Reverse left ventricular remodelling – effect of cardiac rehabilitation exercise training in myocardial infarction patients with preserved ejection fraction

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Word count: 3351

Conflicts of interest and sources of funding

We have no conflicts related to this work.

Keywords: Left ventricular remodelling, exercise training, cardiac rehabilitation, myocardial infarction, NT-pro-BNP.

Structured Abstract

Purpose: In post-myocardial infarction (MI) patients with preserved LV ejection fraction (>45%), the effect of cardiac rehabilitation (CR) exercise training on left ventricular (LV) structure and function is unknown. We therefore sought to examine the reverse LV remodelling effect of CR exercise training in this increasingly prevalent population.

Methods: Within 3-6 weeks of MI, and 10 weeks later, echocardiography and cardiopulmonary exercise testing were performed in a cohort of asymptomatic, non-ischemic patients with LV ejection fraction >45%. An exercise training group (n=33) completed twice weekly gym based cardiovascular exercise at 60-80% VO_2 peak, and a standardised resistance training programme, whilst a non-exercise group (n=17) did not. NT-pro-BNP was measured in a subgroup of exercise training participants at baseline and at the end of the 10 week programme.

Results: In comparison to the non-exercise group, in which there was no change, 10 weeks of exercise training increased VO_{2peak} and reduced LV end diastolic and systolic volumes (all $P<0.05$ vs non-exercise group). Resting NT-pro-BNP was reduced in the sub-group of exercise training participants ($P<0.01$) and correlated positively with the change in LV end diastolic volume ($r = 0.58$, $P<0.01$, $r^2 = 0.33$).

Conclusion: In post-MI patients with preserved LV ejection fraction (>45%), CR exercise training is effective in improving functional capacity and reducing LV volumes. In this previously unstudied population, the measurement of reverse LV volumetric remodelling may prove useful as an indicator of CR exercise programme efficacy. To maximise the potential clinical benefit from reverse LV remodelling, this patient group should be actively encouraged to engage in CR exercise training.

50 **Condensed abstract**

51 Following 10 weeks of Cardiac Rehabilitation (CR) exercise training in a cohort of post-MI
52 patients with preserved LVEF (>45%), exercise capacity was improved and LV volumes reduced.
53 For potential prognostic gain, this increasingly prevalent and often overlooked post-MI
54 population should be encouraged to attend structured CR exercise training programmes.

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Introduction

Myocardial infarction (MI) is associated with molecular disarray, myocyte hypertrophy and extra-cellular matrix degradation, resulting in pathologically increased left ventricular (LV) mass and volume and altered LV geometry[1]. The process of LV remodelling, characterised by structural maladaptation and functional decline, begins with the onset of acute MI and is chronically driven by systemic neurohormonal activation[2]. Mortality is closely linked to the nature and extent of LV remodelling and also to the degree of concurrent neurohormonal activation[3, 4]. Specifically, increased LV volumes and reduced LV ejection fraction (LVEF) are exponentially associated with poor prognosis[5], presenting clinicians with a clear rationale for attenuating or reversing this process. In post-MI patients, pharmacological and electrophysiological interventions improve cardiovascular and all-cause mortality[6, 7]. Despite this, in the first two years after MI, mortality of greater than 25% can be expected in patients with baseline LVEF of 31-40%, compared to less than 15% when LVEF exceeds 50%[5]. It is important therefore to consider adjunctive therapeutic strategies, such as cardiac rehabilitation (CR) exercise training that may enhance the reverse LV remodelling process beyond that seen with medical treatment.

Evidence of reverse LV remodelling, following CR exercise training in post-MI patients is currently equivocal[8]. A number of longitudinal studies have shown a positive effect [9-11], reporting reduced LV end diastolic volume (LVEDV), LV end systolic volume (LVESV), improved LVEF and reduced N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP). However, conflicting data also exist [12, 13], and the conclusions of a recent meta-analysis which showed an overall beneficial effect of CR exercise training on LV remodelling, were limited by the poor

