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Vigorous Exercise Mimics Remote Ischemic Preconditioning and Provides Benefit in Cardiac Rehabilitation Patients

Jayme Rock-Willoughby, Debra Boardley, Dalynn T. Badenhop and Jodi Tinkel

University of Toledo Medical Center, 3000 Arlington Avenue, Toledo Ohio 43614, USA

Abstract

Remote ischemic preconditioning (rIPC) has been shown to reduce the extent of myocardial infarction during an ischemic event as well as prior to a planned cardiac intervention. Vigorous exercise has been shown to have similar cardiovascular benefits to remote ischemic preconditioning in healthy individuals. Despite this effect, many individuals who exercise regularly present with cardiovascular disease. Those individuals who participate in cardiac rehabilitation programs provide a unique opportunity to determine whether the effects of vigorous exercise prior to a cardiac event result in improved outcomes. This investigation analyzed a cardiac rehabilitation database and compared individuals with the highest and the lowest exercise capacity as determined by their peak oxygen consumption on a cardiopulmonary exercise testing (CPX) test prior to initiating a cardiac rehabilitation program to compare baseline characteristics and outcomes. Group 1 (VigEx) includes individuals with higher peak VO_2 (mean peak VO_2 33 and METS 9) and Group 2 (LowEx) includes those with lower peak VO_2 (mean peak VO_2 11 and METS 3). 72% of the subjects in VigEx had a preserved ejection fraction (EF) but only 50% of subjects in LowEx. None of the subjects in VigEx had severely reduced EF, while 28% of LowEx had an EF < 30%. In conclusion, individuals with cardiovascular disease who participate in vigorous exercise prior to their cardiac event have improved EF and may obtain a protective benefit similar to rIPC. Also, given the safety of vigorous exercise in the cardiac rehabilitation population and its similar effects to rIPC, cardiac rehabilitation programs should promote vigorous exercise in capable individuals.

Keywords: Remote ischemic preconditioning; Cardiac rehabilitation; Ejection fraction; Myocardial infarction

Background

Ischemic preconditioning occurs when controlled ischemia in one coronary vascular territory reduces the extent of myocardial damage during a second prolonged ischemic event in the same coronary vascular territory. Remote ischemic preconditioning occurs when controlled ischemia in a distant vascular bed such as a separate coronary artery, a limb or a mesenteric vessel provides a similar protective benefit during an episode of coronary ischemia. Remote ischemic preconditioning (rIPC) has been shown to reduce the extent of myocardial necrosis and infarction during an acute ischemic event [1] as well as prior to a planned cardiac surgery or percutaneous coronary intervention [2,3]. Vigorous exercise has been shown to have cardiovascular benefits similar to rIPC [4,5]. The effect of rIPC and vigorous exercise has been demonstrated to occur via shared mechanisms in the serum and spinal ganglion. It is possible that vigorous exercise prior to an ischemic event may mitigate the extent of myocardial damage in a manner similar to that seen with rIPC.

Individuals who participate in cardiac rehabilitation programs provide a unique opportunity to investigate whether the effects of more vigorous exercise prior to a cardiac event would result in improved clinical outcomes. This investigation used a cardiac rehabilitation database to compare individuals with the highest and the lowest exercise capacity as determined by their peak oxygen consumption (peak VO_2) on a cardiopulmonary exercise test (CPX) prior to initiating a cardiac rehabilitation program to further evaluate this hypothesis. The purpose of this study was to evaluate the associations between previous exercise conditioning and clinical outcomes.

Methods

Patients

The cardiac rehabilitation database, containing > 1600 subjects was queried to identify those individuals with the highest and lowest peak VO_2 on their initial CPX test (95th percentile and 5th percentile). Subjects with incomplete data were excluded. Baseline characteristics were collected and compared between the two groups (Table 1), including risk factors for cardiovascular disease (CVD), medications, ejection fraction (EF), myocardial infarction (MI) at presentation, and need for coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI). The groups were analyzed to test the hypothesis that individuals in the more vigorous exercise (VigEx) group would have a higher EF compared to those in the reduced exercise group (LowEx). 43 subjects were included in the VigEx group and 33 in the LowEx group. The groups were also compared to determine whether those in the VigEx group would have fewer risk factors for CVD, fewer subjects presenting with MI, or requiring CABG compared to the LowEx group.

