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Is isokinetic eccentric exercise dangerous for the heart?

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Abstract.
BACKGROUND: Very strenuous exercises can be performed on an isokinetic dynamometer in order to evaluate the resistance to fatigue of different muscular groups. Good cardiac function is necessary in order to perform these very intensive exercises; otherwise an acute myocardial dysfunction could theoretically appear in predisposed patients.
OBJECTIVE: Our study aimed to observe the cardiovascular impact of a maximal intense isokinetic eccentric exercise performed by a population of sedentary young men.
METHODS: Resting and post-exercise (just after, 3 hours and 24 hours after the exercise) blood samples were taken from 12 young male sedentary healthy subjects. These subjects performed an intense maximal eccentric isokinetic exercise of the quadriceps muscle. We evaluated markers of cardiovascular risk (troponin I, highly sensitive troponin T, NT-proBNP, myoglobin), of inflammation (hsCRP) and of oxidative stress (myeloperoxydase, lipidic peroxides, reduced and oxidised glutathione).
RESULTS: The following observations were made: no significant increase in cardiac (NT-proBNP, troponins) or inflammation (hsCRP) biomarkers; a significant increase in myoglobin, myeloperoxidase, lipidic peroxides, oxidised glutathione just after the exercise.
CONCLUSIONS: No modification in cardiac biomarkers were observed after the maximal eccentric isokinetic exercise. We were thus able to prove that the exercise could be performed without any risk to cardiac function in young sedentary subjects. However, a significant level of oxidative stress was induced by this exercise.

Keywords: Isokinetic, cardiac biomarkers, oxidative stress, maximal eccentric exercise

1. Introduction

Isokinetic exercises are usually employed either to evaluate muscular dysfunction or in rehabilitation after muscle or joint injuries [1–3]. Moreover, it is possible for very strenuous exercises to be performed on an isokinetic dynamometer in order to evaluate the resistance to fatigue of different muscular groups, especially among sportspeople [4–7]. Good cardiac function is necessary in order to perform these very intensive exercises; otherwise an acute myocardial dysfunction could theoretically appear in predisposed patients, even if they seem to be in good health. Indeed, every year, a number of sportspeople die on the field as a result of cardiac event [4–7]. Fortunately, reported deaths while taking part in sports have not usually occurred during isokinetic eccentric exercises.

Cardiovascular diseases (CVD) represents the primary cause of death worldwide [8]. Nowadays, levels of mortality due to cardiac events have stabilised. This situation has occurred notably as a result of improve-

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ment in cardiac disease prevention, developments in medical imagery and technologies and, more recently, modifications in diagnostic approach, with the use of new generation cardiac markers [8]. In spite of this progress, the incidence of CVD remains high because of the increase in life expectancy, the growing number of people with diabetes and the rise in obesity [8]. The incidence of death linked to physical exercise is higher among the elderly than among younger people and also among people who do not practise a regular physical activity [4]. In these groups, cardiac events often occur as a result of the presence of coronary disease of which the sufferer was unaware. The American Heart Association thus recommends cardiovascular screening for athletes of all ages [9,10].

It has been demonstrated that, during a period of rest following a lengthy and intense strain, some biological parameters (e.g. electrolytes, and some cardiac markers) may be come modified [11]. In general, these values return to a normal state within 24–48 h after the exercise, which suggests that these effects are merely transient [12–14]. This might be explained by the relatively short half-life of studied markers, or by water imbalance during and after the event [14]. If these markers remain high (above the specified limit), an acute cardiac disease must be suspected. However, despite the fact that some cardiac biomarkers are known to rise after a strenuous effort, evidence has demonstrated the cardio-vascular benefits gained from the practice of regular physical exercise, thus supporting exercise as the primary prevention strategy against coronary disease and CVD in general [8].

Formerly used in the acute coronary syndrome diagnostic, "cardiac enzymes" (e.g. creatine kinase (CK), aspartate aminotransferase (ASAT), lactate deshydrogenase (LDH) and myoglobin (MYO)) are no longer used today within this context, because they lack sufficient cardiospecificity [15]. Regarded previously as the cardiac "gold standard", nowadays CK-MB isoform determination is only recommended if troponin determination is not available. The cardiospecificity of CK-MB isoform determination is affected by the presence of the enzyme in the skeletal muscle [15]. Cardiac T and I troponins (cTnT and cTnI) are currently regarded as reference markers for myocardial necrosis on the basis of their excellent sensitivity and cardiospecificity [15,16]. New independent markers for the cardiovascular risk, related to troponins, have recently been developed. These emergent markers are likely to bring additional prognostic and diagnostic values to the estimation of cardiovascular risk.

