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ORIGINAL RESEARCH ARTICLE

Exercise training and high-sensitivity cardiac troponin T in patients with heart failure with reduced ejection fraction

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Abstract

Aims Whether an exercise training intervention is associated with reduction in long-term high-sensitivity cardiac troponin T (hs-cTnT) concentration (a biomarker of subclinical myocardial injury) in patients with heart failure with reduced ejection fraction (HFrEF) is unknown. The aims were to determine (i) the effect of a 12 week endurance exercise training intervention with different training intensities on hs-cTnT in stable patients with HFrEF (left ventricular ejection fraction $\leq$ 35%) and (ii) associations between hs-cTnT and peak oxygen uptake (VO_{2peak}).

Methods and results In this sub-study of the SMARTEX-HF trial originally including 261 patients from nine European centres, 213 eligible patients were included after withdrawals and appropriate exclusions [19% women, mean age 61.2 years (standard deviation: 11.9)], randomized to high-intensity interval training (HIIT; *n* = 77), moderate continuous training (MCT; *n* = 63), or a recommendation of regular exercise (RRE; *n* = 73). Hs-cTnT measurements and clinical data acquired before (BL) and after a 12 week exercise training intervention (12 weeks) and at 1 year follow-up (1 year) were analysed using multivariable mixed models. Baseline hs-cTnT was above the 99th percentile upper reference limit of 14 ng/L in 35 (48%), 35 (56%), and 49 (64%) patients in the RRE, MCT, and HIIT groups, respectively. Median hs-cTnT was 16 ng/L at BL, 14 ng/L at 12 weeks, and 14 ng/L at 1 year. Hs-cTnT was statistically significantly reduced at 12 weeks in a model adjusted for randomization group, centre and VO_{2peak}, and after further adjustment in the final model that also included age, sex, creatinine concentrations, N-terminal pro-brain natriuretic peptide, smoking, and heart failure treatment. The mean reduction from BL to 12 weeks in the final model was 1.1 ng/L (95% confidence interval: 1.0–1.2 ng/L, $P < 0.001$), and the reduction was maintained at 1 year with a mean reduction from BL to 1 year of 1.1 ng/L (95% confidence interval: 1.0–1.1 ng/L, $P = 0.025$). Randomization group was not associated with hs-cTnT at any time point (overall test: $P = 0.20$, MCT vs. RRE: $P = 0.81$, HIIT vs. RRE: $P = 0.095$, interaction time × randomization group: $P = 0.88$). Independent of time point, higher VO_{2peak} correlated with lower hs-cTnT (mean reduction over all time points: 0.2 ng/L per increasing $mL \cdot kg^{-1} \cdot min^{-1}$, $P = 0.002$), without between-group differences ($P = 0.19$).

Conclusions In patients with stable HFrEF, a 12 week exercise intervention was associated with reduced hs-cTnT in all groups when adjusted for clinical variables. Higher VO_{2peak} correlated with lower hs-cTnT, suggesting a positive long-term effect of increasing VO_{2peak} on subclinical myocardial injury in HFrEF, independent of training programme.

Keywords Heart failure; Troponin T; Cardiorespiratory fitness; Exercise training interventions; Training intensity

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Introduction

Although exercise training is part of current guidelines for the treatment of chronic heart failure (HF),[1] concerns have been raised that high-intensity exercise may increase myocardial injury in patients with HF, where normal adaptive mechanisms malfunction. In contrast, some studies indicate that exercise as a therapeutic option is underused in patients with HF.[2–4] Measurement of biomarkers of HF and myocardial injury may help to clarify these issues. Cardiac-specific troponin T (cTnT) is part of the contractile apparatus in cardiac muscle cells and leaks out of damaged cells. It is therefore used as a biomarker, and detection in serum plays an important role in the diagnostics of acute and chronic myocardial injury.[5] Chronic elevation of high-sensitivity cTnT (hs-cTnT) above the 99th percentile upper reference limit of 14 ng/L is associated with adverse cardiovascular events.[6,7] In chronic HF, hs-cTnT also independently predicts more robust endpoints, including all-cause and cardiovascular death, as well as cardiovascular hospitalizations, with 18 ng/L as the preferred cut-off.[8]

In patients diagnosed with HF, the effects and safety of exercise training have been questioned.[9,10] However, according to the European Society of Cardiology 2016 HF guideline, regular aerobic exercise training has the highest recommendation in stable patients with HF with reduced ejection fraction (HFrEF), with level of evidence class IA.[4] An unresolved matter is the preferred training intensity in these patients. Peak oxygen uptake (VO_{2peak}) is associated with prognosis in HF,[9,11] and high-intensity interval training (HIIT) has increased VO_{2peak} more efficiently than moderate continuous training (MCT) in stable patients with HFrEF in some studies.[12] This was not confirmed in the index SMARTEX-HF study, and the debate regarding training intensity is therefore still ongoing.[13]

There are few studies assessing the association between long-term cTnT concentrations and endurance exercise training in patients with HFrEF. In the HF-ACTION study evaluating an exercise training programme in patients with stable HFrEF, no changes were found in cTnT concentrations measured at baseline, after 3 months, and after 12 months.[14] However, the employed assay was not a high-sensitivity assay (14% of patients had measurable cTnT). In addition, only MCT with a training duration of 15–35 min was performed, and the training effect was too small to draw definite conclusions. Accordingly, there is a need for studies using hs-cTnT assays and high-intensity exercise training programmes with good adherence.