Statistical methods

All statistical procedures were performed using SPSS software (version 17, SPSS, Inc, Chicago, IL 2008). Group differences in continuous variables were examined using two sample *t* test. For categorical variables, Pearson's chi-square test was used. An exact Pearson's version was used in the cases where there was a cell smaller than 5. Statistical significance was defined as a p value of 0.05 or less.

*Corresponding author: Jodi Tinkel, University of Toledo Medical Center 3000 Arlington Avenue, Toledo Ohio 43614, USA, Tel: (419) 383-3697; Fax: 419-383-3014; E-mail: jodi.tinkel@utoledo.edu

	VigEX (n=41)	LowEX (n=33)
Baseline Characteristics		
Age in years (mean ± SD)	52.3 ± 7.6	64.1 ± 9.8*
Male (number, %)	39 (95%)	2 (5%)
BMI (mean ± SD)	26.0 ± 5.1	34.0 ± 7.4*
CV Risk Factors (number, %)		
≤1	7 (17%)	0 (0%)
2-4	26 (63%)	8 (24%)
≥5	8 (25%)	25 (76%)
Diabetes (number, %)	2 (5%)	19 (59.4%)
Primary Diagnosis (number, %)		
MI	10 (24%)	3 (9%)
CABG	5 (12%)	9 (27%)
PCI	17 (42%)	4 (12%)
Stable Angina	8 (20%)	14 (42%)
Other	1 (2%)	3 (9%)
CPX V0$_2$ (mean ± SD)	33.1 ± 3.2	10.6 ± 1.1*
12 MWD in feet (mean ± SD)	4167.9 ± 549.9	2182.6 ± 713.9*
EF % (mean ± SD)	54.0 ± 9.5	44.5 ± 16.7**

*p < 0.001, ** p < 0.005

Table 1: Baseline Characteristics and Results.

Outcomes

The primary outcome was EF measured by echocardiogram after their presenting ischemic event. Secondary outcomes included total number of risk factors for CVD, presentation with MI and need for CABG.
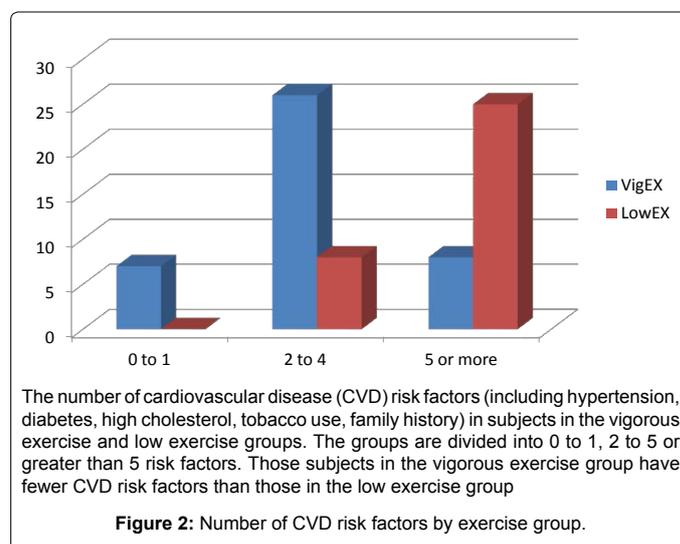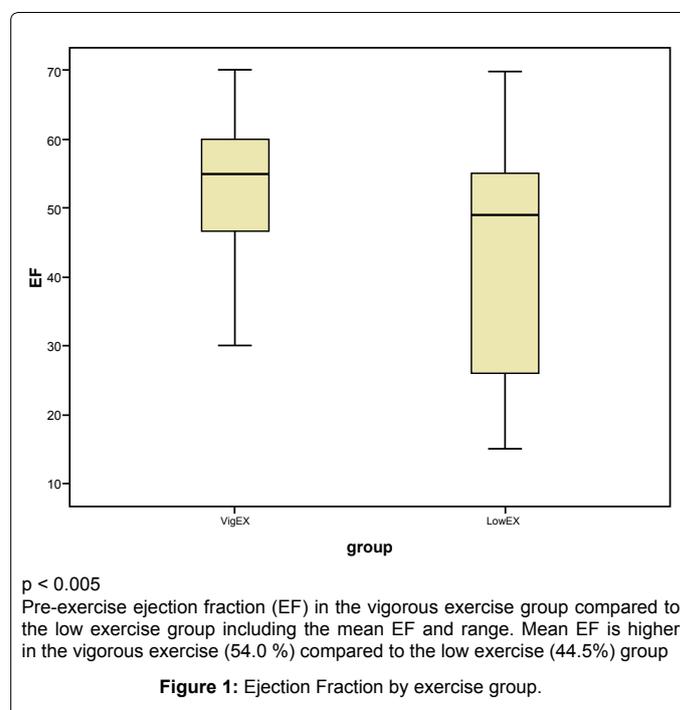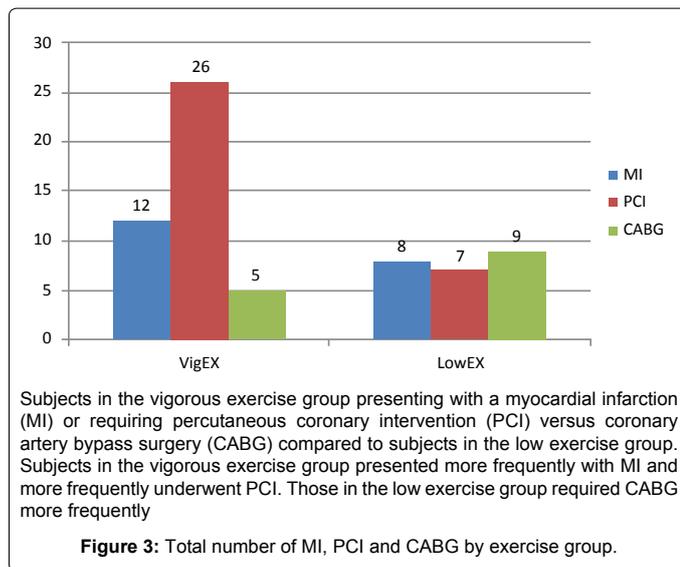
Results

