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ARTICLE

Effect of combined resistive-endurance exercises on myocardial tissue creatine kinase isoenzyme, IL-6 and IL-10 in male patients following cardiac surgery.

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Abstract

Objectives: The aims of the present study were to investigate the effects of concurrent endurance and resistance training upon the healing of cardiac patients following surgery as seen in plasma CK-MB, IL-6 and IL-10 concentrations. *Methods:* The experimental subjects were 63 males who had undergone a coronary bypass, balloon angioplasty or valve replacement. Control subjects were 35 men who had received a similar range of treatments, but were unwilling to enter the rehabilitation program. *Results:* Baseline anthropometric data, ventricular dimensions, ejection fraction and treadmill testing showed good initial matching of clinical status. The experimental group performed a one-hour exercise program 3 times per week for 8 weeks. After training, anthropometric measurements showed a decrease of body fat, and peak aerobic power and 6-minute walking distance showed expected gains. The rehabilitation program led to substantial decreases in CK-MB, IL-6, and IL-10 in the experimental group. The decreases of IL-6 and IL-10 seen in experimental subjects appear to be independent of body fat loss and cardiac healing. *Conclusions:* A combined endurance-resistance training program not only improves physical condition following cardiac revascularization, but also speeds tissue healing relative to individuals of similar initial condition who have declined the option of exercise rehabilitation. **Health & Fitness Journal of Canada 2015;8(2):3-12.**

Keywords: Angioplasty; Cardiac Rehabilitation; Concurrent Endurance-resistance Training, Cytokines; Interleukins

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Introduction

From the immediate viewpoint of the patient, the most important argument in favour of entering a program of rehabilitation following revascularization and other forms of cardiac surgery is an increase of functional capacity, with a resulting improvement in the quality of life (Choo et al., 2007; Jankowska et al., 2008). It is less clear what impact early exercise rehabilitation has upon the process of tissue healing and thus long-term prognosis. We thus decided to explore the latter issue, using serum levels of creatine kinase myocardial band isozyme (CK-MB) as a marker of the healing process, and to examine whether associated decreased in concentrations of the cytokines IL-6 and IL-10 are a part of this process.

There is often a substantial early release of CK-MB following cardiac revascularization (Hake et al., 1990; Otterstad, 2002]. CK-MB levels indicate the extent of cardiac cell damage (Kida et al., 2008). When expressed as a ratio of CK-MB to total CK, values above 3-5% indicate a leakage of myocardial protein into the blood stream, and values > 20% offer a clear indication of myocardial cell damage (Burtis, 2006). Further, such CK-MB levels are linked to subsequent mortality (Abdelmeguid et al., 1996; Brener et al., 2002; Califf et al., 1998; Costa et al., 2001; Klatte et al., 2001; Kong et al., 1997).

The possible contributions of the cytokines IL-6 and IL-10 to this process are less clear. IL-6 is a dual pro- and anti-inflammatory cytokine. Concentrations of IL-6 are increased immediately following myocardial infarction, and in the absence of treatment they may remain elevated for 12 weeks or more (Gabriel et al., 2004; Miyao et al., 1993; Ritsche et al., 2014), possibly as part of an acute phase reaction to tissue injury. Moreover, these humoral responses are accompanied by an increased secretion of the anti-inflammatory cytokine IL-10 (Dizdarević-Hudić L et al., 2004; Krishnamurthy et al., 2009). It has been suggested that the suppression of inflammation by an increased output of IL-10 is helpful in reducing fibrosis and enhancing subsequent myocardial function (Burchfield et al., 2008; Krishnamurthy et al., 2009).

An aerobic exercise training programme reduces both basal plasma levels of IL-6 and the acute exercise-induced increase of IL-6 in healthy individuals (Fischer, 2006) and in patients undergoing coronary rehabilitation (Goldhammer et al., 2005), but an analysis of 4 recent studies of patients with chronic heart failure found no evidence that aerobic training yielding a modest increase of peak oxygen intake (an average increase of 1.4 $mL \cdot kg^{-1} \cdot min^{-1}$) influenced the IL-6 levels of such individuals (Smart et al., 2011). One issue complicating the interpretation of data is that serum levels of IL-6 are also influenced by training-related changes in body fat content (Roytblat, 2000; Kern et al., 2001; Eder et al., 2009).