The randomized multicentre SMARTEX-HF study compared 12 weeks of supervised intervention of HIIT, MCT, or a recommendation of regular exercise (RRE, home-based). Training intensity was measured objectively using heart rate (HR) at all supervised training sessions, and myocardial injury was assessed with hs-cTnT. The compliance to number of supervised sessions was 93.3%.[13] Thus, these study data are well suited for a secondary analysis investigating the association between cTnT and endurance exercise training in patients with HFrEF.

The aim of the present study was to determine the long-term effect of a 12 week endurance exercise training intervention with different training intensities and modes on hs-cTnT in stable patients with HFrEF [left ventricular ejection fraction (LVEF) $\leq$ 35%] and to determine associations between hs-cTnT and VO_{2peak}. We hypothesized (i) that a 12 week endurance exercise training programme is associated with reduced chronic myocardial injury, measured as a decline in hs-cTnT concentrations and that this association will last through the follow-up period; (ii) that different training intensities and modes have different associations to hs-cTnT; and (iii) that changes in hs-cTnT during the study period are associated with changes in VO_{2peak}.

Methods

Patients

High-sensitivity cardiac troponin T was measured in a sub-study of the SMARTEX-HF study that included 261 patients from nine different testing centres. Inclusion criteria and interventions have been described in detail previously.[15] Participants were randomized to three groups: HIIT (n = 90), MCT (n = 85), and RRE (n = 86), stratified by testing centre and ischaemic vs. non-ischaemic aetiology of HF. A total of 215 patients completed the 12 week follow-up, that is, n = 77 in HIIT, n = 65 in MCT, and n = 73 in RRE. For the present study, two patients were excluded due to missing blood samples (both from the MCT group, n = 63 eligible patients). Data were analysed according to the intention-to-treat principle, comprising 213 patients at baseline (BL) and 12 weeks and 191 patients at 52 week follow-up (1 year). Study enrolment, randomization, and loss to follow-up have been detailed earlier.[13] In brief, 14 patients had LVEF $>$ 40% and did not fulfil the inclusion criteria, 16 withdrew, died, or were hospitalized before starting the training intervention, and 16

were excluded during the training intervention (two died, seven stopped due to serious adverse events, five withdrew, and two were lost to follow-up). At 1 year, 5 had died, 6 missed follow-up due to serious adverse events, 1 withdrew, 1 was lost to follow-up, and 11 patients had missing blood samples.[13] In the present sub-study, total loss to follow-up due to all causes was similar in the three groups (HIIT: n = 10, MCT: n = 7, RRE: n = 7, P = 0.80).

Samples and tests

Blood samples were drawn after an overnight fast before starting the training intervention (BL), after completion of the exercise programme (12 weeks), and at 52 week follow-up (1 year). Sampling was done more than 48 h after the last exercise training. Serum hs-cTnT was measured in all samples in a single batch at a core lab using a commercially available assay (Elecsys TnT hs STAT, cobas e 801, Roche Diagnostics). The analytical range was 3 to 10 000 ng/L, and the inter-assay and intra-assay coefficients of variation in the relevant concentration ranges were 2.1–3.5% and 2.2–3.9%, respectively. The samples were analysed by order of randomization number with the three samples from each person in the same run, and the laboratory personnel were blinded to randomization group. All samples had hs-cTnT concentrations within the analytical range.

Cardiopulmonary exercise testing (CPET) was performed after blood samples were drawn. As detailed in previous publications, CPET was performed on either a bicycle or a treadmill, using an incremental protocol with 10 or 20 W increase in workload per minute until exhaustion, starting at 20 or 40 W, respectively. Standard equipment for indirect calorimetry was used to measure the maximal oxygen uptake. VO_{2peak} is the highest measured oxygen uptake during CPET when maximal oxygen uptake is not reached. The mean of the three highest 10 s consecutive measurements was identified as VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$), and for simplicity, the term is used for all test results in the present study.[13,15] BL, 12 weeks, and 1 year tests were performed using the same protocol and exercise modality (treadmill or bicycle) as the training. Left ventricular end-diastolic diameter (LVEDD) and LVEF were assessed by echocardiography according to standard procedure, as detailed previously.[13]

Participants in the MCT and HIIT groups had three supervised exercise training sessions per week, on a treadmill or bicycle. Exercise protocols have been described elsewhere.[12,13,15] In brief, the HIIT group was targeted to exercise at ≥90% of HR_{peak} during the high-intensity intervals and 60–70% of HR_{peak} between these intervals. The MCT group was targeted to exercise at 60–70% of HR_{peak}. The number of participants was calculated based on the primary endpoint in the index SMARTEX-HF study.[15]

The investigation was conducted in conformity with the principles outlined in the *Declaration of Helsinki*.[16] The study was approved by national or institutional ethics committees for medical research in all countries. All patients gave written informed consent.

Statistics

This is a post hoc analysis of the SMARTEX-HF trial. Descriptive data are given as median (25 and 75 percentiles). Due to non-normality and to improve model fit, hs-cTnT concentrations were logarithmically transformed during analysis and back-transformed to the original scale for data presentation. The changes in hs-cTnT and association to VO_{2peak} during the study were investigated using multivariable mixed model analyses. This approach allows for variations in the dependent and independent variables due to the repeated measurements during the study and accounts for different number of cases at each time point. A basic model included hs-cTnT as dependent variable and VO_{2peak}, randomization group, and testing centre (by a categorical variable) as independent variables. The model was then further adjusted with predefined clinical variables selected based on previous literature, that is, age,[1,5] sex,[1,5] creatinine concentration,[1,17] N-terminal pro-brain natriuretic peptide (NT-proBNP),[1] LVEDD,[13] New York Heart Association (NYHA) functional class,[18] LVEF,[18] HR_{peak},[18] workload,[18] and HF treatment, defined as treatment (yes/no) with angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and/or beta-blockers. For adjustment variables with repeated measurements, that is, creatinine, NT-proBNP, LVEDD, LVEF, HR_{peak}, and workload, the values for each time point were included. Sex was a better explanatory variable than body surface area. Non-significant variables were excluded from the final model.