79 methodological quality of some of the included studies[8]. To date, CR exercise training studies
80 have focused almost exclusively on patients with moderate to severe impairment of LV systolic
81 function (LVEF ≤45%). This group of patients are commonly limited by their condition and are
82 thus obvious candidates for CR exercise training. However, advancement in percutaneous
83 coronary artery revascularisation technology with rapid 24 hr access, greater sensitivity of
84 cardiac biomarkers and increased public awareness of chest pain management have led to an
85 increasingly prevalent population of asymptomatic MI survivors with preserved LV systolic
86 function (LVEF>45%)[14, 15]. In the absence of significant functional limitation, these patients can
87 be quickly reintegrated into daily life, making their attendance on CR exercise programmes less
88 likely. This may be ill advised given that 15% of these patients will die or be hospitalised with
89 heart failure within 20 months of MI[16]. Exercise training may be an effective preventative
90 strategy, ameliorating the negative effects of chronic LV remodelling. Yet, the impact of CR
91 exercise training on LV structure and function has not been studied in this group of patients.
92 Therefore, the purpose of the current study was to investigate the effect of CR exercise
93 training on LV structure and function in post-MI patients with preserved LVEF (>45%). It was
94 hypothesised that 10 weeks of CR exercise training would reduce LV volumes and increase
95 LVEF in addition to improving functional capacity.
96

Methods

Study population and protocol

A total of 58 consecutive male participants were recruited to the study. An exercise training group was populated by those who attended CR (n=36) and a non-exercise group by those who were demographically and clinically similar to the exercise group but were unable to attend structured CR due to work or personal commitments (n=20) (table 1). Participants were clinically stable (in accordance with guidelines[17]) following treatment for an acute MI at least three, but not more than six weeks previously. All participants had LVEF >45% and were non-ischemic and asymptomatic following successful percutaneous coronary intervention. Participants who did not meet guidelines for inclusion in exercise training,[17] or who had significant limiting comorbidities were excluded. Both groups were advised on a cardio-protective lifestyle including general physical activity. Approval was gained from the local Research and Ethics Committee and informed consent was obtained. Prior to and on completion of a 10-week supervised exercise training programme or non-exercise control period, transthoracic echocardiography and cardiopulmonary exercise testing were undertaken in all study participants. In addition, resting whole blood samples for the assessment of NT-pro-BNP were obtained in a sub-group (n=21) of exercise training participants at the start and the end of the 10 week programme.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed in accordance with the American Thoracic Society guidelines[18]. Briefly, a standard ramp protocol was conducted on an electronically braked, upright cycle ergometer and continuous respiratory gas exchange measurements of

oxygen uptake (VO_2), carbon dioxide production (VCO_2) and minute ventilation (V_E) were recorded (Oxycon Pro, Care Fusion Corp., San Diego, California, USA). Electrocardiogram, blood pressure and rating of perceived exertion (RPE) were monitored throughout and participants were encouraged to continue until symptom limited volitional fatigue, with a respiratory exchange ratio of >1.15 indicating maximal effort.

Echocardiography

Resting echocardiographic images were acquired in accordance with British Society of Echocardiography guidelines[19] by a single cardiac sonographer, blinded to group allocation. A commercially available ultrasound system (Vivid 7, GE Medical Systems, Horten, Norway) was used to obtain and store images for subsequent off-line analysis (Echo-pac, GE Medical Systems, Horten, Norway, version 7.0.0). Left ventricular internal dimensions and wall thicknesses were measured from the parasternal long axis view, and LV volumes calculated using the Simpson's bi-plane method from apical two and apical four-chamber images. Peak early (E) and late (A) mitral inflow velocity, and the E-wave deceleration time (DT) were measured with pulse wave Doppler in the apical four-chamber view, and the E/A ratio calculated. Finally, tissue Doppler imaging of the septal and lateral mitral annuli in the apical four-chamber view was employed to quantify systolic (s'), early diastolic (e') and late diastolic (a') peak mitral annulus tissue velocities.

Measurement of cardiac biomarkers

Serum was obtained from whole blood samples collected into ethylene diamine teracetic acid tubes via peripheral venepuncture. Clotted samples were centrifuged at 3000rpm for 10 min

and stored at -80 deg C. NT-pro-BNP was determined using the Immulite 2500 electrochemiluminescent immunoassay (Siemens Healthcare Diagnostics, Frimley, UK) with a linear calibration range of 20 to 35,000 pg/mL.