The objectives of our present quasi-experimental investigation were thus to examine whether a rehabilitation program that combined endurance and resistance training would accelerate myocardial healing in patients who had undergone cardiac revascularization and other forms of surgery, using as our index decreases in CK-MB and to determine whether changes in serum levels of IL-6 and IL-10 contribute to the reversal of inflammatory changes. Our hypotheses were that participation in an 8-week course of rehabilitation would accelerate myocardial healing relative to patients who for various reasons did not enter the rehabilitation program, as shown by decreased levels of CK-MB, and that decreases in IL-6 and IL-10 would show a significant relationship to this healing process, after accounting for the known effects of a decrease in body fat content upon serum levels of these cytokines.

Methodology

Participants and experimental plan: All observations were made according to a protocol approved by the Research Ethics Committee of the University of Isfahan, after details of the possible benefits and risks of the experiments had been explained to the patients, and an informed consent form had been completed. Study participants were 98 male patients who were attending the Shahin Shahr Cardiovascular Centre following coronary by-pass surgery, balloon angioplasty, or valvular replacement therapy. Sixty-three of these individuals entered the experimental programme (age 45.2 ± 8.9 yr), whereas the 35 controls (age 51.3 ± 2.4 yr) attended the same clinic over the same period, but were unwilling to undergo rehabilitation (n = 15). The two groups did not differ significantly from each other initially in terms of medications (Table 1), echocardiographic characteristics (Table 2), blood pressures and peak aerobic power (Table 3), and anthropometric characteristics (Table 4).

Participants first attended the center one week before physical and physiological testing. At this visit, they completed the consent form and a health history questionnaire (Ritchie-Gemma et al., 2001). The experimental group entered an 8-week rehabilitation programme after determination of initial anthropometric characteristics, functional capacity and biochemical status. The control group did not exercise regularly, although in consultation with their physician, specific dietary and other lifestyle changes were recommended to reduce cardiac risk factors. Further measurements were made on all subjects at the end of the 8 weeks.

Initial status: Anthropometric parameters included body mass, waist circumference, hip circumference and skinfold thicknesses. Three subcutaneous skinfolds [right triceps, right abdominal (25 mm lateral from and 12 mm below the umbilicus) and right gastrocnemius (medial side of the leg, at the maximum calf circumference, and measured parallel with the long axis)] were measured using Lange calipers. Three measurements were made at each site, and the mean skinfold values were recorded. The cardiac ejection fraction was determined by Simpson's biplane method (Otterstad. 2002), and left ventricular end-systolic and end-diastolic diameters were also measured. The exercise response was estimated by a progressive, symptom-limited treadmill test (Naughton et al., 1963). Functional ability was also assessed by a 6-min walking test (Heyward, 1998). Creatine kinase, IL-6 and IL-10 were determined by the ELISA protocol, using standard laboratory research kits (Pars Azmoon, Tehran, Iran; Boster, Pleasanton, CA, and BenderMed, Vienna, Austria, respectively). The accuracy claimed for each of these tests was < 10 %.

Training program: Criteria for entry into the trial were a cardiac ejection fraction > 30%, the absence of exercise-induced angina, and an exercise-induced ST segmental depression < 2 mm. The training program began between 2 to 4 weeks after surgical treatment. Patients undertook 3 formal exercise sessions per week and were also encouraged to engage in home aerobic activities such as walking for 30 to 45 minutes 1-3 times a week (Adams et al., 2006). The formal sessions combined endurance and resistance exercise, and followed currently accepted guidelines (Fletcher et al., 2001). The endurance component, performed on a cycle ergometer, comprised a 5-10 minutes warm-up, 15-20 minutes of aerobic exercise (initially at 50 to 70 percent, and rising to 60-80 percent of maximal heart rate based on the Karvonen formula (Karvonen and Vuorimaa, 1988) and a final 5-10 minutes cool-down of unloaded pedaling. Resistance exercise with weights was performed for 10-15 minutes per session, using 11 movements recommended by the American Association of Cardiovascular and Pulmonary Rehabilitation (Fletcher, 2001). The intensity of effort was initially set at 20-30% of the 1 RM value, and was adjusted upwards as necessary so that the patient could lift the weights 8-15 times; if the individual was able to complete 15 lifts, the load was gradually (Glowacki et al., 2004). All of the experimental subjects attended all of their 24 supervised sessions over the 8-week trial, and they were not advised to undertake any supplementary exercise at home. The control subjects continued with their "usual care" regimen.