To assess the robustness of the results, two sensitivity analyses were performed. Sensitivity analysis 1 investigated whether supervised training had a different effect on hs-cTnT than recommendation of exercise. Thus, data from the exercise training groups were pooled, making one intervention group (MCT + HIIT; n = 142) and one control group (RRE; n = 73) in the analysis. In sensitivity analysis 2, we included patients training 'on target', that is, 60–70% of HR_{peak} in the MCT group and ≥90% of HR_{peak} in the HIIT group, to better assess the effect of the target intensity difference between the two training groups. All patients in the RRE group were included in order to permit comparisons among the three randomization groups.

Two-sided P-values < 0.05 were considered significant, and Sidak adjustment was used where necessary for comparison among the three randomization groups. Model fit was assessed by checking residuals and using the Akaike information criterion and Bayesian information criterion. These

criteria indicate how well different models represent the pattern in the data and penalize unnecessary variables and interactions. Statistical analyses were performed using Stata, Version 16 (StataCorp, College Station, TX).

Results

High-sensitivity cardiac troponin T concentrations

Descriptive data are shown in *Table 1*. Baseline concentrations of hs-cTnT were above the 99th percentile upper reference limit in 35 (48%), 35 (56%), and 49 (64%) patients in the RRE, MCT, and HIIT groups, respectively. Main testing results are shown in *Table 2*. Hs-cTnT at any time point and changes in hs-cTnT during the study period were not significantly associated with randomization group in the adjusted analysis (overall test for randomization group: $P = 0.20$, MCT vs. RRE: $P = 0.81$, HIIT vs. RRE: $P = 0.095$, interaction by time and randomization group: $P = 0.88$) (*Figure 1*). Hs-cTnT concentrations decreased significantly by time, independently of randomization group in both the basic and adjusted models (overall test: basic model: $P = 0.014$, adjusted model: $P < 0.001$). From BL to 12 weeks, mean reduction of hs-cTnT was 1.1 ng/L (95% confidence interval: 1.0–1.2; $P < 0.001$) in the model adjusted for clinical variables. The reduction was maintained at 1 year in the adjusted model (from BL to 1 year: 1.1 ng/L, 95% confidence interval: 1.0–1.1; $P = 0.025$). There was no significant difference between 12 weeks and 1 year regarding hs-cTnT ($P = 0.82$).

Correlation between high-sensitivity cardiac troponin T and peak oxygen uptake

Higher VO_{2peak} correlated with lower hs-cTnT concentrations for all time points, that is, BL, 12 weeks, and 1 year (mean

Table 1 Baseline characteristics

Characteristics	RRE ($n = 73$)	MCT ($n = 63$)	HIIT ($n = 77$)
Age, years	60 (51–70)	60 (54–67)	65 (55–72)
Women, *n* (%)	14 (19.2%)	12 (19.1%)	14 (18.2%)
Heart failure < 12 months, *n* (%)	14 (19.4%)	7 (11.1%)	14 (18.2%)
New York Heart Association class, *n* (%)			
II	54 (74.0%)	40 (63.5%)	55 (71.4%)
III	19 (26.0%)	23 (36.5%)	22 (28.6%)
Left ventricular ejection fraction, %	30.0 (23.9–33.9)	29.1 (23.5–34.0)	29.3 (24.0–34.0)
Ischaemic aetiology, *n* (%)	41 (56.2%)	37 (58.7%)	46 (59.7%)
History of myocardial infarction, *n* (%)	32 (43.8%)	34 (54.0%)	44 (57.1%)
History of coronary artery bypass surgery, *n* (%)	17 (23.3%)	13 (20.6%)	20 (26.0%)
History of percutaneous coronary intervention, *n* (%)	33 (45.2%)	21 (33.3%)	32 (41.6%)
Device therapy, *n* (%)			
Pacemaker	2 (2.7%)	0 (0%)	2 (2.6%)
Implantable cardioverter defibrillator	31 (42.5%)	36 (57.1%)	27 (35.1%)
Cardiac resynchronization therapy	13 (17.8%)	4 (6.4%)	14 (18.2%)
Atrial fibrillation, *n* (%)			
Paroxysmal	13 (17.8%)	5 (7.9%)	11 (14.3%)
Persistent	6 (8.2%)	8 (12.7%)	14 (18.2%)
History of hypertension, *n* (%)	36 (49.3%)	23 (36.5%)	22 (29.0%)
History of diabetes mellitus, *n* (%)	14 (19.2%)	20 (31.8%)	16 (20.8%)
History of chronic obstructive pulmonary disease, *n* (%)	4 (5.5%)	7 (11.1%)	4 (5.2%)
Smoking			
Previous smoker	35 (48.0%)	30 (47.6%)	38 (49.4%)
Present smoker	18 (24.7%)	6 (9.5%)	14 (18.2%)
Alcohol consumption, units per week	1 (0–4)	2 (0–6)	1 (0–7)
Medications, *n* (%)			
ACE inhibitor/ARB	70 (95.9%)	58 (92.1%)	71 (92.2%)
Beta-blockers	71 (97.3%)	59 (93.7%)	73 (94.8%)
Diuretics	51 (69.9%)	47 (74.6%)	58 (75.3%)
Digoxin or digitoxin	6 (8.2%)	7 (11.1%)	17 (22.1%)
Statins	45 (61.6%)	45 (71.4%)	50 (64.9%)
Anticoagulation	28 (38.4%)	20 (31.8%)	27 (35.1%)
Body mass index, kg/m^2	27.7 (24.6–31.4)	27.5 (25.0–32.3)	27.6 (24.9–31.3)
Systolic blood pressure, mmHg	120 (110–131)	120 (110–131)	115 (105–129)
Diastolic blood pressure, mmHg	75 (70–82)	73 (65–80)	71 (65–80)
N-terminal pro-brain natriuretic peptide, ng/L	895 (407–1618)	976 (462–1635)	1052 (435–2285)
Left ventricular end-diastolic diameter, mm	68 (63–72)	69 (64–74)	68 (62–74)

