity analysis without this study showed that heterogeneity was lower for all univariate and multivariate analyses (Appendix A, Table 2). Although the effect sizes decreased, energy expenditure and programme length, intensity and duration remained significantly associated with improvement of exercise capacity in the univariate analyses. In addition, none of the characteristics were significantly associated with improvement of exercise capacity after adjustment for energy expenditure. Detailed results of the regression analyses are provided in Appendix C.

3.4. Others (study and reporting quality, publication bias)

Results of the TESTEX assessment are provided in Appendix D and showed that study and reporting quality was moderate to good (mean study quality 3 out of 5 points, mean reporting quality 7 out of 10 points). The funnel plots (Appendix D) showed little evidence for publication bias.

4. Discussion

The present study showed that total energy expenditure of exercise programmes is a strong determinant of the effect of ECR on exercise capacity in CAD patients. Whereas the meta-regression analysis showed that session duration, programme length and training intensity were all related to the improvement in exercise capacity, no independent

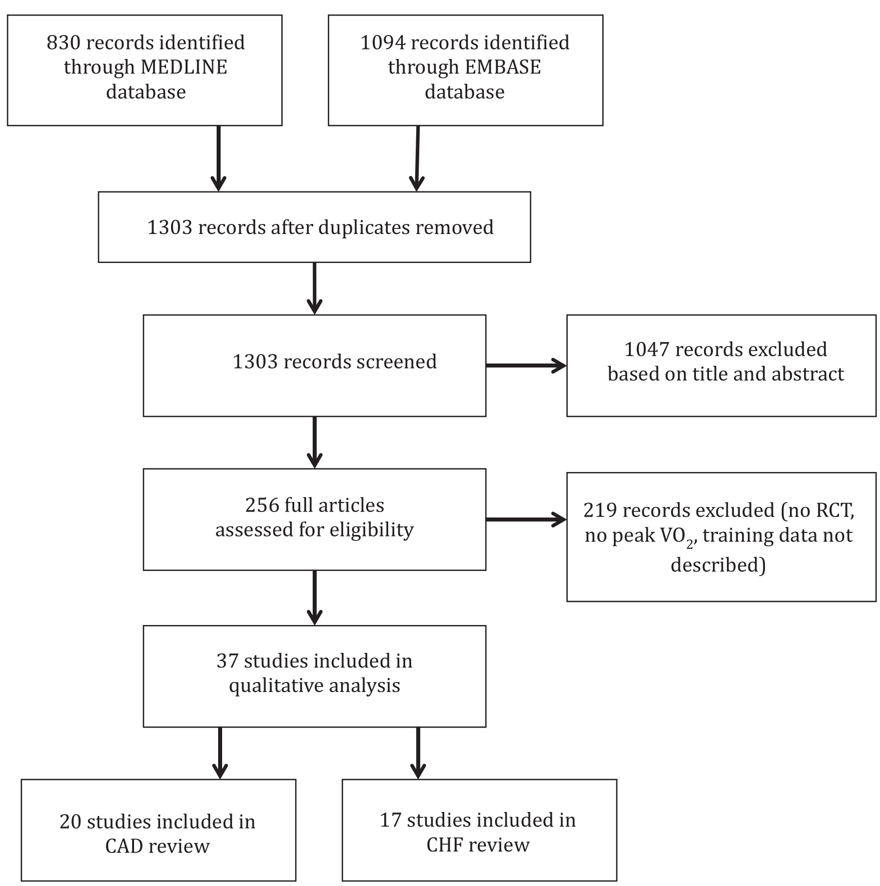

Fig. 1. Inclusion flowchart of the selected studies.

Table 1
Exercise programme characteristics of included studies.