The VigEx group includes individuals with higher peak VO$_2$ (mean peak VO$_2$ = 33.1 +/- 3.2 and METS 9.5 +/- 0.9) and the LowEx group includes those with lower peak VO$_2$ (mean peak VO$_2$ = 10.7 +/- 1.1 and METS 3.1 +/- 0.6). The mean EF was 54 +/- 9 % in the VigEx group compared to 45 +/- 16% in the LowEx group (p <0.05) (Figure 1). 72% of the subjects in VigEx had a preserved EF but only 50% of subjects in LowEx. None of the subjects in the VigEx group had severely reduced EF, while 28% of LowEx had an EF < 30%. The EF ranged from 35-70% in the VigEx group and from 20-65% in the LowEx group. Only 5 % of VigEx subjects had diabetes, whereas 60% of LowEx had diabetes. VigEx had 17% of its subjects with 0-1 CVD risk factors compared to none of the subjects in LowEx (Figure 2). LowEx had 36% with >5 CVD risk factors but only 7% of VigEx had > 5 CVD risk factors. Only 12% of VigEx subjects required CABG and 41% underwent PCI (Figure 3). In LowEx, 27% required CABG and 12% underwent PCI. 28% of the VigEx group presented with an MI, compared to 24% of the LowEx group.

Discussion

Myocardial infarction as a primary event as well as peri-procedurally carries a poor prognosis. The resulting increase in troponin levels and reduction in EF also carries prognostic value. An increase in troponin by as little as 1.5 ng/ml resulted in a 6 fold increase in mortality at 6 months [6]. Troponin levels are increased during acute coronary syndromes but can also rise above this low threshold during elective PCI and CABG. During an ischemic event, extensive coronary infarction involving more than 20% of the left ventricle results in a reduced ejection fraction, causing pathological myocardial stretch and congestive heart failure [7]. However, if one can limit the amount of ischemic myocardium at risk that then goes on to infarction from 75%

to 45%, this pathological remodeling and its clinical consequences may be prevented. Many clinical therapies given during the ischemic event, including glycoprotein IIb/IIIa inhibitors and statins, aim to reduce the extent of myocardial necrosis and ischemia reperfusion injury. Individuals with angina prior to their infarction have a reduction in the extent of myocardial necrosis, and this effect is thought to be due to the effects of ischemic preconditioning [8]. Exercise protects against ischemia-reperfusion injury and may mitigate the extent of myocardial injury that is suffered during a clinical myocardial infarction. The safety of vigorous exercise in subjects with cardiovascular disease during cardiac rehabilitation has been established [9]. In fact, individuals with a higher exercise capacity have significant reductions in overall mortality and CVD mortality that is independent of other cardiovascular risk factors [10]. The mechanism for this reduction in mortality is not fully elucidated but appears to be related to that which occurs during IPC.

p < 0.005
Pre-exercise ejection fraction (EF) in the vigorous exercise group compared to the low exercise group including the mean EF and range. Mean EF is higher in the vigorous exercise (54.0 %) compared to the low exercise (44.5%) group

Figure 1: Ejection Fraction by exercise group.

