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REVIEW

High-sensitivity troponin after running – a systematic review

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ABSTRACT

A systematic review was carried out to study the pattern of high-sensitivity cardiac troponin release after running (search performed on PubMed, ISI Web of Knowledge and Scopus databases). A total of ten reports were identified as meeting the pre-specified criteria (eight using high-sensitivity troponin T and two using high-sensitivity troponin I). The papers were published between 2009 and 2013, amounting to a total of 479 participants under study. Eight reports provided data comparing post-running troponin levels with the 99th percentile reference value. A total number of 296 participants, out of 424, showed post-running high-sensitivity troponin values higher than the 99th percentile reference value (69.8%). In conclusion, using high-sensitivity cardiac troponin assays, studies have shown that elevated post-running values are seen in more than two-thirds of runners. Whether troponin release in this setting represents a fully reversible phenomenon is currently unknown; the effects of strenuous running on long-term health are also uncertain.

KEYWORDS

Running, high-sensitivity troponin

INTRODUCTION

Cardiac troponin has been shown to act as a most useful biomarker in the context of acute myocardial infarction, and is usually believed to act as a marker of necrosis in this setting.[1-3]

However, research carried out in other settings has shown that increased plasma levels of cardiac troponin are a relatively frequent finding, including in patients with chest pain of other causes, sepsis, pulmonary embolism, aortic valve disease, and heart failure.[3]

Running is a normal physiological phenomenon in humans. Studies carried out since 1987 have shown that prolonged and/or strenuous running is associated to increased plasma levels of cardiac troponin.[4]

Previous systematic reviews have been published on this topic.[5,6] However, technical improvements in laboratory techniques have led to the current availability of high-sensitivity assays – usually believed to be more reliable in the evaluation of plasma cardiac troponins, namely in what concerns values closer to the detection limit of the assay.[7]

The aim of this systematic review was to present the current state of the art concerning cardiac troponin level changes associated with running, including long distance or strenuous running, as supported by studies carried out using the high-sensitivity assays. It is, to our knowledge, the first systematic review to consider exclusively high-sensitivity troponin assays in the evaluation of this interesting and common phenomenon.

METHODS

Search strategy

The study started with a search on three databases, Medline (PubMed), ISI Web of Knowledge and Scopus, using the query "troponin" + "running". In PubMed, the additional keyword "marathon" was also used ("troponin AND ((running) OR (marathon))").

The search took place between April and May 2013, and no articles were excluded based on publication date. The aim of our search was to identify studies evaluating the levels of cardiac troponins (either T or I) using high-sensitivity assays, as defined by the authors, in association with a period of running (regardless of intensity, duration of exercise or length, or of previous physical exercise practice).

The query resulted in 157 articles on the PubMed database, 259 on ISI Web of Knowledge and 181 on Scopus. No additional studies were found after searching the references of previous review articles.

Inclusion criteria

Only prospective observational human studies were included. It was mandatory for the studies to evaluate the levels of cardiac troponins before and after the race, and only studies using high-sensitivity troponin assays (as defined by the authors in the title and/or abstract) met the inclusion criteria.

Exclusion criteria

Articles in which the subjects were selected because they had a specific pathology, case reports and articles that did not use high-sensitivity troponin assays were excluded. Articles written in languages other than English, as well as mechanistic and animal studies, were also excluded. Studies containing less than ten subjects were excluded too. Studies evaluating exercise but not specifically running, such as cycling or triathlon, were excluded because, although of importance, they were outside the scope of the present report.