Study	Programme length (weeks)	Session frequency (n/week)	Session duration (min)	Intensity (% $peakVO_2$)	Total training volume (min)	EE total^{-1} ($J \cdot kg^{-1}$)	EE week^{-1} ($J \cdot kg^{-1}$)	$\Delta PeakVO_2$ ($ml \cdot min^{-1} \cdot kg^{-1}$)	$\Delta PeakVO_2$ ($ml \cdot min^{-1} \cdot kg^{-1}$)
								INT	CON
Aamot et al. (2010) [28]	4	2	32.5	44.5	260	74.0	18.5	0.1	0.9
Balen et al. (2008) [29]	3	5	45	55.0	675	155.2	51.7	3.2	0.6
Belardinelli et al. (2001) [30]	26	3	30	60.0	2340	545.8	21.0	5.1	−1.1
Benetti et al. (2010a) [27]	12	5	45	78.9	2700	1300.1	108.3	12.4	−2.4
Benetti et al. (2010b) [27]	12	5	45	66.3	2700	1197.2	99.8	5.9	−2.4
Blumenthal et al. (2005) [31]	16	3	45	73.2	2160	631.3	39.5	1.9	−0.8
Giallauria et al. (2006a) [32]	13	3	30	60.0	1170	239.2	10.7	4.5	−0.4
Giallauria et al. (2006b) [33]	13	3	30	70.0	1170	279.0	21.5	4.2	0.8
Giallauria et al. (2011) [34]	26	3	30	68.4	2340	548.6	21.1	4.6	−0.4
Giallauria et al. (2012) [35]	26	3	30	65.0	2340	413.3	15.9	4.0	1
Giallauria et al. (2013) [36]	26	3	30	65.0	2340	445.0	17.1	4.0	1
Hambrecht et al. (2000) [23]	4	42	10	72.6	1680	612.0	153.0	2.8	−0.2
Lee et al. (2009) [37]	12	3	20	62.5	720	208.8	17.4	2.8	−0.3
Legramante et al. (2006) [38]	2	12	30	78.9	720	206.7	103.4	2.6	0.9
Mameletzi et al. (2011) [39]	28	3	30	60.0	2520	663.6	23.7	4.6	−0.9
Oliveira et al. (2014) [40]	8	3	30	69.0	720	288.5	36.1	2.1	−0.1
Oliveira et al. (2015) [41]	8	3	30	69.5	720	290.6	36.3	2.2	−0.1
Ribeiro et al. (2012) [42]	8	3	35	60.0	840	324.4	40.6	3.1	0.3
Su et al. (2011) [43]	12	3	20	62.5	720	211.6	17.6	2.6	0.6
Takeyama et al. (2000) [44]	2	14	30	55.0	840	126.5	63.2	3.0	1.1
Wu et al. (2006) [45]	12	3	45	63.2	1620	335.7	28.0	8.5	3.5

Data provided as mean ± standard deviation, unless stated otherwise.
INT = intervention; CON = control; $peakVO_2$ = maximal oxygen consumption; EE = energy expenditure.

effect of any of the training characteristics was observed after correction for total energy expenditure.

Although the beneficial effects of exercise training on exercise capacity have already been documented extensively in prior clinical trials and meta-analyses [3,46], the effect of individual training characteristics on improvement in exercise capacity was not well established. Results from our meta-analysis indicate that total energy expenditure is an important determinant of improvement in exercise capacity, and that the effects of the individual training characteristics disappear when we adjust for energy expenditure. This is in line with studies comparing