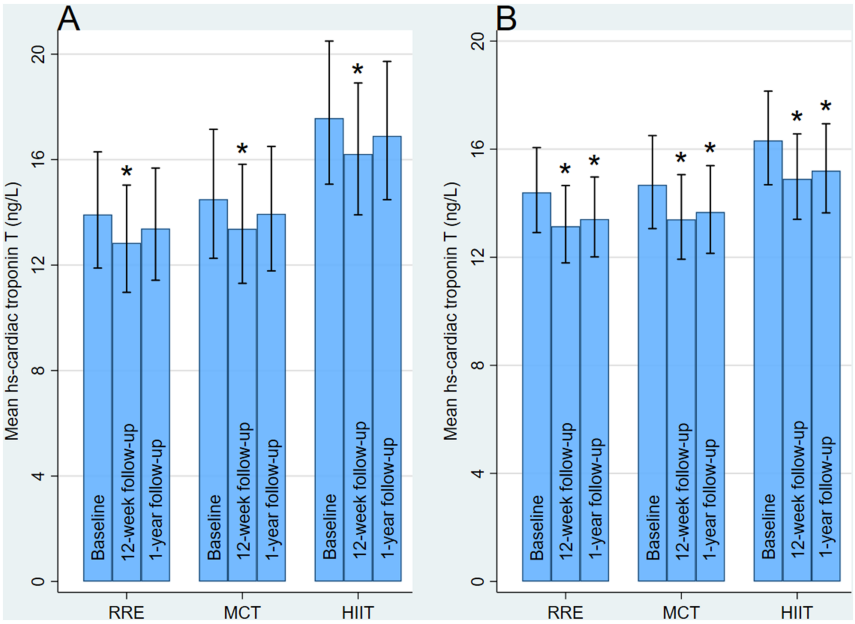
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; HIIT, high-intensity interval training; MCT, moderate continuous training; RRE, recommendations of regular exercise.
Data are given as median (25 and 75 percentiles) due to mostly non-normally distributed data or *n* (%) as indicated.

Table 2 Main testing measures at baseline, 12 weeks, and 1 year with unadjusted changes

	RRE (n = 73)	MCT (n = 63)	HIIT (n = 77)
Hs-cTnT, ng/L (95% CI)			
Baseline	14 (12, 18)	15 (14, 18)	17 (15, 20)
12 week follow-up	12 (10, 15)	15 (13, 17)	16 (13, 19)
1 year follow-up	12 (10, 16)	14 (12, 17)	15 (12, 20)
Delta hs-cTnT, ng/L			
Baseline to 12 week follow-up	0 (−1, 0)	−1 (−2, 0)	−1 (−2, 0)
Baseline to 1 year follow-up	0 (−1, 1)	−1 (−1, 0)	−1 (−1, 1)
VO_{2peak}, mL·kg^{-1}·min^{-1} (95% CI)			
Baseline	18.4 (16.8, 19.6)	16.2 (15.3, 18.7)	16.8 (15.8, 17.8)
12 week follow-up	17.4 (15.7, 19.8)	17.0 (15.7, 19.8)	18.2 (16.3, 20.0)
1 year follow-up	18.2 (15.8, 20.0)	16.2 (15.0, 18.6)	17.1 (15.5, 18.6)
Delta VO_{2peak}, mL·kg^{-1}·min^{-1} (95% CI)			
Baseline to 12 week follow-up	−0.1 (−0.9, 0.4)	1.1 (0.5, 1.8)	0.9 (0.0, 1.4)
Baseline to 1 year follow-up	−0.4 (−1.3, 0.4)	1.2 (−0.2, 1.4)	0.1 (−0.4, 1.0)

HIIT, high-intensity interval training; Hs-cTnT, high-sensitivity cardiac troponin T; MCT, moderate continuous training; RRE, recommendations of regular exercise; VO_{2peak}, peak oxygen uptake.
Data are given as median with 95% confidence interval (CI) of the median due to non-normally distributed data.