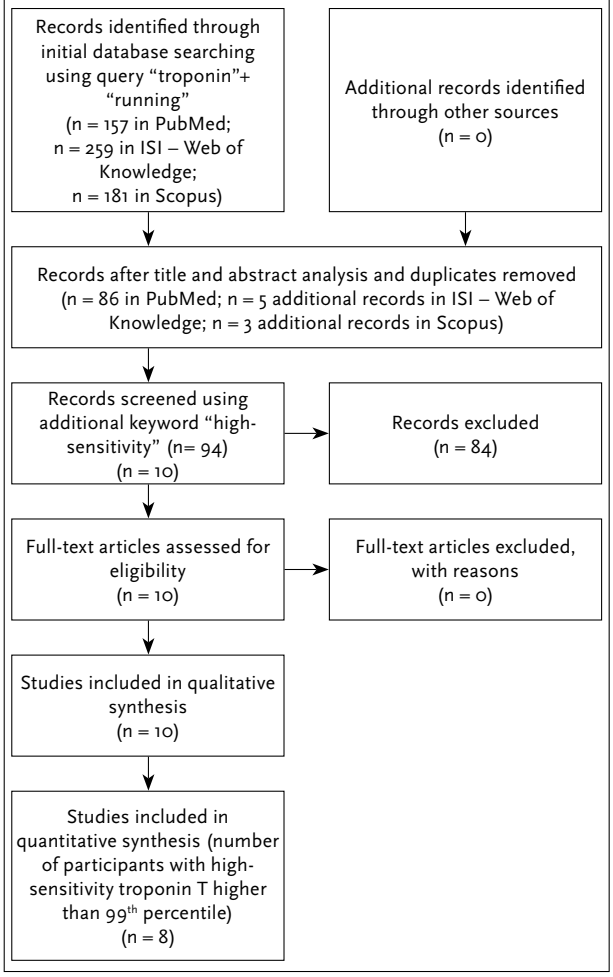
Summary measure

The primary summary measure in the quantitative analysis was the determination of the number of participants with high-sensitivity troponin values greater than the 99th percentile after the race. The number of participants in some studies were calculated from the published value corresponding to the percentage.

Quality assessment of studies and data extraction

Study quality and eligibility were individually assessed by four investigators. Different opinions regarding the relevance of articles were solved by consensus between the authors.

Figure 1. *Flowchart showing the literature search method (n = number)*



RESULTS

From title and abstract analysis, ten articles were included that met the pre-specified criteria, and this set of articles was analysed by the authors.[8-17] A flowchart showing the literature search method, as well as the resulting number of articles selected, is displayed in *figure 1*. The total of ten articles that were selected for qualitative review were published between 2009 and 2013, amounting to a total of 479 subjects in which high-sensitivity cardiac troponin was assessed.

Table 1 presents the main characteristics of the subjects involved in each study. For the quantitative synthesis regarding the percentage of participants with high-sensitivity troponin greater than the 99th percentile (*table 2*), a total of eight trials were assessed, amounting to 424 runners (381 males), of which 296 had high-sensitivity troponin levels greater than the 99th percentile (69.8% of the total). In this synthesis, 392 runners had high-sensitivity troponin T assessed, and 273 of those patients (69.6% of the total) had troponin levels greater than the 99th percentile, when evaluated after the race (immediately or within six hours after the race). Thirty-two runners had high-sensitivity troponin I assessed, and 23 of those (71.9% of the total) had levels greater than the 99th percentile, when evaluated after the race (within six hours of completion).

Table 3 presents an overview of the main conclusions in the studies included in the qualitative review.

DISCUSSION

In the present report, a systematic review was undertaken to look at changes in plasma troponin levels after running – an important physiological activity of the human body. Only reports dealing with high-sensitivity troponin were chosen, since these new assays are usually believed to be more reliable in the evaluation of plasma cardiac troponins,