Exercise has been shown to increase the production of reactive oxygen species to a point that can exceed antioxidant defenses, thereby causing oxidative stress [17]. Characteristics of exercise such as its intensity or duration seem to be associated with oxidative damage [18]. Acute short duration exhaustive aerobic exercise in the form of a novel volitional fatigue test is capable of inducing oxidative stress [17]. However, it has been demonstrated that acute incremental exercise to maximal performance does not cause alterations to the serum oxidant levels of healthy young individuals. This observation is probably due to an adaptive mechanism of the body in sportspeople developed through trainings [17,18]. Moreover, a study of women participant in an 8-week endurance training program showed that exercise taken seemed to have favorable effects on antioxidant capacity, observable in a decrease in LDL oxidation, cholesterol, LDL-cholesterol, triglycerides and apo B [19].

The very low risk of a cardiac event or sudden death after a vigorous physical effort has been described in a range of previous studies [4–6,9,10] but not for strenuous eccentric isokinetic exercises. The present study therefore aimed to examine the most recent cardiac markers in highly sensitivity cardiac troponin T (hsTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP). In addition, levels of cardiac troponin I (TnI II) and myoglobin (MYO) were measured. Finally, we measured level of highly sensitive C-reactive protein (hsCRP) and of biomarkers for oxidative stress, such as myeloperoxydase (MPO), lipidic peroxide (POXL), oxidised low density lipoprotein (OLDL), reduced glutathione (GSH), oxidised glutathione (GOX) and peroxidase glutathione (GPX).

2. Material and methods

The protocol was approved by the Ethic Committee of the University Hospital of Liège.

Twelve healthy male non-smoker, sedentary (less than 2 hours of sport per week) volunteers (22.5 $\pm$ 2.15 yo) were enrolled in the study. They gave their informed consent. The subjects were checked to ensure they were in good health. A history of systemic disease or injury to the leg to be tested, which might interfere with the exercise were considered as exclusion criteria. Subjects were required to fasted for at least 8 hours prior to the experiment (in order to avoid errors in the measurement of biomarkers for oxidative stress) and they were prohibited from undertaking additional physical activity for the duration of the study.

An eccentric contraction was performed using an isokinetic dynamometer (Cybex Norm, Henley Healthcare, Sugar Land, TX, USA) [21]. During the experiment, the subjects were placed in a supine position in order to induce a maximal lengthening of the rectus femoris. A standardised warm-up protocol consisting of 10-min of cycling on a bicycle ergometer (50 watts) followed by familiarization with quadriceps muscle contractions on the isokinetic device was applied before the maximal eccentric exercise. At the end of this familiarisation procedure, the subjects performed the eccentric contraction, which consisted of three sets of 30 maximal eccentric contractions of the quadriceps muscle group at 60°/s angular velocity throughout the same range of motion as used for the familiarization [21]. Each set was separated by 30 s of rest [21]. The choice of leg for this unilateral maximal eccentric exercise was randomly assigned. During each contraction, the subjects were verbally encouraged to produce their maximal performance. The effort developed by the muscle group was computed by the dynamometer after each set of 30 repetitions and summed to obtain cumulative performance [21].

Four blood samples were taken: just before (T1), just after (T2), 3 hours after (T3) and 24 hours after (T4) the maximal eccentric isokinetic exercise. In all cases, blood samples were drawn from an antecubital vein into a heparinized or EDTA tube according to the analysis to be performed. Both tubes were immediately centrifuged for 10 minutes (3500 RPM). Where it was not possible to carry out the analyses on the same day, plasma was frozen at −80°C within 20 minutes after blood collection.

Three analyzers were used to perform serial determinations: Modular E170 (Roche Diagnostics) for CK, hsTnT, NT-proBNP, MYO, hsCRP; Hitachi 917 (Roche Diagnostics) for POXL, OLDL, GSH, GOX; Architect i1000SR (Abbott Diagnostics) for TnI II.

A T-test was calculated for all analyses. The p-value was significant below 0.05. The software used was Statistica version 9.1.

3. Results

Table 1 shows the evolution of the different investigated parameters (mean ± SD) before (T1), just after (T2), three hours after (T3) and 24 hours after the isokinetic test (T4).