Exercise training

Participants attended University Hospital, Coventry twice weekly for 10 weeks with an adherence rate of 85% (17 of 20 sessions) designated as the required standard for inclusion. Cardiovascular exercise was split equally between treadmill, cycle ergometer, rowing machine and cross-trainer. A 10 min treadmill or cycle warm up was followed initially by 25 min of continuous cardiovascular exercise. A 5 min cool down walk was performed prior to and on completion of a standardised resistance training programme as previously described[17]. Aerobic exercise intensity was initially set at a heart rate corresponding to 60-80% peak oxygen uptake ($VO_{2\ peak}$) from cardiopulmonary exercise test and after two sessions the supervisory team ensured that participants were exercising at a heart rate equivalent to 80% $VO_{2\ peak}$. Exercise intensity and training heart rate range were re-prescribed every two weeks based on RPE. The duration of exercise was progressively increased from 25 to 40 min by the fifth week and was maintained thereafter until the end of the study.

Statistical analyses

Baseline characteristics and continuous variables are presented as mean ± standard deviation (SD). Differences between the exercise training and non-exercise group at baseline were determined using unpaired Student's *t*-tests. Further to confirmation of normality with the Kolmogorov-Smirnov test, the change in outcome variables by group over time was assessed

with either a two-way mixed model analysis of variance (ANOVA) or paired Student's *t*-tests. Pearson's product-moment correlation coefficient was used to determine relationships between the relative change (Δ) in NT-pro-BNP and the absolute change (Δ) in LV volumetric parameters over the 10 week period.

Results

Recruitment

Of the 36 participants in the exercise training group, 33 completed ≥ 17 of 20 sessions during the training period with an average attendance of 88.3%. Two participants were lost to follow-up and one failed to meet the minimum adherence target. In the non-exercise group, a further three participants were lost to follow up. Accordingly, data from 50 participants (exercise training, n=33 and non-exercise, n=17) was analysed to assess the effects of CR exercise training on LV structure and function. Baseline demographic and clinical characteristics were similar between groups (table 1), medication remained unchanged during the study period, and no cardiovascular complications or other adverse effects were experienced by the participants.

Cardiopulmonary Exercise Testing

In comparison to the non-exercise group, maximum workload (W_{max}), $VO_{2\ peak}$, ventilatory threshold (VT) and exercise time increased in response to exercise training (all $P<0.05$) (table 2). In the exercise training group, $VO_{2\ peak}$ increased by 16%, W_{max} by 19%, VT by 18%, and exercise time by 16% (all $P<0.0001$) (table 2). In the non-exercise group, no changes were noted. Furthermore, there were no statistical differences in body mass index (BMI), resting heart rate (HR_{rest}), systolic blood pressure (BP_{sys}) or diastolic blood pressure (BP_{dia}) in either group between baseline and post-study measures (table 2).

Effect of cardiac rehabilitation exercise training on left ventricular structure and function

On completion of the exercise training programme, LVEDV and LVEDV/BSA (both $P<0.05$), and LVESV and LVESV/BSA (both $P<0.01$) were decreased in comparison to the non-exercise group. As depicted in figure 1, 10 weeks of exercise training resulted in a 5% reduction in LVEDV and LVEDV/BSA (both $P<0.001$) and a 9% reduction in LVESV and LVESV/BSA (both $P<0.001$), whereas volumetric parameters remained unchanged in the non-exercise group ($P>0.05$). No changes in either group were observed in LV linear dimensions, mass or geometry during the study period ($P>0.05$). Furthermore, the exercise training programme had no impact on systolic or diastolic function (table 3).

Relationship between NT-pro-BNP and left ventricular volumetric parameters

In the sub group of exercise training participants (n=21), resting NT-pro-BNP was significantly reduced further to completion of the 10 week programme (267 ± 232 vs 158 ± 121 pg/mL, $P<0.01$). Additionally, the relative change in resting NT-pro-BNP (%) from baseline to 10 weeks correlated positively with the absolute change in LVEDV (ml) ($r = 0.58$, $P<0.01$, $r^2 = 0.33$) (figure 2). There was no significant relationship between the relative change in NT-pro-BNP and the absolute change in either LVESV ($r = 0.10$, $P>0.05$, $r^2 = 0.01$) or LVEF ($r = 0.17$, $P>0.05$, $r^2 = 0.03$) (figure 2).