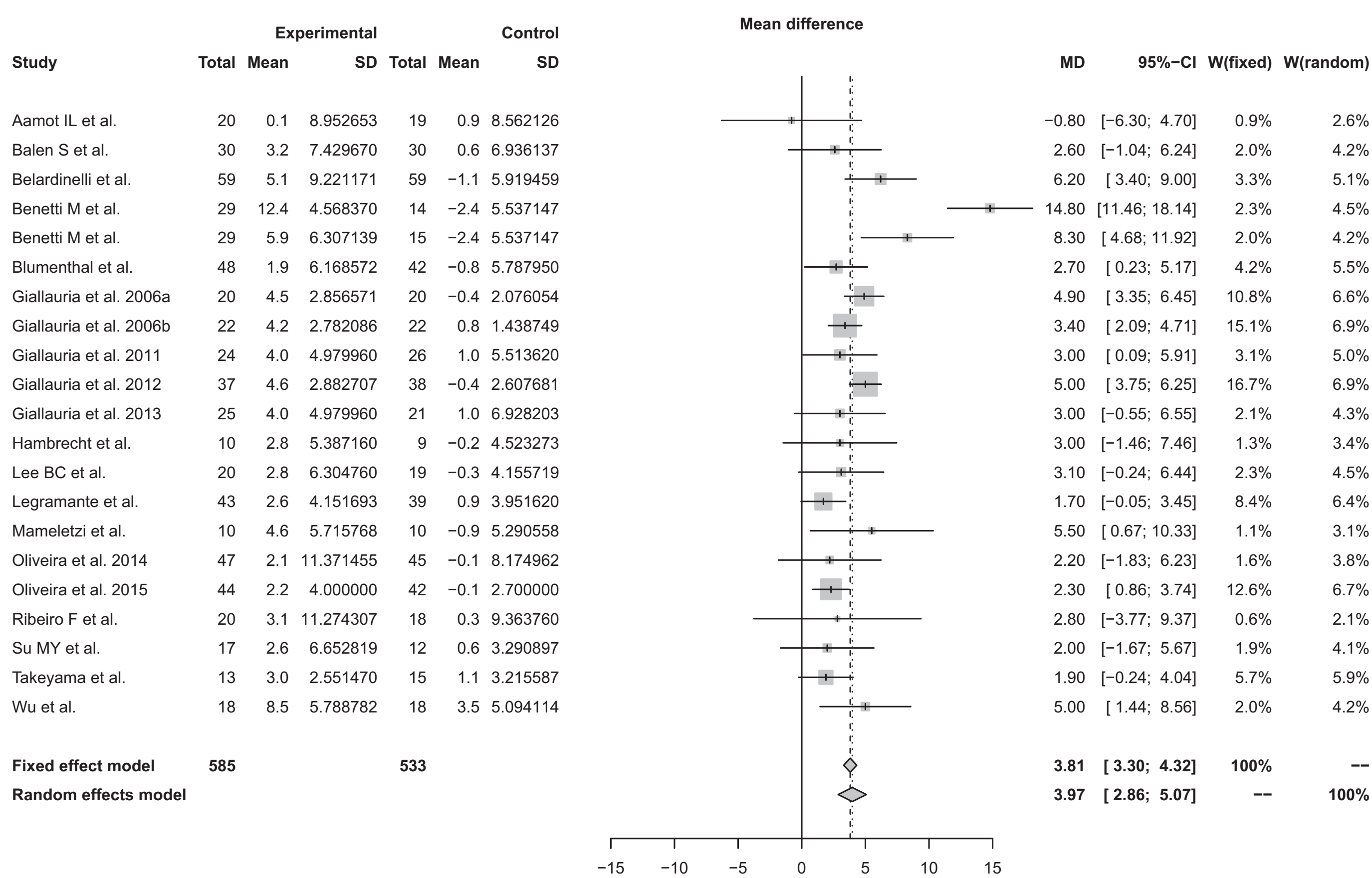

Fig. 2. Forest plot describing the effect of exercise training on $peakVO_2$. Heterogeneity: *t*-squared = 73.7%, tau-squared = 4.18, $p < 0.0001$.

Table 2
Results of the regression analyses, with and without correction for energy expenditure.

Training characteristics	Effect scale	Effect Size ($ml \cdot min^{-1} \cdot kg^{-1}$)	95% CI ($ml \cdot min^{-1} \cdot kg^{-1}$)	*p*-value	I^2	AIC
Univariate regression analyses						
Total EE	100 $J \cdot kg^{-1}$	0.91	0.77–1.06	<0.001*	33.4	82.7
Session duration	10 min	1.25	0.94–1.56	<0.001*	69.6	102.4
Training intensity	10% $peakVO_2$	0.61	0.45–0.78	<0.001*	73.7	104.7
Programme length	2 weeks	0.49	0.34–0.63	<0.001*	75.9	110.0
Session frequency	1 session/week	0.21	0.03–0.38	0.019	90.8	122.9
Multivariate regression analyses, correcting for energy expenditure						
Session duration	10 min	0.24	−0.17 to 0.65	0.243	29.8	80.5
Training intensity	10% $peakVO_2$	0.09	−0.10 to 0.28	0.339	31.6	81.1
Session frequency	1 session/week	−0.02	−0.12 to 0.08	0.702	36.7	81.3
Programme length	2 weeks	0.05	−0.10 to 0.21	0.504	33.8	81.3

Effect size is given as change in $peakVO_2$. Ranked according to I^2.
I^2 = residual heterogeneity; AIC = Akaike's information coefficient (model fit); $peakVO_2$ = maximal oxygen consumption; EE = energy expenditure.
* Significant at $p < 0.01$.

individual training characteristics using isocaloric exercise programmes [16,17,22]. Therefore, if ECR programmes are aimed at inducing the largest effect on exercise capacity, we recommend that ECR programmes are designed to have high total energy expenditure without specific preference for a high training intensity or other training characteristics.