Just after the maximal eccentric isokinetic exercise (total effort of each set: 22134.52 ± 3292 J), no significant increase in NT-proBNP was observed, but a decrease was noticed later on (between T1 and T3, and T1 and T4). However, these modifications were not significant for our purposes, as they did not exceed the references values.

A significant increase in CK was observed between T1 and T4 ($p = 0.001$).

No differences were noticed for TnI II, hsTnT, hsCRP, OLDL or GSH between the 4 different times.

Among the antioxidants, no significant changes were observed in the level of reduced glutathione during the entire study protocol. In contrast, the concentration of MYO significantly increased between T1 and T2 ($p = 0.0011$), T1 and T3 ($p < 0.001$), T2 and T4 ($p = 0.014$), and MPO significantly increased between T1 and T2 (0.023).

A significant level of oxidative stress was noticed with similar significant differences between T1 and T2 and T2 and T3 for POXL ($p = 0.002$), T2 and T4 ($p = 0.018$) for GOX, T2-T3 ($p = 0.014$) and T2–T4 (0.0023) for GPX.

For the GSH/GOX ratio, significant differences between T1 and T2 ($p = 0.007$), T1 and T3 ($p = 0.011$), T1 and T4 ($p = 0.0002$), T2 and T4 ($p = 0.023$) were observed.

4. Discussion

To our knowledge, the cardiac impact of the maximal isokinetic eccentric exercise has never previously been studied. However, this exercise could be used in the diagnosis of muscular weakness or dysfunction especially in sportspeople [21–23]. Thus it would very interesting to prove that these very strenuous exercises are not harmful to the heart. This study enabled us to evaluate the cardiac impact and the level of oxidative stress induced by a maximal isokinetic eccentric exercise. Interestingly, another study has demonstrated that, during a state of rest following a lengthy and intense strain, some biological parameters (electrolytes, cardiac markers) may become modified [24].

New independent markers of cardiovascular risk, related to troponins, have recently been developed [24]. These emergent markers are likely to bring additional prognostic and diagnostic values in the estimation of cardiovascular risk. Interpretations of levels of TnI II and hsTnT are very cardiospecific [8,13,24] and these troponins are regarded as markers approaching the ideal cardiac biomarker. As such, these markers, very pertinent to evaluating the impact of exercise on car-

Table 1
Results of the studied biologic markers before (T1), just after (T2), 3 hours after (T3) and 24 hours after the isokinetic test (T4). * = $p < 0.05$; ** = $p < 0.01$

Biological markers	T1	T2	T3	T4
CK (UI/l)	213.25 ± 156.59	278.75 ± 186.96	366.64 ± 181.67	546.30 ± 380.37** (T1<T4)
TnI II (ng/ml)	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00
hsTnT (ng/ml)	0.003 ± 0.001	0.003 ± 0.001	0.004 ± 0.002	0.006 ± 0.008
hsCRP (mg/l)	7.01 ± 14.59	6.96 ± 16.81	6.72 ± 16.12	7.19 ± 15.23
NT-proBNP (pg/ml)	35.75 ± 26.19	34.18 ± 23.26 (T1<T2)	28.45 ± 17.39	28.09 ± 22.67
MYO (μg/l)	42.69 ± 30.51	89.91 ± 50.72* (T1<T2)	645,73 ± 1037.60** (T1<T2; T1<T3)	254.09 ± 332.74* (T2<T4)
MPO (ng/ml)	25.67 ± 31.48	30.80 ± 41.46* (T1<T2)	25.56 ± 31.73	32.38 ± 40.36
OLDL (ng/ml)	453.10 ± 470.29	354.25 ± 301.56	257.50 ± 246.04	306.75 ± 295.16
POXL (μmol/l)	236.80 ± 231.68	306.88 ± 244.61** (T1<T2)	261.25 ± 248.46** (T1<T2)	264.25 ± 201.46
GPX (UI/g)	45.92 ± 7.74	49.00 ± 8.87	47.55 ± 9.87* (T2<T3)	161.09 ± 384.12** (T2<T4)
GSH (μmol/l)	886.23 ± 165.08	862.73 ± 208.76	828.27 ± 190.90	787.00 ± 227.61
GOX (μmol/l)	8.88 ± 16.18	2.82 ± 3.67	18.13 ± 18.76* (T2<T3)	32.04 ± 19.49* (T1<T4;T2<T4)
GSH/GOX (μmol/l)	434.33 ± 388.10	559.22 ± 313.88** (T1<T2)	333.44 ± 364.23*	28.22 ± 15.12**

diomyocytes. Our results are very reassuring because they demonstrated that the maximal eccentric exercise performed on isokinetic dynamometer is not harmful to the heart.