Discussion

The aim of the present study was to evaluate the reverse remodelling effect of CR exercise training in a cohort of post-MI patients with preserved LVEF (>45%). We hypothesised that, in addition to an improvement in functional capacity, LV volumes would be reduced and LVEF increased. The primary findings, which allow our hypotheses to be partially accepted, were an improvement in exercise capacity and a reduction in LV volumes in response to CR exercise training. Specifically, VO_2 peak improved by 16%, with a concurrent 5% and 9% reduction in LVEDV and LVESV respectively. Given the association between reduced LV volumes and improved clinical outcome[6] these data provide additional impetus to recommend CR exercise training to post-MI patients with preserved EF.

Reverse volumetric remodelling with CR exercise training

In patients with significant LV systolic dysfunction, a reduction in LV volumes is highly desirable, demonstrating a clear relationship with improved survival [16]. Whilst data confirming this association are primarily derived from pharmacological rather than exercise trials, CR exercise training has consistently been shown to reduce cardiovascular and all-cause mortality in patients with MI [20]. The mechanisms responsible for this remain to be fully confirmed, but are likely to include both structural and functional cardiac adaptation. The reduction in LV volumes observed in the current study confirm findings from a recent meta-analysis which, although not providing a causative link between reverse LV remodelling and mortality, reported a positive effect of exercise training on LV volumes in post-MI patients with impaired LVEF[8]. Unique to the current study is evidence of reverse LV remodelling in post-MI patients with preserved LVEF (>45%). In this population, where LV volumes are within normal limits, the

234 significance of reverse volumetric LV remodelling, whether it be medically mediated or
235 exercise-induced, is yet to be fully evaluated. However, it is possible that improved prognosis
236 as a result of reduced LV volumes may not be exclusive to those with pronounced LV systolic
237 dysfunction, rather, it may also extend to less compromised patients. Abnormal
238 hemodynamics following MI are a product of the pathological imbalance between LV
239 pressures, cavity dimensions and wall thicknesses and can result in functional impairment [21].
240 Ultimately, left untreated, this may lead to a progressive decline in cardiac function and
241 exercise capacity, with resultant prognostic implications [6]. Recent reports have indicated that,
242 despite preserved function, 15% of post-MI patients with LVEF >45% will die or be admitted to
243 hospital with heart failure within 20 months of their event[16]. For these patients, a reduction in
244 LV volumes may provide the environment for the maintenance, or restoration, of more
245 'normal' LV hemodynamics and may prevent a progressive decline in LV function. On this basis,
246 asymptomatic patients with normal LV volumes and preserved LVEF, who are likely to return
247 relatively quickly and seamlessly to activities of daily living and work, should be encouraged to
248 participate fully in supervised CR exercise training.
249
250 **NT-pro-BNP as an indicator of reverse volumetric remodelling**
251 The higher concentration of NT-pro-BNP observed prior to exercise training in the current
252 study likely reflects a degree of hemodynamic compromise and increased LV wall stress [22].
253 Raised NT-pro-BNP is related to a worse prognosis throughout the spectrum of cardiac
254 disease[14]. The significant decrease in NT-pro-BNP observed following CR exercise training is
255 indicative of an improvement in the overall neurohormonal and hemodynamic environment.
256 The positive correlation of this change in NT-pro-BNP with a reduction in LV volumes may

suggest that this biomarker could be used as a simple, cheap and effective measure of reverse LV remodelling following CR exercise training. Similar associations have been previously reported. Giallauria and colleagues demonstrated a positive correlation between changes in NT-pro-BNP and LVEDVI (r=0.86, *P*<0.001) in patients with significant LV systolic dysfunction (LVEF<45%)[11]. Furthermore, reduced NT-pro-BNP was shown to correlate with improved early diastolic filling (E-wave) (r= -0.44, *P*<0.001)[11], E/A ratio (r= -0.59, *P*<0.001)[23] and LV elastance (r= -0.58, *P*<0.01)[24]. The direct and indirect molecular and cellular adaptations associated with exercise training likely reduce LV wall stress and, therefore, NT-pro-BNP. Although we did not witness an improvement in diastolic filling as demonstrated previously[11,23] , this may be explained by the fact that diastolic function was relatively well preserved in our patients following MI. Unlike LVEDV, there was no association between the changes in NT-pro-BNP and either LVESV or LVEF. This is a reflection of the mechanism of NT-pro-BNP secretion, for which the predominant stimulus is cardiac myocyte 'stretch'[22]. Further to MI, regional and global LV dysfunction can lead to increased LV diastolic filling pressures and volume overload, promoting the release of NT-pro-BNP[26]. The very nature of this biomarker, therefore, means it is better suited to evaluating changes in LVEDV. Rather than diminish the utility of NT-pro-BNP in the CR setting, this observation may allow targeted evaluation of a specific and important marker of LV remodelling.