Statistical analyses

After assuring the normality of data distribution by the Kolmogorov-Smirnov test, paired sample t-tests, univariate and multivariate analyses were performed using the SPSS program (version 17). The level of probability was set at $p < 0.05$ throughout. Although multiple comparisons were made, this was not an issue of concern, since without exception the experimental data showed consistent changes in the variables examined, and no changes were seen in the control group. Most positive findings for the experimental group reached a probability much smaller than $p < 0.05$.

Results

Most of the experimental subjects had undergone coronary arterial bypass graft surgery (19/38) or balloon angioplasty (18/38); three of the group were receiving antihypertensive medication (Table 1). A similar distribution of treatments was seen among the 15 male controls.

The initial ejection fraction (EF) of both experimental and control subjects showed a moderate reduction relative to expected normal values (Table 2), whereas LV end-systolic (LVESD) and LV end-diastolic (LVEDD) diameters were higher than normal (anticipated ranges: LVESD <33 mm, LVEDD <50 mm). Following training, the experimental group showed substantial and statistically significant improvements in ejection fraction, LVESD and LVEDD, whereas figures for the control group remained unchanged. The training programme induced significant reductions in both resting systolic and diastolic pressures and exercise pressures for the experimental group, whereas data for the control subjects showed no change. The training programme also induced a substantial gain of peak oxygen intake, whereas exercise test data for the control subjects showed no change at the end of the 8 weeks (Table 3).

Table 4 shows that the combination of resistance and endurance exercise significantly reduced body mass ($p = 0.016$), abdominal circumference ($p = 0.031$), hip circumference ($p = 0.003$) and the summed thickness of the 3 subcutaneous skinfolds ($p = 0.028$) in the experimental subjects. The 6-minute walking distance was also increased after rehabilitation ($p = 0.001$). Again, values for the control group showed no significant changes over the course of the study.

Table 1: Use of medications in experimental and control groups.

Variable		Experimental (n = 63)	Control (n = 35)
Medications	Antihypertensive	13	2
	Anti-lipid drugs	6	7
	Nitroglycerine group	15	15
	Aspirin and other anticoagulants.	24	16
Type of treatment	Coronary arterial bypass surgery	29	23
	Angioplasty	29	17

Table 2: Echocardiographic parameters for experimental (n = 63) and control (n = 35) groups (mean ± SD).

Variable	Initial		Final		Significance	
	Experimental	Control	Experimental	Control	Experimental	Control
Ejection fraction (%)	52 ± 12	49 ±14	66 ± 9	51 ± 1	0.014*	0.74
Left ventricular end systolic diameter (mm)	40 ± 7	41 ± 7	28 ± 7	39 ± 8	0.017*	0.61
Left ventricular end-diastolic diameter (mm)	52 ± 7	52 ± 8	42 ± 3	50 ± 2	0.001*	0.59

*significant difference between initial and final data for experimental group.

Table 3: Initial parameters for experimental (n = 63) and control (n = 35) groups during peak treadmill exercise test (mean ± SD).

Variable	Initial		Final		Significance	
	Experimental	Control	Experimental	Control	Experimental	Control
Resting systolic blood pressure (mm Hg)	131 ± 4	127 ± 3	117.1 ± 8	121 ± 7	0.011	0.59
Resting diastolic blood pressure (mm Hg)	72 ± 6	76 ± 5	66 ±1	75 ± 3	<0.000	0.71
Peak systolic blood pressure (mm Hg)	163 ± 12	162 ± 15	130 ± 5	151 ± 9	0.008	0.87
Peak diastolic blood pressure (mm Hg)	85 ± 5	89 ± 2	71 ± 1	79 ± 4	0.001	0.77
Peak aerobic power ($mL \cdot kg^{-1} \cdot min^{-1}$)	31.9 ± 9.8	32.6 ± 8.4	38.9 ± 6.7	32.6 ± 9.5	0.015	0.697

*Significant difference between initial and final data for experimental group.

The rehabilitation program led to substantial decreases in CK-MB, IL-6 and IL-10 in the experimental group, but each of these measures remained unchanged in the control subjects (Table 5).