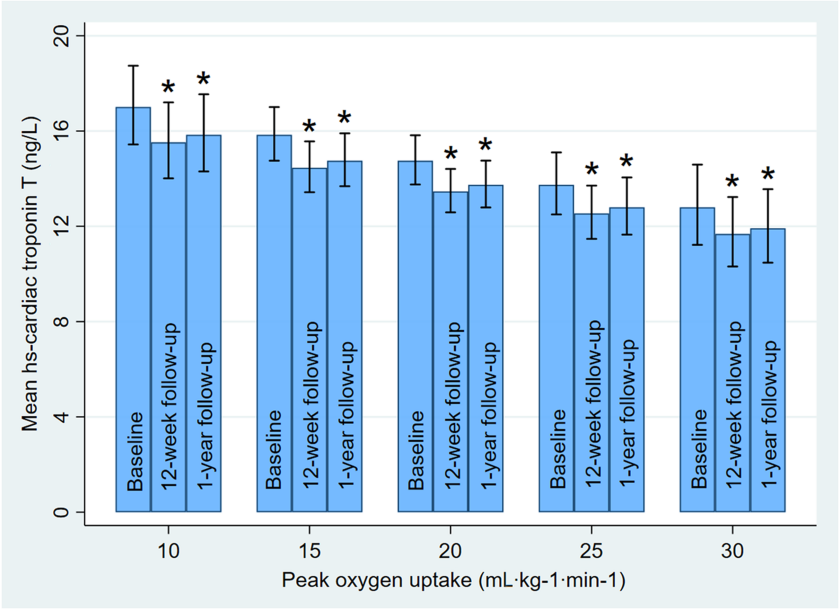
Figure 1 Mean high-sensitivity (hs) cardiac troponin T for each randomization group. (A) Measured concentrations. (B) Concentrations following adjustment for testing centre, randomization group, age, sex, creatinine, peak oxygen uptake, N-terminal pro-brain natriuretic peptide, left ventricular end-diastolic diameter, and heart failure treatment. There were no significant differences among the groups. Hs-cardiac troponin T is back-transformed from logarithmic values. *$P < 0.05$ compared with baseline in the same group. HIIT, high-intensity interval training; MCT, moderate continuous training; RRE, recommendation of regular exercise.



reduction of hs-cTnT over all time points: 0.2 ng/L per increasing mL·kg^{-1}·min^{-1}, P = 0.002, interaction by time: P = 0.88), independent of randomization group (interaction by randomization group: P = 0.19) (*Figure 2*). Because data for each of the repeated measurements were included in the mixed model, the design ensured that changes in VO_{2peak} for each patient were considered in parallel with changes in hs-cTnT.

Clinical adjustment variables associated with higher hs-cTnT were higher creatinine concentrations (P = 0.001), higher age ($P < 0.001$), and higher NT-proBNP ($P < 0.001$) (*Figure 3*). Variables associated with lower hs-cTnT were female sex ($P < 0.001$), ever smoking (P = 0.034), and treatment with beta-blockers (P = 0.028). LVEDD (P = 0.098), LVEF (P = 0.097), HR_{peak} (P = 0.39), NYHA (P = 0.59), and other HF medications (P = 0.90) were not significantly associated

Figure 2 Association between high-sensitivity (hs) cardiac troponin T and peak oxygen uptake. The five groups correspond to the 10th, 25th, 50th, 75th, and 90th percentiles of peak oxygen uptake. Hs-cardiac troponin T is back-transformed from logarithmic values. *$P < 0.05$ compared with baseline in the same group.



with hs-cTnT and were therefore not included in the final model. Higher maximal workload during CPET was associated with lower hs-cTnT when VO_{2peak} was not included in the model (P = 0.004), but VO_{2peak} was a better explanatory variable. Thus, to avoid collinearity, maximal workload was not included in the final model. Model fit was considered acceptable.

Sensitivity analyses

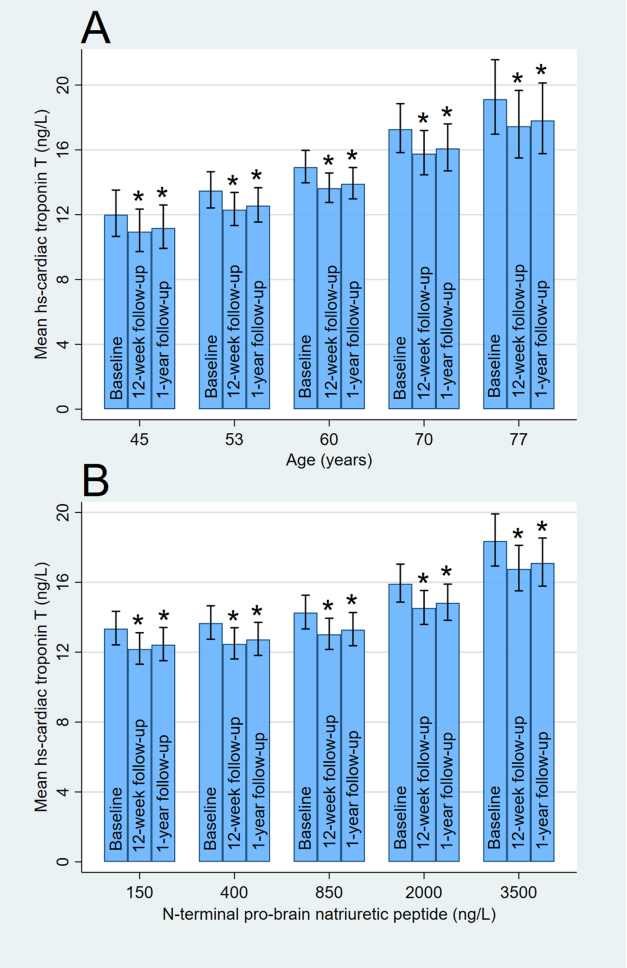
In the first sensitivity analysis, pooling of the two supervised exercise training groups did not change the results: hs-cTnT at any time point was not associated with randomization group (P = 0.24); that is, there was no difference between participants randomized to supervised exercise training and those in the control group. In the second sensitivity analysis, only including participants who trained 'on target', there was no significant difference between the two training groups (P = 0.76) and no significant difference between the training groups and the control group (P = 0.83). However, only eight patients (12.7%) in the MCT group trained on target at 60–70% of HR_{peak}, and only 38 patients (49.4%) in the HIIT group trained on target at ≥90% of HR_{peak}. As previously reported, 55 (86.3%) in the MCT group trained above the target, whereas 39 (50.6%) in the HIIT group trained below the target.[13]

Discussion

In this SMARTEX-HF sub-study of 213 patients with HFrEF undergoing a 12 week endurance exercise training programme or given recommendations for regular exercise, hs-cTnT concentrations were reduced at 12 weeks in all randomization groups when adjusted for clinical variables. This reduction was maintained at 1 year. Higher VO_{2peak} correlated with lower hs-cTnT concentrations independently of randomization group and time point, suggesting reduced chronic subclinical myocardial injury with increasing VO_{2peak}. In other words, the exercise programme by which the participants increased their VO_{2peak} was not decisive for the decrease in hs-cTnT concentration.