Reverse functional remodelling with CR exercise training

The positive change in LV volumes in the present study was not accompanied by a change in functional parameters, i.e. SV and LVEF. These data do not, therefore, corroborate previous findings of the coexistence of volumetric and functional adaptation[8]. Haykowsky et al

reported improvements in both LV volumes (LVEDV and LVESV) and LVEF with CR exercise training. In the current study, however, within group analysis did indicate an improvement in LVEF in the exercise training group (*P*=0.011), whilst there was no change in the non-exercise group. It is likely that with greater statistical power the between groups comparison of LVEF may have proved significant. Alternatively, the mild impairment of LVEF in this cohort, as opposed to the marked dysfunction in previous studies may, by definition, dictate limited scope for improvement.

Mechanisms facilitating reverse LV remodelling

Current knowledge of the underpinning mechanisms promoting reverse LV remodelling with medical therapy and exercise training is limited, although recent animal and human investigation has provided some insight into molecular and cellular adaptation. There is good evidence, however, of the counteractive effect of exercise training on the associated compensatory neurohormonal mechanisms[27]. It is well known from pharmacological trials that suppression of these mechanisms can reduce their destructive effects [28-30]. This appears to be important in preventing the progression of maladaptive LV remodelling. In addition, in combination with specific vascular adaptation to exercise i.e. improved endothelial function, reduced neurohormonal activation contributes to the normalisation of LV afterload [31, 32]. It is likely that this helps restore normal LV loading conditions and thus facilitates the process of reverse LV remodelling. The magnitude of this effect, however, may prove less significant than originally thought, in light of findings from recent animal investigations[33]. The direct effect of exercise training on the myocardium has been demonstrated in a number of animal models and is increasingly verified as a key contributor to the process of reverse LV remodelling[34-37]. A

303 plethora of exercise induced, biomolecular adaptations interfere with maladaptive signalling
304 pathways which results in attenuation of hypertrophy, fibrosis and apoptosis. It is, therefore,
305 likely that the reverse remodelling effect attributed to CR exercise training in the current
306 study, is a result of the combined influence of these and as of yet unidentified processes.
307
308 Limitations of the current study warrant discussion. Firstly, due to ethical constraints,
309 participants were not assigned randomly to exercise training or non-exercise. Secondly, sample
310 size was relatively small, particularly in the non-exercise group. Finally, the study population
311 was exclusively male reflecting a very small percentage of female patients in this CR population
312 as a whole. Future randomised studies to confirm our results are recommended.
313
314 **Conclusions**
315 Ten weeks of CR exercise training improved functional capacity and had a reverse LV
316 remodelling effect in the previously unstudied population of post-MI patients with relatively
317 preserved LVEF (>45%). Not only does this serve to confirm the general therapeutic benefit of
318 CR exercise training, but may also indicate the potential contribution of cardiac adaptation to
319 the well documented reductions in cardiovascular and all-cause mortality. To date, these
320 improvements can be only partially explained by data relating to ventilatory, skeletal muscle
321 and vascular endothelial adaptation. The measurement of reverse LV remodelling, which may
322 be adequately quantified with NT-pro-BNP, may prove useful as an indicator of CR exercise
323 programme efficacy and may aid in the long-term management of the post-MI population.
324 Patients with normal LV volumes and preserved LVEF, who may otherwise resume normal daily

activities at the expense of CR, should be actively encouraged to attend structured CR exercise programmes to maximise the potential clinical gains from reverse LV remodelling.

