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Editorial

Exercise-induced cardiac troponin in the era of high sensitivity assays: What makes our heart sweat?

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Circulating cardiac troponins (cTn) are the most commonly used biomarkers in cardiovascular medicine. cTn concentrations are used to diagnose myocardial infarction and to risk-stratify and guide treatment strategies in patients with acute coronary syndrome [1]. The evolution of high sensitivity cardiac troponin (hs-cTn) assays have enabled the detection and measurement of circulating cTn also in asymptomatic adults free of overt cardiovascular disease (CVD) [2,3].

cTn levels rise in response to exercise even in patients without coronary heart disease [4]. While this phenomenon was first reported in 1987 [5], it is not yet fully understood. Despite past disputes, most current researchers view the increase in cTn following exercise as a physiological response [4]. Both cTn T and I peak between 2 and 6 h post-exercise and normalize within 24–48 h [4] (Fig. 1). This rise in cTn levels occurs in both moderate and high-intensity exercise, such as marathons and bike cycling races.

A few underlying mechanisms have been proposed (Fig. 1). cTn may be released due to reversible myocyte injury; increased membrane permeability, with leakage of loosely bound cTn from the cytosol; increased wall tension and ventricular strain; stretch-induced apoptosis; and/or transient ischemia due to increased myocardial energy demands. And while more than one of these mechanisms are likely to be present, this exercise-induced cTn release is probably not caused by myocardial cell death/necrosis [4].

cTn release following exercise has been repeatedly evaluated in relatively small study samples and in different settings of physical activity. And yet, a few key questions remain unanswered: 1) *What predicts exercise-induced concentrations of cTn*? 2) What *is a "normal" increase in hs-cTn after exercise*? and 3) *What are the clinical implications*? Above all, we need to examine whether we can use this physiological increase in cTn to detect and/or predict pathological processes in the heart.

In this week's issue of the *International Journal of Cardiology*, Kleiven et al. [6] present the largest study ever conducted to determine the predictors of exercise-induced increase of cTn. A total of 1002 recreational cyclists without known CVD or use of medication, participating in a 91-km mountain bike race, were tested for hs-cTn at three different time points; 24 h prior to, and 3 and 24 h after the race. Higher systolic blood pressure at baseline and shorter race duration were identified as independent predictors of both hs-cTn I and T following exercise. The investigators are to be commended for this large-scale logistic effort that allowed a comprehensive assessment of all study participants at three different time points. The large study sample, along with the use of both hs-cTn I and T provide important evidence to the existing knowledge on the kinetics and predictors of the exercise-induced cTn response.

A few points should be highlighted. First, roughly 84% of the participants had hs-cTn concentrations that exceeded the 99th percentile of the assay 3 h after race completion. At 24 h after the race, hs-cTn declined in practically all subjects and yet ~18% still had levels that exceeded the 99th percentile of the assay. Second, the multiple regression models explained only 15–36% of the variance in cTn concentrations following exercise. It seems that additional, as yet undefined factors are involved in the exercise-induced cTn response.

So how can we predict cTn elevation following exercise? *Is it a matter of the individual athlete or rather the exercise being performed*? (Fig. 1).

In terms of baseline parameters, Kleiven et al. [6] report systolic blood pressure at rest as the main predictor of cTn elevation following exercise. Previously reported predictors such as body mass index, age, and sex [4] were of less significance in their analysis. It should be noted that this study population consisted primarily of middle-aged recreational athletes (median age 47 years) [6]. Baseline hs-cTn levels