Table 1. *Overview of trials meeting the pre-specified criteria*

Study (year)	N	Male/ female ratio	Mean age (years)	Type of race (length in km)	Biomarkers assessed	Timing of sample collection
Mingels *et al.* (2009)[8]	85	70/15	47	Marathon (42.2 km)	TnI TnT HSTnT CK Albumin	0-2 hours before the race <1 h after the race
Giannitsis *et al.* (2009)[9]	10	10/0	52	Ultramarathon (216 km)	HSTnT NT-proBNP	Baseline After first half marathon, full, double and quadruple marathon Shortly after the finish
Mingels *et al.* (2010)[10]	43; 38; 10; 85	24/19; 31/7; 8/2; 70/15	45; 47; 43; 47	5, 15, 21, 42 km	HSTnT NT-proBNP Albumin	0-2 hours before the race <1 h after the race
Saravia *et al.* (2010)[11]	78	78/0	56 (median)	Marathon (presumably, 42.2 km)	TnT HSTnT Leukocytes CRP IL-6 NT-proBNP	Before the race <20 minutes after finishing the race Nearly two weeks after the race
Scherr *et al.* (2011)[12]	102	102/0	42	Marathon (42.195 km)	HSTnT NT-proBNP h-FABP TNF-α IL-6 IL-10 Hs-CRP Cystatin C Hg Haematocrit Albumin	During the week before the race Within 1 h after the race 24 hours after the race 72 hours after the race
Lippi *et al.* (2012)[13]	15	15/0	41	Ultramarathon (60 km)	TnI HSTnI	Before the race (20 minutes before warm-up) Within 10 minutes after the race
Tian *et al.* (2012)[14]	13+13	26/0	14.1; 24	Constant load treadmill run for 90 minutes	HSTnT NT-proBNP Hg Haematocrit	Pre-exercise Immediately post-exercise 1, 2, 3, 4, 5, 6, and 24 hours post-exercise
Lippi *et al.* (2012)[15]	17	17/0	47	Half marathon (21 km)	TnI HSTnI	Before the race (30 minutes before warm-up) Immediately after the race, and at 3, 6 and 24 hours after the race
Wilhelm *et al.* (2012)[16]	10	10/0	34.9	Mountain marathon	HSTnT Pro-ANP HS-CRP IL-6 TNF-α Leukocytes Hg Haematocrit Plasmatic sodium	Baseline Within 15 minutes after the race 1 and 8 days after the race
Baker *et al.* (2013)[17]	45	-	-	Marathon (41.84 km)	TnI TnT HSTnT BNP	Before the race Within 15 minutes after the race

n = number of runners; BNP = brain natriuretic peptide; CK = creatine kinase; h-FABP = heart-type fatty acid binding protein; Hg = haemoglobin; HS-CRP = high-sensitivity C reactive protein; IL-6 = interleukin 6; NT-proBNP = N-terminal pro-hormone of brain natriuretic peptide; pro-ANP = pro-atrial natriuretic type; TNF-α = tumour necrosis factor α; TnI = cardiac troponin I; TnT = cardiac troponin T; HSTnI = high-sensitivity troponin I; HSTnT = high-sensitivity troponin T.

namely in what concerns values closer to the detection limit of the assay.[7]

The main finding was that a considerable percentage of the study participants were shown to have increases in plasma troponin values, not only when compared with baseline values, but also when compared with the 99th percentile value for the biomarker under study.

According to one point of view,[18] elevated cardiac troponin plasma values would always correspond to cardiomyocyte necrosis – a theory that, in the case of strenuous running, and in the light of the present report, would correspond to a majority of runners having undergone cardiac cellular necrosis – although, presumably, of low grade. This theory, however, and in the case of running, is currently not

Table 2. *Number of participants with high-sensitivity cardiac troponin values, measured up to six hours after the race, higher than the 99th percentile, presented as a fraction of the total number of participants (number of participants in some studies were calculated from the published value corresponding to the percentage)*

Mingels *et al.* (2009)[8]	73/85
Giannitsis *et al.* (2009)[9]	4/10
Mingels *et al.* (2010)[10]	0/ 43 (5 km) 5/ 38 (15 km) 4/10 (21 km)
Saravia *et al.* (2010)[11]	73/78
Scherr *et al.* (2011)[12]	91/102
Lippi *et al.* (2012)[13]	12/15
Tian *et al.* (2012)[14]	12/13 (adolescents) 11/13 (adults)
Lippi *et al.* (2012)[15]	11/17
Total	296/424 (69.8%)

Table 3. *Major findings concerning high-sensitivity cardiac troponin, in ten articles selected in the course of the systematic review*

Study (year)	Major findings concerning high-sensitivity troponin
Mingels *et al.* (2009)[8]	Reference values of high-sensitivity troponin T higher for males 100% of runners with increase in troponin I and high-sensitivity troponin T after the race
Giannitsis *et al.* (2009)[9]	10 cases with a rise of high-sensitivity troponin T 1 case with early rise of high-sensitivity troponin T, followed by decrease to baseline value Heterogenous behaviour of troponin concentration in different runners
Mingels *et al.* (2010)[10]	Troponin concentrations significantly higher with increasing running distance except in the 5 km race group
Saravia et al. (2010)[11]	High-sensitivity troponin T increased significantly after the race 2 weeks after the race troponin levels were comparable with baseline levels Larger number of participants with increased troponin levels with high-sensitivity assay, when compared with older types of assays
Scherr *et al.* (2011)[12]	Increase above threshold was observable in 89% of participants immediately after the race, in 27%, 24 h after the race, and in 4%, 72 h after the race
Lippi *et al.* (2012)[13]	80% of participants with high-sensitivity troponin I >99th percentile, after the race
Tian *et al.* (2012)[14]	Post-exercise high-sensitivity troponin T elevation occurred in all runners, peaked 3-4 hours post-exercise, and the peak concentration was higher in adolescents than adults During the recovery phase, high-sensitivity troponin T significantly higher in adolescents than in adults
Lippi *et al.* (2012)[15]	High-sensitivity troponin I significantly increased from the mean baseline value of 2.9-4.8 ng/l after the run, 9.0 ng/l at 3 hours, 12.3 ng/l at 6 hours, and 4.5 ng/l at 24 hours 65% of participants with high-sensitivity troponin I >99th percentile 6 hours after the race
Wilhelm *et al.* (2012)[16]	High-sensitivity troponin T increased significantly after the race and returned to baseline during follow-up
Baker *et* al. (2013)[17]	Mean high-sensitivity troponin T increased after the race from 3-47 ng/l 100% runners with detectable levels of high-sensitivity troponin T