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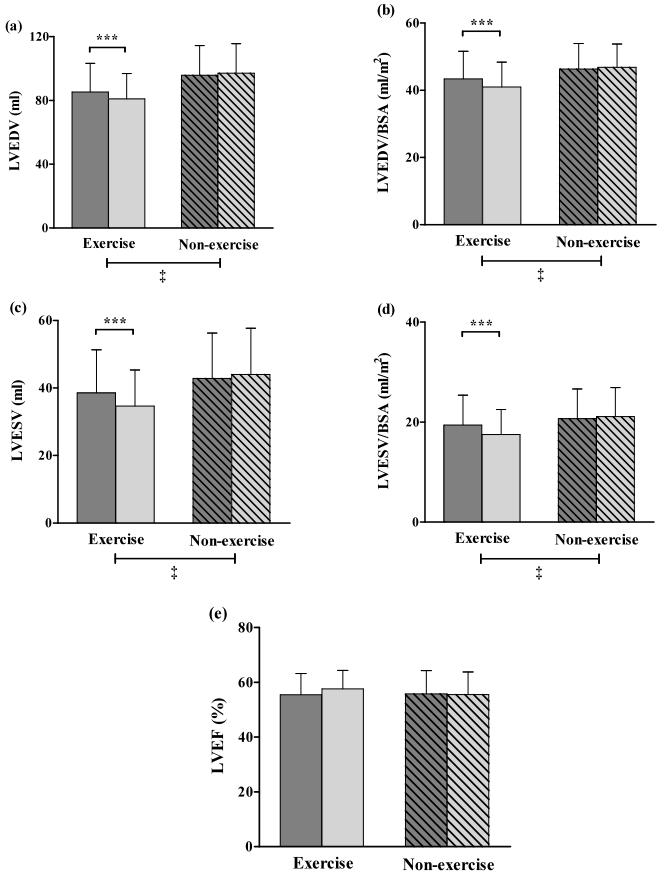

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331 **Figure 1.** Left ventricular (LV) volumetric parameters at baseline (dark grey bars) and at 10 weeks (light
332 grey bars) in the exercise training group (solid bars) and non-exercise group (striped bars) (a) LV end
333 diastolic volume (ml) (b) LV end diastolic volume/BSA (ml/cm^2), (c) LV end systolic volume (ml), (d) LV
334 end systolic volume/BSA (ml/cm^2), (e) LV ejection fraction (%). Data as mean ± SD. ‡ *P*<0.05 group × time
335 interaction effect (ANOVA), ****P*<0.001

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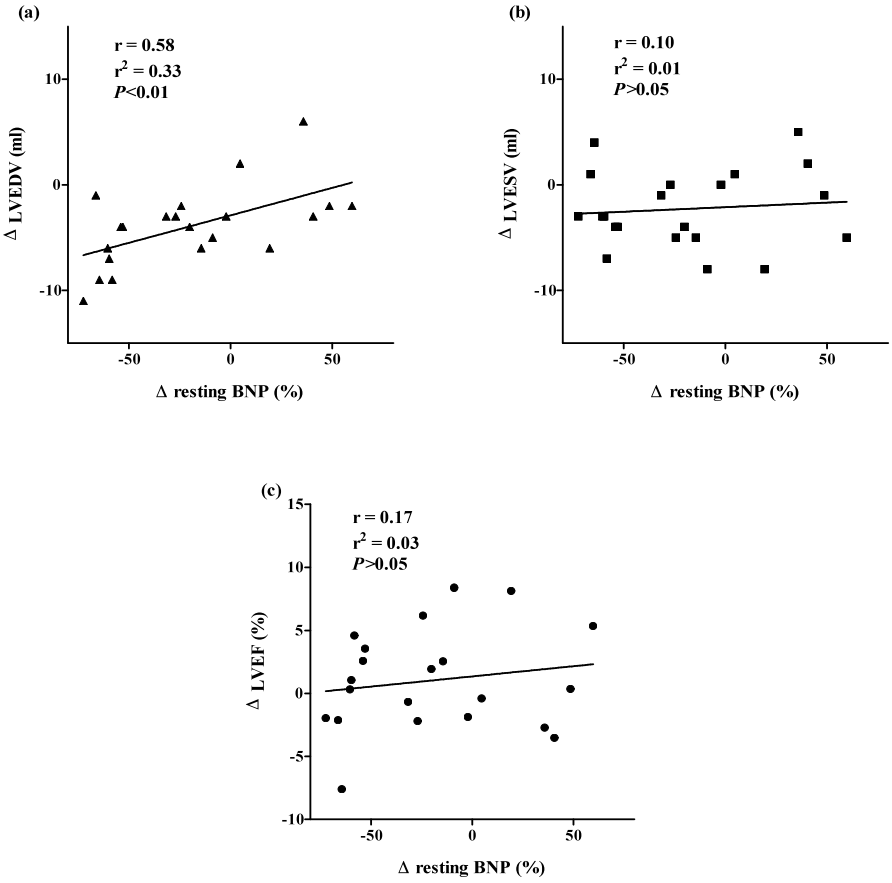