Although the exact mechanism of cTnT release has not yet been made clear, the elevation of this isoform is either due to necrosis of cardiomyocytes (aused by irreversible injury), or to a transitory and reversible modification of their membrane permeability [24]. Some authors have suggested that after long distance running, the increase of cTnT could be attributed to cytosolic release of the biomarker, not to the true breakdown of the myocyte [24,25]. In an eccentric exercise model not using isokinetic dynamometer, a modest increase in hsTnT (13%) was recorded immediately after exercise [26,27]. This slightly increase could have been the result of a skeletal muscular injury [26,27]. In a review of studies on cardiac troponins, the free myocyte cytosolic pool of cTnT was estimated to 6–8% [28].

It is assumed that the rise in tension at the level of the myocardial walls, associated with intense exercise, is responsible for the increased liberation of BNP and NT-proBNP. BNP and the inactive cleaved NT-proBNP fragment are synthesised by cardiomyocytes. High blood concentrations reflect a high myocardial parietal tension due to the stretching of myocytes. This stretching is caused by an increase in pressure or volume and neurohormonal activation in the case of heart dysfunction, heart failure, cardiac myopathies, acute coronary syndromes and other cardiac disorders. Elevation of these rates has been associated with the length of exercise taken and the age of the athlete [29]. Shorter but more intense exercise has also been shown to result in an increase in those markers among healthy sportsmen and untrained individuals. However, this increase is shorter in duration and does not exceed the upper reference limit among healthy athletes [29]. As a marker of heart dysfunction, physical exercise can induce modifications in the serum and plasma levels of BNP and NT proBNP among healthy athletes. In addition, rates higher than the upper limit have been documented after intense and prolonged exercise [29]. An elevation of BNP expression has been demonstrated in vitro when cardiomyocytes are stretched [29]. In addition, catecholamines seem to induce the myocardial expression of BNP [29].

Even though, in the present study, MYO was found to increase significantly among our population after maximal isokinetic eccentric exercise, these results need to be put into perspective. It must be remembered that this necrosis marker is not cardiospecific but is also present in skeletal muscles [15]. Furthermore, such an intense exercise will provoke a muscular effort capable of inducing a massive release of this marker [30–32]. MPO is an inflammation biomarker as well as a marker of the activation of neutrophils during an intense physical effort [29]. Moreover, it is also involved in LDL oxidation, infiltration of macrophages and neutrophils, unstable atherosclerotic plaque formation and plaque rupture [29].

Unsurprisingly, an increase in CK was observed. This increase has been widely observed in cases of eccentric exercises that result in muscular damage [33, 34]. Indeed, it is possible that this increase in CK, accompanied by an increase in myosin heavy chains is associated with an increase in T2 signal intensity in the loaded muscles, closely related to damage to structurally bound contractile filaments of some muscle fibers (both fast and slow-twitch fibers) [34]. In the same way, an older study, demonstrated that CK and skeletal muscle isoforms of tronopin I were more sen-

sitive than 1.5 Tesla MRI in detecting limited muscle fiber injury after eccentric exercise [35].

Inflammation that occurs during physical exercise may explain the increase in MPO during our isokinetic exercise [33]. However, we found no signs of systemic inflammation, demonstrated by the fact that hsCRP levels remained stable during the 4 check point times. MPO is an oxidative stress biomarker. This may be the reason why levels of this protein were found to increase greatly in this exercise, i.e. because the level of oxidative stress was significant and was found to be associated with the intensity of the effort. Indeed, this observation suggests a physiological counter regulatory process rather than a simple increase in myocardial damage related to the intensity of the exercise. The significant increase found in the other oxidative stress markers (POXL, GOX, GPX) and the ratio between GSH and GOX confirmed the presence of oxidative stress. These increases, particularly in the levels of lipid peroxides, provide proof of oxidative damage. However, we were not able to demonstrate whether this stress was located only in the heart.

5. Conclusion

The results of this study demonstrate that there was no release of cardiac biomarkers, and thus no sign of cardiac necrosis, following a maximal isokinetic eccentric exercise. Thus we can conclude that the maximal eccentric isokinetic exercise used had no cardiac impact on the participants. This would indicate that this exercise may be performed without any risk to the patient's heart. This is very reassuring for practitioners who perform these techniques in all patients without knowing their cardiac function status. However, it is important to be aware that this type of strenuous exercises does initiate a significant level of oxidative stress.

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