supported by empirical data – since pathological studies indicating the presence of necrosis were not found in the literature.

In studies assessing both troponin release and cardiac magnetic resonance imaging, no detectable myocardial necrosis was observed after marathon running.[19-22] A half marathon was associated to an increase in right ventricular end-diastolic volume, with a reduction in the right ventricular ejection fraction.[23]

Breuckmann *et al.* described late gadolinium enhancement in 12 out of 102 healthy marathon runners, a value which was compared with four cases in a control population, yielding a p value of 0.077.[24] The study did not involve either troponin measurements or pre-marathon cardiac studies,[24] and was of an observational nature, thus unable to establish causality. Cyclists from the Tour de France were shown to have an increased average longevity, when compared with the general population.[25]

The results presented in the present report point in the direction that cardiac troponin release associated with running, including marathon running, occurs in more than two-thirds of the participants studied. Previous systematic reviews looking at data obtained prior to the development of high-sensitivity troponin testing have been published. Shave *et al.* reported troponin T to exceed assay detection limit in 52% of participants in running events.[6] Regwan *et al.* reported an incidence of post-marathon troponin elevation of 51%.[5] Data obtained with high-sensitivity troponin testing, in summary, shows troponin release after running to be a more generalised phenomenon than previously thought.

Cardiomyocyte necrosis could be the mechanism behind troponin release in this setting – as stated above, an unsubstantiated allegation, in as much as no histological proof for this phenomenon has been put forward. Even the data presented by Breuckmann *et al.*, which could have causes other than running, show a strikingly low value of 12% for the presence of late gadolinium enhancement,[24] when compared with a 69.8% mean value of running participants with troponin release, now reported. The time course of troponin release in this setting – with a relatively rapid decrease in plasma cardiac troponin values after peak values are reached – would also argue in favour of a reversible phenomenon. Cardiac strain[26,27] could be an explanation for the phenomenon of troponin release after strenuous running, in good agreement with data obtained under experimental conditions, perhaps implicating integrin stimulation as a mechanism behind troponin release.[28]

Study limitations

Given the heterogeneous nature of the data (physical pre-conditioning of the subjects, intensity, length and duration of the running period) and the possible presence of confounding factors (such as associated pathologies, especially cardiovascular disease and its protean manifestations) it is difficult to regard the data presented above as a set obtained in a homogeneous population. Many of the studies only included male participants, and the pattern of troponin release after running in the female gender should be further clarified in future studies. It is also clear (as shown in *table 1*) that most studies assessed high-sensitivity troponin T, whereas high-sensitivity troponin I was assessed in only two studies.[13,15] As Lippi *et al.* suggest[13] the data obtained with the two biomarkers seem to be comparable, but more data on this matter would be desirable. On the other hand, while the value corresponding to the 99th percentile was the same regarding the high-sensitivity troponin I assay in both trials (i.e. 8.6 ng/l), this was not the case for the high-sensitivity troponin T assays, different values being used in this latter case.

Further studies are needed to better establish the clinical significance, if any, and the long-term prognosis associated with high-sensitivity troponin elevations in this setting.

In conclusion, in the present systematic review, using data obtained with high-sensitivity cardiac troponin assays, elevations of cardiac troponin plasma levels were shown to exist in more than two-thirds of the participants studied, pointing to a more generalised phenomenon than previously thought.

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