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337 **Figure 2.** Correlation between the relative change (Δ) in NT-pro-BNP (%) and the absolute change (Δ) in

338 left ventricular (LV) (a) end diastolic volume (EDV) (ml), (b) end systolic volume (ESV) (ml) and (c)

339 ejection fraction (EF) (%) in the exercise training group

340 **Table 1 Demographic, clinical and exercise test parameters at baseline and 10 weeks**

	Exercise training (n=33)		Non-exercise (n=17)	
	Baseline	***Week 10***	***Baseline***	***Week 10***
Demographics				
Male gender (%)	100	-	100	-
Age (yrs)	55.8 ± 9.2	-	56.2 ± 10.8	-
Height (m)	1.7 ± 0.1	-	1.8 ± 0.1	-
Body mass (kg)	82.7 ± 10.2	83.1 ± 10.5	90.4 ± 14.2	90.5 ± 14.3
BMI (kg/m^2)	27.4 ± 2.6	27.6 ± 2.7	29.2 ± 4.1	27.6 ± 2.7
BSA (m^2)	2.0 ± 0.1	2.0 ± 0.1	2.1 ± 0.2	2.1 ± 0.2
Clinical				
STEMI (n)	20	-	13	-
NSTEMI (n)	13	-	4	-
Time post MI (days)	33.7 ± 8.9	-	35.7 ± 7.7	-
HR_{rest} (bpm)	59 ± 8	58 ± 7	56 ± 7	56 ± 7
BP_{sys} (mmHg)	113 ± 17	110 ± 16	118 ± 12	117 ± 12
BP_{dia} (mmHg)	71 ± 8	71 ± 8	70 ± 9	70 ± 9
Exercise test				
$VO_{2\ peak}$ ($L.min^{-1}$) † ‡	2.0 ± 0.4	2.3 ± 0.4****	1.9 ± 0.4	1.8 ± 0.5
$VO_{2\ peak}$ ($ml.kg^{-1}.min^{-1}$) † ‡	24.0 ± 4.1 §	27.5 ± 4.6****	20.8 ± 3.1	20.2 ± 4.1
W_{max} (watts) † ‡	148 ± 27	175 ± 30****	146 ± 28	150 ± 31
VT ($ml.kg^{-1}.min^{-1}$) † ‡	12.5 ± 2.8	14.6 ± 3.5****	11.2 ± 1.7	10.8 ± 2.3
Exercise time (mins) † ‡	8.6 ± 1.0	9.9 ± 1.2****	8.3 ± 1.4	8.2 ± 2.7

341

342 Data as mean ± SD. BMI, body mass index; BSA, body surface area; STEMI, ST elevation myocardial
343 infarction; NSTEMI, non ST elevation myocardial infarction; MI, myocardial infarction; HR_{rest}, resting
344 heart rate; BP_{sys}, systolic blood pressure; BP_{dia}, diastolic blood pressure; $VO_{2\ peak}$, peak oxygen uptake;
345 W_{max}, maximum workload; VT, ventilatory threshold. § $P<0.05$ vs. non-exercise at baseline, † $P<0.05$
346 time effect (ANOVA), ‡ $P<0.05$ group × time interaction effect (ANOVA), ****$P<0.0001$ vs. baseline