The number of cardiovascular disease (CVD) risk factors (including hypertension, diabetes, high cholesterol, tobacco use, family history) in subjects in the vigorous exercise and low exercise groups. The groups are divided into 0 to 1, 2 to 5 or greater than 5 risk factors. Those subjects in the vigorous exercise group have fewer CVD risk factors than those in the low exercise group

Figure 2: Number of CVD risk factors by exercise group.

Subjects in the vigorous exercise group presenting with a myocardial infarction (MI) or requiring percutaneous coronary intervention (PCI) versus coronary artery bypass surgery (CABG) compared to subjects in the low exercise group. Subjects in the vigorous exercise group presented more frequently with MI and more frequently underwent PCI. Those in the low exercise group required CABG more frequently

Figure 3: Total number of MI, PCI and CABG by exercise group.

A landmark study published in 1993 established the benefit of remote ischemic preconditioning (rIPC) by demonstrating that controlled ischemia in the circumflex territory reduced the extent of myocardial necrosis during left anterior descending artery occlusion [11]. Since then, this benefit has been extrapolated to ischemia in an extra-coronary remote vascular bed such as the upper or lower extremity, where rIPC continued to provide a protective benefit in reducing myocardial necrosis. Clinical outcomes studies have also supported the use of rIPC prior to a planned ischemic event such as PCI, open heart surgery for congenital heart disease or CABG or prior to abdominal aortic aneurysm repair [12,13]. Subjects who underwent a rIPC protocol prior to their CABG had a 43% reduction in their peri-operative troponin rise compared to controls [14]. The protective effect may extend to organs other than the myocardium at risk for ischemia reperfusion injury as shown by Ali et al with a reduction in acute renal injury and rise in serum creatinine as well as troponin in the preconditioned group [12].

The response to the ischemic event by the tissue supplied by the remote vascular bed and thus its mechanism is as yet unclear. However, it is clear that three key components must be in place for benefit to occur: First, the distant tissue or "source" must respond to the stimulus (i.e. rIPC or vigorous exercise). Second, the protective effect must be transmitted from the distant tissue to the heart (i.e. humorally and/or neuronally transmission). Finally, the myocardium or "target" must be receptive to the transmitted protection.

In vivo studies have sought to mechanistically explain the benefit of rIPC. After early studies demonstrated a reduction in infarct size due to IPC in the same coronary vascular bed and then rIPC in a separate coronary vascular bed, Birnbaum et al compared infarct size following femoral artery stenosis, rapid electric stimulation of the gastrocnemius muscle and the combination to controls [15]. Infarct size, which is expressed as a percentage of the myocardium supplied by the occluded artery and thus at risk of necrosis, was 26% in controls, 36% in the femoral artery stenosis group, 30% in the muscle stimulation group but was reduced to 9% in the combination group. This study demonstrated that both a humoral and neuronal stimulus to the distant source was involved in rIPC. rIPC has been demonstrated after femoral nerve stimulation and resulting loss of benefit when both the femoral and sciatic nerve is severed, suggesting a neuronal stimulus

to the distant source as well as a partially intact neuronal pathway from the source to the target is required to transmit this benefit [16]. Additional studies have supported the impact the neuronal pathway plays during ischemic preconditioning of trauma (IPT) seen during an abdominal wall incision or application of topical capsaicin, which provide protection similar to rIPC [17]. This benefit can be blocked by intrathecal injection of naloxone [18]. In addition, groups of rats that underwent rIPC, femoral nerve stimulation and application of topical capsaicin had their serum dialysate applied to a separate group of rats who then underwent an ischemic event, and each of these models of infarct received benefit from rIPC [19]. This would indicate that the mechanism of rIPC requires an intact humoral and neuronal system to include both a stimulus to the source and transmission of its response to the target and that its mechanism is shared by performance of vigorous exercise and by IPT.