Morris and Chen (2019) recently stated that cardiac rehabilitation and exercise are underused in patients with HFrEF, despite robust scientific proof concerning safety and inclusion in current guidelines.[4] Other studies of cardiac rehabilitation from European hospitals have shown that cardiac rehabilitation is not offered to all eligible patients. Reasons given are primarily logistics and lack of resources, but in some cases, the perception of lack of safety has been stated.[2,3] If HIIT were harmful to patients with HFrEF over time, one would expect increases in chronic myocardial injury, that is, hs-cTnT in this group, which was not the case in the present study. Exercise training is generally recommended in chronic HF. However, transient increases in hs-cTnT after exercise training have

Figure 3 Associations between high-sensitivity (hs) cardiac troponin T and selected adjustment variables. (A) Age. (B) N-terminal pro-brain natriuretic peptide. The five groups correspond to the 10th, 25th, 50th, 75th, and 90th percentiles of the respective adjustment variable. Hs-cTnT is back-transformed from logarithmic values. *$P < 0.05$ compared with baseline in the same group.



been demonstrated, and there is an ongoing discussion whether this represents a physiological response or a pathological process indicating increased risk for future cardiovascular events.[19] In the present study, sampling was performed more than 48 h after exercise training to avoid confounding the evaluation of chronic myocardial injury with such transient increases. Thus, differences in acute transient increases of hs-cTnT among the randomization groups cannot be assessed. The present study did not have the necessary power to assess associations to serious adverse events. Occurrence of serious adverse events has been reported previously, and a brief summary is given in the Supporting Information.[13]

As previously reported, many participants in the HIIT group exercised below their prescribed target HR, whereas many participants in the MCT group trained above their prescribed target HR.[13] This made the two supervised training interventions more similar than intended and could thereby confound the results. The sensitivity analyses supported the main results regarding associations between hs-cTnT and randomization groups. They are also in line with a recent meta-analysis, which found HIIT not to be superior to MCT regarding improvements in VO_{2peak} in patients with HFrEF when isocaloric protocols were compared.[20]

Published data showed that the RRE group also had an improvement in VO_{2peak},[13] suggesting that many of the patients in the control group performed exercise as recommended during the study period. However, there are no objective data on how and how much the RRE group exercised. There are several possible explanations why patients in the RRE group also increased their VO_{2peak}. Recommendations of regular exercise may be sufficient for some patients to increase their daily activity. Additionally, being part of a research study in which VO_{2peak} was measured three times in 1 year may be an extra motivational factor. This is supported by a recent study in a general

population of older adults, which showed that the control group exercised with higher intensity than the MCT group.[21] Assuming that the RRE group followed the recommendations they were given, the present study therefore indicates that performing activities leading to improved VO_{2peak}, including supervised exercise training but not excluding other activities, is accompanied by reductions in hs-cTnT in patients with HFrEF. The study also confirmed the hypothesis that exercise training could lead to reduced chronic subclinical myocardial injury as measured by hs-cTnT, even if the mean absolute reduction was numerically small. This may be related to the fact that the patients were optimally medically treated or that the average potential for cardiac improvement in the included patients was not very large. Furthermore, there were individual differences with larger effects in some patients, and hs-cTnT increases in others. Despite the findings of reduced mean myocardial injury, the present study did not show differences among HIIT, MCT, and RRE, suggesting that training intensity and mode (supervised vs. home-based training) did not affect chronic myocardial injury. These findings are in line with the well-known positive effects of exercise training on contractility and remodelling in skeletal muscle.[22]

The SMARTEX-HF trial found that exercise training increased VO_{2peak} and reduced LVEDD.[13] The increase in VO_{2peak} was also associated with increased HR_{peak} from BL to 12 weeks, the ability to increase workload during the training period, lower NYHA class, higher LVEF, and lower age. Thus, younger and less symptomatic patients had a better training response than older and more symptomatic patients.[18] Of the factors previously associated with increased VO_{2peak}, only age was independently associated with hs-cTnT concentrations in the present analysis. Effects on hs-cTnT by the other mentioned factors could seem to be mediated or confounded by VO_{2peak}.

In the HF-ACTION study, no associations between cTnT and exercise training were found when comparing a training programme comprising 36 supervised sessions with usual care.[14] However, whereas the training programme in the present study included three supervised exercise sessions per week, each session lasting 37–48 min depending on the training method, the 36 sessions in the HF-ACTION study took place over a median time of 3.8 months and the participants exercised a median time of 76 min/week during the first 3 months.[14] Thus, there is reason to believe that the participants in the present study had a higher training load between baseline and follow-up at 12 weeks. Myocardial injury in HF-ACTION was measured using a contemporary cTnT analysis and not the high-sensitivity assay. The combination of higher compliance and intensity of the training programme and the use of hs-cTnT in the present study enabled the detection of small changes in cTnT concentrations during the training period.

Clinical implications

Motivating patients with HFrEF to improve their VO_{2peak} may help reduce chronic myocardial injury as indicated by hs-cTnT. HIIT did not seem to differ from MCT or RRE in this respect, revealing that exercise intensity did not influence hs-cTnT. Thus, cardiac rehabilitation in HFrEF should aim at finding the optimal way to increase VO_{2peak} for each individual patient, including motivation and practical implementation as important aspects.