Table 2 Left ventricular structural parameters at baseline and 10 weeks

	Exercise training (n=33)		Non-exercise (n=17)	
	Baseline	***Week 10***	***Baseline***	***Week 10***
LV size				
LVIDd (cm)	4.8 ± 0.5	4.8 ± 0.5	4.9 ± 0.5	4.9 ± 0.5
LVIDs (cm)	3.2 ± 0.5	3.3 ± 0.5	3.4 ± 0.6	3.4 ± 0.5
LVIDd/BSA (cm/m^2)	2.2 ± 0.6	2.4 ± 0.2	2.4 ± 0.6	2.4 ± 0.2
LVIDs/BSA (cm/m^2)	1.7 ± 0.3	1.7 ± 0.2	1.6 ± 0.3	1.7 ± 0.2
LV mass and geometry				
LV mass (g)	209 ± 46	217 ± 57	234 ± 51	217 ± 45
IVSd (cm)	1.3 ± 0.2	1.3 ± 0.2	1.4 ± 0.3	1.3 ± 0.2
LVPWd (cm)	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2
IVSs (cm)	1.7 ± 0.2	1.7 ± 0.2	1.8 ± 0.3	1.8 ± 0.3
LVPWs (cm)	1.5 ± 0.3	1.5 ± 0.2	1.5 ± 0.3	1.5 ± 0.3
RWT (cm)	0.45 ± 0.08	0.45 ± 0.08	0.46 ± 0.11	0.45 ± 0.10
LV mass/BSA (g/m^2)	106 ± 20	109 ± 25	115 ± 26	105 ± 19

Data as mean ± SD. LV, left ventricular; LVIDd, LV internal diameter in diastole; BSA, body surface area; LVIDs, LV internal diameter in systole; LVEDV, LV end diastolic volume; LVESV, LV end systolic volume; IVSDd, inter-ventricular septal wall in diastole; LVPWd, LV posterior wall in diastole; IVSs, inter-ventricular septum in systole; LVPWs, LV posterior wall in systole; RWT, relative wall thickness

354 **Table 3 Left ventricular functional parameters at baseline and 10 weeks**

	Exercise training (n=33)		Non-exercise (n=17)	
	Baseline	***Week 10***	***Baseline***	***Week 10***
LV systolic function				
Fractional shortening (%)	31.9 ± 7.2	32.1 ± 5.3	31.9 ± 7.2	31.5 ± 7.3
Stroke volume (ml)	46.8 ± 9.5	46.3 ± 8.3	52.9 ± 11.9	53.1 ± 9.8
Lateral s'(cm/s)	8.1 ± 2.9	8.3 ± 2.4	9.1 ± 2.3	8.5 ± 3.0
Mean s'(cm/s)	8.0 ± 1.9	8.0 ± 1.6	8.4 ± 1.6	8.1 ± 2.0
LV diastolic function				
E/A ratio	1.15 ± 0.33	1.06 ± 0.24	1.14 ± 0.36	1.17 ± 0.37
DT (ms)	215 ± 34	224 ± 44	217 ± 67	245 ± 67
Lateral e'(cm/s)	9.5 ± 3.3	10.0 ± 3.1	10.0 ± 3.3	9.8 ± 2.9
Lateral a'(cm/s)	8.6 ± 2.4	9.2 ± 2.4	8.9 ± 1.4	8.8 ± 2.3
Lateral e'/a' ratio	1.2 ± 0.5	1.1 ± 0.4	1.2 ± 0.4	1.2 ± 0.5
Lateral E/e' ratio	7.3 ± 2.6	6.6 ± 2.0	6.6 ± 2.0	6.2 ± 2.8
Mean e'(cm/s)	8.1 ± 2.3	8.6 ± 2.1	8.9 ± 2.4	8.8 ± 2.1
Mean a'(cm/s)	8.9 ± 1.6	9.2 ± 1.3	8.9 ± 1.2	8.6 ± 1.9
Mean e'/a' ratio	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.3	1.1 ± 0.4
Mean E/e' ratio	8.4 ± 2.0	7.6 ± 1.6	7.5 ± 1.7	7.0 ± 2.9

355

356 Data as mean ± SD. s', peak systolic mitral annulus tissue velocity; E/A ratio, ratio of peak early
357 (E) to late (A) mitral inflow velocity; DT, rate of deceleration of early mitral inflow; e' peak early
358 diastolic mitral annulus tissue velocity; a', peak late diastolic mitral annulus tissue velocity; e'a'
359 ratio, ratio of peak early to late diastolic mitral annulus tissue velocity; E/e' ratio, ratio of peak
360 early mitral inflow velocity to peak early diastolic mitral annulus tissue velocity; IVRT, iso-
361 volumic relaxation time. † $P<0.05$ time effect (ANOVA), ** $P<0.01$ vs. baseline.

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Acknowledgements

We would like to extend our thanks to the Cardiac Rehabilitation team at University Hospital, Coventry for their expert assistance with exercise training and to the Pathology team for processing the blood samples.