An animal model of exercise in rats found that exercise results in a reduction in post-exercise systolic and diastolic blood pressure [20]. This effect appears related to changes in red blood cell concentrations of adenosine and may indicate one mechanism of benefit in exercise. In humans, a group of healthy individuals underwent both vigorous exercise and then rIPC, and dialysate from their serum provided similar protective benefit on a rabbit model of ischemia [5]. This study supports the hypothesis that vigorous exercise and rIPC act via similar mechanisms and that the mechanism of benefit requires in some part humoral transmission and is tranferable between species. Indeed, a group of elite Olympic athletes who performed similar training regimens underwent a cycle of rIPC and thereafter improved their personal record during a timed swim [4]. In turn, their serum dialysate reduced infarct size in the animal infarct model. These findings suggest that vigorous exercise produces effects at the cellular level that are beneficial in both the healthy individual as well as in a subject prior to an incident ischemic event.

Certain subgroups may lose some or all of the benefit from rIPC, including chronic diabetics with neuropathy and those with prior myocardial infarction. There are also variations depending on baseline characteristics like age, sex, medications and comorbid conditions. It is unclear where the break in the pathway is from the distant source to the target, the myocardium in these subgroups. Diabetes in particular represents a complex clinical syndrome to evaluate [21,22]. Evidence shows that the target, the myocardium undergoes changes in metabolism both in acute diabetes and in chronic diabetes and that those changes seen in chronic diabetes may make the myocardium no longer capable of benefitting from preconditioning [23]. Diabetic neuropathy may also inhibit rIPC by disruption of the neuronal response at the source or of transmission to the target [24]. No studies have been performed to evaluate whether the remote vascular bed in diabetics is impacted, but all of the three key requirements for rIPC may be affected. Several studies in subjects undergoing open heart surgery for CABG or valve replacement have not shown benefit from rIPC [25]. These mixed results in clinical benefit may reflect these subgroup differences and could also reflect differences in the type of anesthesia used and the timing of administration of the rIPC (before or after surgical induction or aortic cross clamping) [26].

The most frequently used protocol of 3 to 4 cycles of 5 minutes of ischemia and reperfusion using a blood pressure cuff and an upper limb 1-3 hours prior to the planned event may not be effective in all groups. The timing of the rIPC to the ischemic event required to provide benefit is has not been established. One study showed that as the timing between the rIPC and the ischemia increased beyond 30

minutes, the protective benefit decreased and was abolished at 360 minutes [1]. A second study however showed the benefit returned after 24 hours [27]. This timing relates to one protocol of rIPC-ischemia. It is unclear in individuals who regularly undergo vigorous exercise or who regularly undergo cycles of rIPC what the ideal timing, frequency and duration of the cycles would be necessary to maintain its protective benefit. In animal models as well as in clinical outcomes trials, there is clear evidence for an early, short term benefit prior to a planned ischemic event and to a second window of benefit at about 12-24 hours after preconditioning that lasts up to 48 hours.

Historically, evaluating subgroups has created several problems. First, clinical trials have not always excluded subgroups that may not benefit from rIPC. Second, animal models that reflect these differences are not available to study in a more controlled environment. Animal models most often use animals of a uniform age, sex and diet to avoid confounders [28]. Human subjects with diabetes and other risk factors and varying exercise regimens and functional capacities present a much more heterogeneous population to study. Medications like sulfonylureas or propofol may interfere with rIPC and must be controlled for in clinical trials [29].

Summary

Our database analysis indicates that individuals who could participate in vigorous exercise prior to their incident ischemic event had improved EF, reduction in their requirement for CABG, and fewer CVD risk factors in spite of the fact that more of them in the VigEx group presented with MI.

Study Limitations

Our data is hypothesis generating only and indicates an observational but not causal relationship between the benefits of vigorous exercise and improved clinical outcomes and the possibility of a shared mechanism with rIPC. Our groups are small. Exercise capacity could be reduced in the LowEx group due to increased age, BMI, CVD risk factors and reduced EF rather than due to lack of exercise prior to their ischemic event. Subjects presenting with a myocardial infarction are more likely to suffer damage from ischemia-reperfusion injury compared to those who present for an elective procedure. However, the VigEx group presented more commonly with myocardial infarction than the LowEx group. Further study is needed to clarify these trends.

Conclusion

Cardiac rehabilitation participants with higher initial peak VO_2 values on CPX testing have a reduction in the extent of myocardial damage as evidenced by improved EF, supporting the hypothesis that engaging in vigorous exercise prior to an ischemic event provides a protective benefit whose mechanisms may mimic rIPC.

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