Journal of Theoretical Biology 392 (2016) 48–52

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Serum cardiac troponin I analysis to determine the excessiveness of exercise intensity: A novel equation

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HIGHLIGHTS

- Exercising at a vigorous intensity may stress the myocardium.
- The turning point – 'too much of a good thing' – is hard to quantify subjectively.
- Post-exercise cardiac troponin I levels strongly correlate with exercise intensity.
- We present the first method to determine relative exercise intensity in retrospect.
- This equation relies primarily on serum cardiac troponin I assessments.

ARTICLE INFO

Article history:
Received 22 July 2015
Received in revised form
4 December 2015
Accepted 16 December 2015
Available online 25 December 2015

Keywords:
Physical exercise
Cardiac troponin I
Exercise intensity
Equation

ABSTRACT

Physical exertion is often promoted because of its beneficial health effects. This only holds true, however, as long as the optimal exercise intensity is not exceeded. If physical exertion becomes too strenuous or prolonged, cardiac injury or dysfunction may occur. Consequently, a significant elevation of the serum concentration of the sensitive and specific cardiac biomarker troponin I can be observed. In this article, we present the derivation of a novel equation that can be used to evaluate to what extent the intensity of conducted endurance exercise was excessive, based on a post-exercise assessment of serum cardiac troponin I. This is convenient, as exercise intensity is difficult for an athlete to quantify accurately and the currently used heart rate indices can be affected by various physiological and environmental factors. Serum cardiac troponin I, on the other hand, is a *post-hoc* parameter that directly reflects the actual effects on the myocardium and may therefore be a promising alternative. To our knowledge, this is the first method to determine relative exercise intensity in retrospect. We therefore believe that this equation can serve as a potentially valuable tool to objectively evaluate the benefits or harmful effects of physical exertion.

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1. Introduction

Physical activity is frequently conducted because of the expected improvement in fitness. Indeed, the beneficial effects of regular, moderate-intensity exercise on cardiovascular risk factors and mortality have long been recognized (Fletcher et al., 1996; Mittleman et al., 1993). Emerging evidence, however, indicates cardiac injury and a considerable (transient) impairment of left and right ventricular diastolic and systolic function after prolonged and strenuous physical exertion (La Gerche, 2013; Shave and Oxborough, 2012). This is accompanied by a significant elevation of the serum concentration of cardiac troponin I (cTnI), a highly sensitive and specific cardiac biomarker, in many cases even above the clinical cut-off value for myocardial infarction (Eijsvogels et al., 2012; Eijsvogels et al., 2014a; Shave et al., 2007; Shave et al., 2010). Accordingly, there seems to be an optimal exercise intensity; when exceeded, this may be associated with negative health sequelae. This contradiction of advantageous effects of (sub)optimal exercise intensity on the one hand and potentially harmful effects of extreme exertion on the other is also known as the 'paradox of exercise' and poses a public health concern (Maron, 2000).

In the light of our growing understanding of the impact of exercise intensity on cardiac (dys)function, it would be helpful to relate the intensity of conducted exercise to an optimal target intensity. In this way, it will be possible to minimize the harmful effects of future sports practice and thus to achieve maximal health benefits. As it is very difficult, if not impossible, to quantify the excessiveness of

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[1] Both authors contributed equally to this work (conducted the literature search, drafted the manuscript, and approved the final version of the article).

http://dx.doi.org/10.1016/j.jtbi.2015.12.009
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exercise intensity based on information provided by athletes, a logical next step is to find a way to determine this parameter objectively. A frequently used index in current physiological practice is the percentage of the maximum heart rate ($\%HR_{max}$) (Garber et al., 2011). The maximum heart rate in healthy people that do not use chronotropic medication predominantly depends on age and is practically not influenced by exogenous factors (Tanaka et al., 2001). Therefore, it is warrantable to use this parameter in the denominator of the fraction to determine relative exercise intensity. Heart rate during exercise, on the other hand, fluctuates regularly and can be profoundly affected by – amongst other factors – hydration status, ambient temperature, and altitude (Achten and Jeukendrup, 2003). As a result, $\%HR_{max}$ may not always precisely reflect true exercise intensity under field conditions. To obtain an accurate reflection of reality, we believe that the numerator of the fraction – in contrast to the currently used indices – should be a *post-hoc* parameter that is less dependent on exogenous variables.

Exercise-induced release of cTnI from cardiomyocytes has been shown to strongly correlate with exercise intensity (r=.752, $P<.001$) and remains measurable in serum for a few days (Eijsvogels et al., 2012; Eijsvogels et al., 2014a). Based on these observations, we present the derivation of a novel equation that can be used to assess the ratio between the intensity of the conducted endurance exercise (I) and an optimal target intensity (I_{target}) as a function of serum cTnI concentration (C_τ) at time $t=\tau$ after physical exertion. It should be noted that (the derivation of) this equation, though based on the results of previous empirical data, provides a theoretical framework; a novel experimental validation of the equation therefore falls beyond the scope of this paper.