Table 4: The effect of rehabilitation on anthropometric parameters and 6-minute walk test in experimental group (n = 38), with comparable values for control group (n =15). Mean ± SD of data.

Variable	Initial		Final		Significance	
	Experimental	Control	Experimental	Control	Experimental	Control
Body mass (kg)	81 ± 19	84 ± 22	73 ± 6	81 ± 1	0.016*	0.69
Abdominal circumference (cm)	98 ± 11	94 ± 9	88 ± 8	93 ± 9	0.031*	0.87
Hip circumference (cm)	17 ± 4	17 ± 4	16 ± 2	17 ± 4	0.003*	0.74
Sum of Three Skinfolds (mm)	79 ± 9	69 ± 9	60 ± 9	60 ± 10	0.028*	0.51
Walk test (m)	478 ± 30	491 ± 33	598 ± 64	487 ± 20	0.001*	0.76

*There were no significant initial difference between experimental and control subjects; significant difference between initial and final data for experimental group marked with asterisk.

Table 5: The effect of rehabilitation on blood levels CK-MB, IL-6 and IL-10 in experimental group (n = 63), with corresponding values for controls (n = 35).

Variable	Initial		Final		Significance	
	Experimental	Control	Experimental	Control	Experimental	Control
CK-MB (ng/mL)	260 ± 78	248 ± 65	150 ± 98	251 ± 75	0.001*	0.84
IL-6 (ng/mL)	7 ± 2	6 ± 2	2 ± 2	7 ± 2	0.004*	0.59
IL-10 (ng/mL)	11 ± 3	11 ± 3	4 ± 2	12 ± 2	0.026*	0.09

*Significant difference between initial and final data for experimental group.

Multivariate analyses (Table 6) related changes in IL-6 amd IL-10 to both the healing process (as indicated by the change in CK-MB) and to the decrease in body fat (as shown by the summated skinfolds). Changes in cytokine concentrations were not significantly related to either of these markers.

Discussion and Conclusions

In accord with our first hypothesis, following 8 weeks of combined endurance/resistance exercise-based rehabilitation, the experimental subjects showed not only the anticipated decreases in body fat (Lavie et al., 2008) and enhanced functional ability (Murray and Beller, 1983), but also substantial decreases in blood levels of CK-MB relative to individuals who for various

Table 6: Multivariate analyses relating changes in cytokine concentrations to changes in CK-MB and skinfold thicknesses in experimental participants.

Equation 1 for Exp group: Δ IL-6 = -0.022± 0.69 (Δ CK-MB) + 6.749 ± 0.755 SS_{reg} = 0.033 SS_{error} = 2.953, r=-0.55 Equation 1 for CON group: Δ IL-6 = -0.12± 0.61 (Δ CK-MB) – 0.409 ± 0.199 SS_{reg} = 0.721 SS_{error} = 1.684, r = -0.55
Equation 2 for EXP group: Δ IL-10 = -0.31± 0.033(Δ CK-MB) + 10.184± 3.653 SS_{reg} = 0.64 SS_{error} = 0.683 Equation 2 for CON group: Δ IL-10 = -0.001± 0.00 (Δ CK-MB) -0.839 ± 0.206 SS_{reg} = 0.000 SS_{error} = 1.765, r = 0.65
Equation 3 for EXP group: Δ IL-6=0.023± 040 (Δ skinfolds) +3.938± 0.781 SS_{reg} = 0.1 SS_{error} = 2.886 Equation 3 for CON group: Δ IL-6= -0.153± 0.074 (Δ skinfolds) – 0.031± 0.133 SS_{reg} = 0.764 SS_{error} = 1.605, r = 0.568
Equation 4 for EXP group: Δ IL-10 = -0.04± 0.016(Δ skinfolds) + 7.6 ± 0.302 SS_{reg} = 0.316 SS_{error} = 0.431, r = 0.651 Equation 4 for CON group: Δ IL-10 = 0.02± 0.077 (Δ skinfolds) – 0.847 ± 0.139 SS_{reg} = 0.013 SS_{error} = 1.752, r = 0.087
Equation 5 for EXP group: Δ IL-6 = -0.017± 0.073 (Δ CK-MB) + 0.021± 0.043 (Δ skinfolds) + 5.834± 2.811 SS_{reg} = 0.12 SS_{error} = 2.866, r = 0.2 Equation 5 for CON group: Δ IL-6 = -0.097± 0.056 (Δ CK-MB) - 0.125± 0.69 (Δ skinfolds) – 0.285± 0.190 SS_{reg} = 1.203 SS_{error} = 1.166, r = 0.71
Equation 6 for EXP group: Δ IL-10 = -0.040± 0.024 (Δ CK-MB) -0.014± 0.11 (Δ skinfolds) + 12.048± 2072 SS_{reg} = 0.425 SS_{error} = 0.322, r = 0.754 Equation 6 for CON group: Δ IL-10 = -0.005± 0.068 (Δ CK-MB) + 0.022± 0.084 (Δ skinfolds) – 0.861± 0.232 SS_{reg} = 0.015 SS_{error} = 1.751, r = 0.091