Strengths and limitations

This was a large multicentre randomized controlled trial with two different intervention groups and a control group where the patients were recommended to perform exercise. The intervention groups were closely followed and had good adherence to number of sessions. However, the differences between the training groups were smaller than anticipated due to variability in training intensity and exercise response. Physical activity data from the RRE group were limited. We cannot exclude that these participants also trained with high intensity. Blood samples were collected at times when the potential interference from recent exercise was small; that is, measured hs-cTnT was not biased from possible transient increase related to exercise, as demonstrated in other studies.[23,24] Myocardial injury was measured using a highly sensitive biomarker with high analytical precision. Because samples were analysed in random order, small variations due to measurement accuracy would not systematically affect the results. The cardiac form of troponin T may be expressed in damaged and regenerating skeletal muscle,[25] which may result from exercise training. However, this would tend to increase concentrations, contrary to the study results showing decreased concentrations following the exercise intervention.

Conclusions

In patients with stable HFrEF, a 12 week exercise training intervention was associated with reduced serum hs-cTnT concentrations in all randomization groups (HIIT, MCT, and RRE) when adjusted for clinical variables. The effect was maintained at 1 year follow-up. There was no significant difference in chronic myocardial injury among patients performing supervised training at high or moderate intensity and those being recommended to exercise at home. Those with higher VO_{2peak} had lower hs-cTnT at all time points. Increases in VO_{2peak} were associated with reductions of myocardial injury, measured as hs-cTnT. The effect was independent of randomization group and was

maintained at 1 year follow-up, suggesting a long-term positive effect of increasing VO_{2peak} in HFrEF regardless of training method.

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Contributors to the main SMARTEX-HF study are given in Ellingsen (2017).[13] For the present study, Heidi Strand performed the hs-cTnT analyses.

Conflict of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Summary of serious adverse events in patients starting the 12-week training intervention (n = 231).
Table S2. Mean hs-cTnT concentrations in eligible patients (n = 213).

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESCSD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
2. Bjarnason-Wehrens B, McGee H, Zwisler AD, Piepoli MF, Benzer W, Schmid JP, Dendale P, Pogosova NG, Zdrenghea D, Niebauer J, Mendes M, Cardiac Rehabilitation Section European Association of Cardiovascular P, Rehabilitation. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. *Eur J Cardiovasc Prev Rehabil* 2010; **17**: 410–418.
3. Piepoli MF, Binno S, Corra U, Seferovic P, Conraads V, Jaarsma T, Schmid JP, Filippatos G, Ponikowski PP, Committee on Exercise P, Training of the Heart Failure Association of the ESC. ExtraHF survey: the first European survey on implementation of exercise training in heart failure patients. *Eur J Heart Fail* 2015; **17**: 631–638.
4. Morris JH, Chen L. Exercise training and heart failure: a review of the literature. *Card Fail Rev* 2019; **5**: 57–61.
5. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Mickley H, Crea F, Van de Werf F, Bucciarelli-Ducci C, Katus HA, Pinto FJ, Antman EM, Hamm CW, De Caterina R, Januzzi JL, Apple FS, Alonso Garcia MA, Underwood SR, Canty JM, Lyon AR, Devereaux PJ, Zamorano JL, Lindahl B, Weintraub WS, Newby LK, Virmani R, Vranckx P, Cutlip D, Gibbons RJ, Smith SC, Atar D, Luepker RV, Robertson RM, Bonow RO, Steg PG, O'Gara PT, Fox KAA, Hasdai D, Aboyans V, Achenbach S, Agewall S, Alexander T, Avezum A, Barbato E, Bassand J-P, Bates E, Bittl JA, Breithardt G, Bueno H, Bugiardini R, Cohen MG, Dangas G, de Lemos JA, Delgado V, Filippatos G, Fry E, Granger CB, Halvorsen S, Hlatky MA, Ibanez B, James S, Kastrati A, Leclercq C, Mahaffey KW, Mehta L, Müller C, Patrono C, Piepoli MF, Piñeiro D, Roffi M, Rubboli A, Sharma S, Simpson IA, Tendera M, Valgimigli M, van der Wal AC, Windecker S, Chettibi M, Hayrapetyan H, Roithinger FX, Aliyev F, Sujayeva V, Claeys MJ, Smajić E, Kala P, Iversen KK, El Hefny E, Marandi T,

Porela P, Antov S, Gilard M, Blankenberg S, Davlouros P, Gudnason T, Alcalai R, Colivicchi F, Elezi S, Baitova G, Zakke I, Gustiene O, Beissel J, Dingli P, Grosu A, Damman P, Juliebø V, Legutko J, Morais J, Tatu-Chitoiu G, Yakovlev A, Zavatta M, Nedeljkovic M, Radsel P, Sionis A, Jemberg T, Müller C, Abid L, Abaci A, Parkhomenko A, Corbett S. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019; **40**: 237–269.

6. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E. Prevention of Events with Angiotensin Converting Enzyme Inhibition Trial I. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med* 2009; **361**: 2538–2547.
7. Welsh P, Preiss D, Hayward C, Shah ASV, McAllister D, Briggs A, Boachie C, McConnachie A, Padmanabhan S, Welsh C, Woodward M, Campbell A, Porteous D, Mills NL, Sattar N. Cardiac troponin T and troponin I in the general population. *Circulation* 2019; **139**: 2754–2764.
8. Aimo A, Januzzi JL Jr, Vergaro G, Ripoli A, Latini R, Masson S, Magnoli M, Anand IS, Cohn JN, Tavazzi L, Tognoni G, Gravning J, Ueland T, Nymo SH, Brunner-La Rocca HP, Bayes-Genis A, Lupon J, de Boer RA, Yoshihisa A, Takeishi Y, Egstrup M, Gustafsson I, Gaggin HK, Eggers KM, Huber K, Tentzeris I, Tang WHW, Grodin J, Passino C, Emdin M. Prognostic value of high-sensitivity troponin T in chronic heart failure: an individual patient data meta-analysis. *Circulation* 2018; **137**: 286–297.
9. Cattadori G, Segurini C, Picozzi A, Padeletti L, Anza C. Exercise and heart failure: an update. *ESC Heart Fail* 2018; **5**: 222–232.
10. McDonald CD, Burch GE, Walsh JJ. Prolonged bed rest in the treatment of idiopathic cardiomyopathy. *Am J Med* 1972; **52**: 41–50.
11. Mediano MFF, Leifer ES, Cooper LS, Keteyian SJ, Kraus WE, Mentz RJ, Fleg JL. Influence of baseline physical activity level on exercise training response and clinical outcomes in heart failure: the HF-ACTION trial. *JACC Heart Fail* 2018; **6**: 1011–1019.
12. Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, Tjonna AE, Helgerud J, Slordahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najjar SM, Ellingsen O, Skjaerpe T. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation* 2007; **115**: 3086–3094.
13. Ellingsen O, Halle M, Conraads V, Stoylen A, Dalen H, Delagardelle C, Larsen AI, Hole T, Mezzani A, van Craenenbroeck EM, Videm V, Beckers P, Christle JW, Winzer E, Mangner N, Woitek F, Hollriegel R, Pressler A, Monk-Hansen T, Snoer M, Feiereisen P, Valborgland T, Kjekshus J, Hambrecht R, Gielen S, Karlsen T, Prescott E, Linke A, Group SHFS. High-intensity interval training in patients with heart failure with reduced ejection fraction. *Circulation* 2017; **135**: 839–849.
14. Ahmad T, Fiuzat M, Mark DB, Neely B, Neely M, Kraus WE, Kitzman DW, Whellan DJ, Donahue M, Zannad F, Pina IL, Adams K, O'Connor CM, Felker GM. The effects of exercise on cardiovascular biomarkers in patients with chronic heart failure. *Am Heart J* 2014; **167**: 193–202, e191.
15. Stoylen A, Conraads V, Halle M, Linke A, Prescott E, Ellingsen O. Controlled study of myocardial recovery after interval training in heart failure: SMARTEX-HF—rationale and design. *Eur J Prev Cardiol* 2012; **19**: 813–821.
16. Rickham PP. Human experimentation. Code of ethics of the World Medical Association. Declaration of Helsinki. *Br Med J* 1964; **2**: 177.
17. Liesirova K, Abela E, Pilgrim T, Bickel L, Meinel T, Meisterernst J, Rajeev V, Sarikaya H, Heldner MR, Dobrocky T, Siqueira E, El-Koussy M, Fischer U, Gralla J, Arnold M, Mattle HP, Hsieh K, Jung S. Baseline Troponin T level in stroke and its association with stress cardiomyopathy. *PLoS One* 2018; **13**: e0209764.
18. Karlsen T, Videm V, Halle M, Ellingsen O, Stoylen A, Dalen H, Delagardelle C, Larsen AI, Hole T, Mezzani A, Em VANC, Beckers P, Pressler A, Christle JW, Winzer EB, Mangner N, Woitek FJ, Hollriegel R, Snoer M, Feiereisen P, Valborgland T, Linke A, Prescott E. Baseline and exercise predictors of $VO_{2\text{-}peak}$ in systolic heart failure patients: results from SMARTEX-HF. *Med Sci Sports Exerc* 2020; **52**: 810–819.
19. Omland T, Aakre KM. Cardiac troponin increase after endurance exercise. *Circulation* 2019; **140**: 815–818.
20. Gomes Neto M, Duraes AR, Conceicao LSR, Saquetto MB, Ellingsen O, Carvalho VO. High intensity interval training versus moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis. *Int J Cardiol* 2018; **261**: 134–141.
21. Stensvold D, Viken H, Steinshamn SL, Dalen H, Stoylen A, Loennechen JP, Reitlo LS, Zisko N, Baekkerud FH, Tari AR, Sandbakk SB, Carlsen T, Ingebrigtsen JE, Lydersen S, Mattsson E, Anderssen SA, Fiatarone Singh MA, Coombes JS, Skogvoll E, Vatten LJ, Helbostad JL, Rognmo O, Wisloff U. Effect of exercise training for five years on all cause mortality in older adults—the Generation 100 study: randomised controlled trial. *BMJ* 2020; **371**: m3485.
22. Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metab* 2013; **17**: 162–184.
23. Fu F, Nie J, Tong TK. Serum cardiac troponin T in adolescent runners: effects of exercise intensity and duration. *Int J Sports Med* 2009; **30**: 168–172.
24. Kleiven O, Omland T, Skadberg O, Melberg TH, Bjorkavoll-Bergseth MF, Auestad B, Bergseth R, Greve OJ, Aakre KM, Orn S. Race duration and blood pressure are major predictors of exercise-induced cardiac troponin elevation. *Int J Cardiol* 2019; **283**: 1–8.
25. Rittoo D, Jones A, Lecky B, Neithercut D. Elevation of cardiac troponin T, but not cardiac troponin I, in patients with neuromuscular diseases: implications for the diagnosis of myocardial infarction. *J Am Coll Cardiol* 2014; **63**: 2411–2420.