The results from our regression analyses provide additional information compared to the systematic reviews and randomised controlled trials previously performed. The regression analysis calculates an effect size for each individual training characteristic. The effect sizes illustrate how we can enhance the effect of the exercise programme if energy expenditure is not taken into account. If we assume that the range of the included studies determines practice variation, a maximum improvement of 1.68 $ml \cdot min^{-1} \cdot kg^{-1}$ $peakVO_2$ can be achieved by increasing intensity from 45 to 79% of $peakVO_2$. Similarly, according to the results of the sensitivity analysis, an improvement of 0.49 $ml \cdot min^{-1} \cdot kg^{-1}$ is achieved by an increase in session frequency from 2 to 5 sessions per week, while an improvement of 2.57 $ml \cdot min^{-1} \cdot kg^{-1}$ $peakVO_2$ is achieved by increasing session duration from 20 to 45 min per session and 5.50 $ml \cdot min^{-1} \cdot kg^{-1}$ $peakVO_2$ by increasing programme length from 2 to 28 weeks. However, these results are based on the assumption that there is a linear dose-response relationship for exercise training. Previous studies indicated that the beneficial effects of exercise deteriorate with vigorous exercise [8]. Therefore, the results are primarily applicable within the range described in this review.

In our first analysis, all training characteristics were significantly related to improvement in exercise capacity. However, these effects were absent after correction for total energy expenditure. This implies that prescription of an exercise programme should primarily be focused on total energy expenditure rather than on one specific training characteristic. Therefore, factors such as training adherence, patients' preference and determinants of sustainability of training effects should be taken into account when designing an exercise programme. First, a high training adherence improves the effectiveness of ECR [47]. Previous studies indicated that a high training intensity can reduce training adherence, whereas an increase in session frequency or session duration are not associated with a reduction in adherence [48–50]. Second, an exercise programme aligned with the preferences of a patient (e.g. training type, training characteristics, location) improves motivation and training adherence, indirectly influencing the improvement in exercise capacity [48,51]. In view of the abovementioned facts, an exercise programme can be translated to the home-environment for patients who prefer exercise training at home. Furthermore, the development of telemonitoring opportunities to sustain guidance in the home environment (i.e. wearable sensors and increased connectivity) provides an opportunity to design a feasible and effective home-based training programme that can induce an optimal short-term and long-term training effect [52,53].

5. Limitations

First, due to strict criteria in the inclusion and exclusion procedure, sample size and variation in training characteristics such as session frequency and duration among the included studies was low. Studies that lacked information concerning the training characteristics were excluded from the analyses. Consequently, the unaccounted variability in the univariate regression analyses was high, indicating a low model fit. Therefore, the results must be interpreted with caution. In particular, we should not expect that the estimated effect of individual training characteristics generalise beyond the range of our data.

Second, we assumed a linear dose-response relationship in exercise training. However, previous literature showed that excessive exercise may hamper the improvement in exercise capacity [54]. Therefore, our results can only be interpreted with respect to the variance of training characteristics in the included studies. Because the variance of the included studies is within the borders of a regular ECR programme, we expect that our results and recommendations are applicable to ECR programmes.

Third, our analyses were based on the exercise programme reported in the included studies. However, the actual exercise performed during the programme often deviates from the prescribed exercise programme, which is reported in the study. Conraads et al. showed that the actual training intensity in a high intensity training group was lower than prescribed in the exercise programme, while the actual intensity of the moderate intensity training group was higher than prescribed [22,55]. They discussed that this could be an important factor influencing the improvement in exercise capacity in both groups, and suggested that the adherence to the prescribed programme should be measured during the exercise programme and reported in the study. Because our analyses are based on the prescribed exercise programmes, the results could be different when both the performed exercise programmes and the prescribed exercise programmes were reported and included in the analyses.

Finally, several studies reported no standard deviation of the change from baseline in $peakVO_2$. Therefore, a correlation between baseline and follow-up assessment of $peakVO_2$ was assumed at $p = 0.7$. This could have affected the results.

6. Conclusion

This study showed that total energy expenditure of an exercise programme is the main determinant of improvement in exercise capacity in CAD patients. To increase total energy expenditure, all four training characteristics appear suitable for adjustment.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.07.051.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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