2. Mathematical model

2.1. Derivation

In separate papers, Eijsvogels et al. (2012, 2014a) have demonstrated a logarithmic relationship between exercise intensity (I), which is expressed as a percentage of the maximum heart rate, and the post-exercise release of cTnI (Fig. 1).

Therefore, the relationship between the peak serum concentration of cTnI (C_{max}) and exercise intensity can be described as follows:

$$\ln(C_{max}) = \ln(C_0) + \alpha I \tag{1}$$

In which α represents the slope of the graph, estimated to be 0.057 μg/L/$\%HR_{max}$. The parameters $\ln(C_{max})$ and $\ln(C_0)$ represent the natural logarithms of the peak and baseline serum cTnI concentrations (μg/L), respectively. Rearranging the equation above produces:

$$C_{max} = C_0 e^{\alpha I} \tag{2}$$

cTnI is cleared by the kidneys according to first-order kinetics (Fig. 2) (Dunn et al., 2011; Laugaudin et al., 2015; Solecki et al., 2015). Therefore, its rate of elimination from the body is dependent on its serum concentration and can be described by a straightforward first-order differential equation:

$$-\frac{dC}{dt} = k_e C \tag{3}$$

The elimination constant k_e for cTnI in serum, which is expressed in hour^{-1}, can be calculated from the half-life by $k_e = \frac{\ln(2)}{t_{\frac{1}{2}}}$. By definition, this parameter is not assay-specific (i.e., no different values for different assays) and has previously been established to be 0.087 h^{-1} in a healthy population of marathon runners (the post-exercise half-life of cTnI being approximately 8 h) (Traiperm et al., 2012). At time $t=\tau$ (h), the serum concentration of cTnI (C_τ) can be described by the following equation:

$$C_\tau = C_{max} e^{-k_e \tau} \tag{4}$$

Rearranging this equation results in:

$$C_{max} = \frac{C_\tau}{e^{-k_e \tau}} = C_\tau e^{k_e \tau} \tag{5}$$

The derived expressions for C_{max} (Eqs. (2) and (5)) can be equated, which produces:

$$C_\tau e^{k_e \tau} = C_0 e^{\alpha I} \tag{6}$$

The term I can be isolated from the equation above as follows:

$$I = \frac{1}{\alpha}\left[\ln\left(\frac{C_\tau}{C_0}\right) + k_e \tau\right] \tag{7}$$

As described before, the exercise intensity is expressed as a percentage of the maximum heart rate, with an optimal value ranging from 55/65% to 90% of HR_{max} (Anonymous, 1998). Furthermore, the following relationship, described by Tanaka et al. (2001), exists between the maximum heart rate of a person and his or her age in years (A):

$$HR_{max} = 208 - 0.7A \tag{8}$$

Provided that the upper limit for an optimal exercise intensity (I_{target}) is maintained at a fraction β, this means:

$$I_{target} \approx HR_{target} = \beta(208 - 0.7A) \tag{9}$$

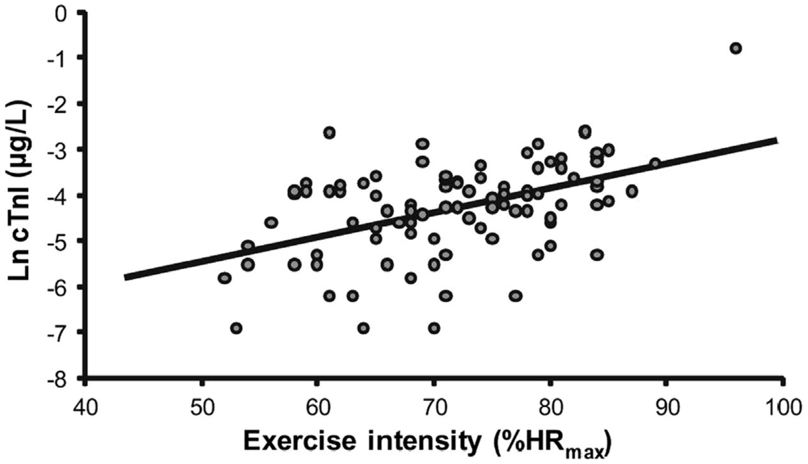

Fig. 1. Logarithmic relationship between the serum concentration of cardiac troponin I (cTnI) and exercise intensity, expressed in terms of percentage of maximum heart rate ($\%HR_{max}$). Figure originally published by SpringerOpen (Eijsvogels et al., 2012).

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