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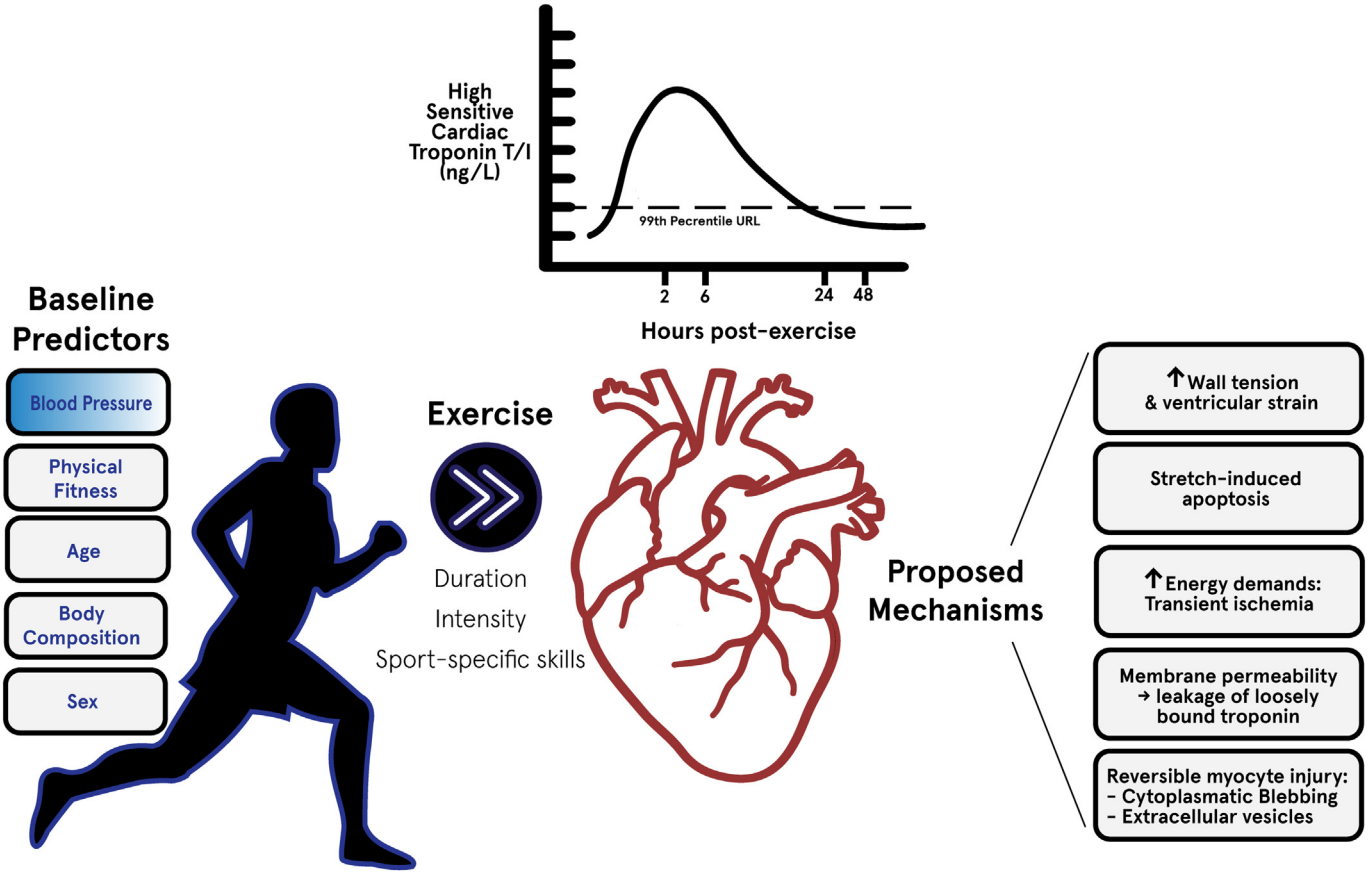

Fig. 1. Circulating cardiac troponin elevation following exercise. High-sensitive cardiac troponin (hs-cTn) T/I concentrations peak between 2-6 h following exercise and normalize within 24–48 h. Peak levels far-exceed the 99th percentile upper reference limit of the standard rest hs-cTn assay. Suggested predictors for exercise-induced hs-cTn elevation relate to both baseline characteristics of the athlete performing the exercise (left side), along with various aspects of the exercise being performed. Numerous underlying mechanisms have been proposed (right side). URL- upper reference limit.

increase with age and therefore their findings may not apply to older individuals. The authors present an impressive sex-specific analysis for all reported thresholds and conclude that their findings are consistent for both men and women. The male majority (78%) in the current study, as in previously published reports, emphasizes the need to include equal numbers of men and women in future studies. Baseline hs-cTn levels are generally lower in women [7] and the use of sex-specific thresholds are crucial in order to translate findings into clinical practice.

In terms of the exercise being performed, Kleiven et al. conclude that race duration was inversely correlated with hs-cTn levels following exercise. Exercise duration is a variable with a complex interpretation and multiple contributing factors, such as physical fitness, sport specific technical skills, exercise intensity and the duration of high-intensity work (Fig. 1). Previous reports have highlighted exercise intensity as a significant predictor of exercise-induced cTn levels [4,8]. If we wish to use hs-cTn following exercise in clinical settings, then future large-scale studies would need to include physical fitness and exercise-intensity assessment in their study protocols. Accordingly, the measurement of metabolic equivalents (METS) or max VO_2 values should be considered [9].

Looking ahead, hs-cTn assays will continue to improve sensitivity levels. Practically all individuals will probably present some degree of circulating cTn. hs-cTn levels at rest have already been shown to predict future cardiovascular events in the general population [2]. These rest levels have also been associated with cardiac structural changes in pre-symptomatic adults [10]. In the context of exercise-induced hs-cTn, we therefore need to start tackling the above-mentioned questions: 1) *What is a "normal" increase in hs-cTn after exercise*? and 2) *What are the clinical implications of an abnormal exercise-induced cTn response*?

Kleiven et al. are expected to prospectively follow-up study participants for 20 years, with the first follow-up being made 5 years post-race. Their results are highly anticipated.

As stated, the type of exercise, its duration and intensity all influence cTn levels after exercise, and therefore will have to be taken into consideration when interpreting the definition of "normal" values. Future studies with standardized exercise protocols and substantial follow-up periods are needed in order to start tackling this ambitious goal.

The increase in hs-cTn following exercise seems to be a physiological response. Whether we can use this response in order to better stratify risk for future CVD is yet to be determined.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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