reasons did not enter the rehabilitation programme. However, contrary to our second hypothesis, decreases in IL-6 and IL-10 were not significantly related to changes in either CK-MB or body fat content.

The high initial levels of CK-MB reflect a continued leakage of cardiac isoenzyme into the blood stream following surgery. Studies in healthy experimental animals (Miller et al., 1989) have shown little influence of endurance training upon cardiac CK-MB levels, although the cardiac CK-MB levels of diabetic rats are reduced by training (Mokhtar et al., 1992). Training was also associated with decreased blood levels of IL-6 and IL-10 in our subjects. The decrease of body fat with training might be conceived as contributing to the decreased inflammation in the experimental subjects (Christen et al., 2006), but the lack of correlation between changes in cytokines and skinfold readings argues strongly against this explanation. Other factors more directly linked to training of the myocardium are probably involved. Given the associated decreases in IL-10 concentration that were also observed, there seems to have been a training-related reduction of the overall inflammatory process, with less production of IL-6, less need for an anti-inflammatory IL-10 response, improved cardiac function (as shown by the gains of aerobic power), and a potential for less final myocardial scarring. However, this response was not closely associated with healing of the cardiac muscle, at least as indicated by changes in CK-MB concentrations. Possibly, metabolic adaptations in the skeletal muscles induced by the resistance training (Fischer, 2006) may also have contributed to the lower concentrations of IL-6 in the experimental group.

Patients are sometimes reluctant to attend cardiovascular rehabilitation centres for a sustained course of rehabilitation following revascularization surgery (Ritchie Gemma, 2001), in part because of the time commitment involved in travelling to a centre that is often in the heart of a congested city. The likely functional improvement is certainly one persuasive argument to present to patients who are debating their need for a supervised rehabilitation programme, but the more rapid healing of the myocardium, as shown by the CK-MB measurements, is another powerful reason to urge their enrolment in such programmes.

The strengths of the present study are the implementation of an exercise protocol within weeks of surgery, and the use of circulating biomarkers to examine biological changes and to explore potential mechanisms. Plainly, there are also some limitations to the research we have completed to date. Ethical considerations precluded conducting a true randomized controlled trial, and although the initial functional status was quite well matched, there were inevitably some differences between experimental and control subjects. The sample size was also relatively small, although most of the changes observed in the experimental group reached statistical significance. Further studies are needed on men in other age groups and in women of all ages.

Most cardiac rehabilitation programmes to date have been based largely upon endurance activity, although there is growing appreciation of the need to supplement such training by resistance activity to strengthen both cardiac and skeletal muscle (Adams et al., 2006; Karapolat et al., 2007). It would be interesting to compare the impact of a conventional, endurance-based exercise program upon functional ability, CK-MB and cytokine levels, relative to a programme that included both endurance and resistance training. More discussion of reasons for poor compliance with available rehabilitation programmes is also required, with the weighing of potential techniques to enhance patient motivation. Finally, longer-term and larger scale research should determine whether the lower levels of IL-6 and IL-10 induced by our rehabilitation programme are indeed accompanied by an enhanced prognosis. If this is indeed the case, the complex underlying cellular mechanisms (Burchfield et al., 2008) should be explored in greater detail.

Authors' Qualifications

The authors' qualifications are as follows: Saeid Rostrami PhD Student; Roy J. Shephard, C.M., M.B.B.S., M.D.[Lond.], Ph.D., D.P.E.,LL.D., D.Sc.; Bijan Rajaeian PhD.

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