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Project thesis

A systematic review of exercise-induced cardiac troponins in healthy individuals

A systematic literature review

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Abstract

Objectives

The aim of this thesis is to review the literature on exercise-induced cardiac troponin elevations in healthy individuals and to elucidate how different factors such as exercise intensity and duration may influence this post-exercise cTn response. In addition, I wanted to consider the possible clinical implications of exercise-induced cTn elevations.

Methods

This thesis is based on a systematic literature search in the Embase database. To extend my search, I searched for human studies using a combination of subject headings (Emtree-words) and text-words (tw). A total of eighteen articles were included in this systematic review.

Results

Articles included in this review found that compared to the rest, both prolonged and shorter duration of strenuous exercise result in significantly increased concentrations of cardiac troponins in healthy individuals. This was observed for both cTnI and cTnT, despite differences in exercise modes, sampling times and Tn-assays. Exercise intensity, exercise duration, age, blood pressure and training experience have been discussed as potential factors influencing the cTn response following exercise in multiple articles. However, main findings show that both exercise intensity and duration are important factors affecting the cTn response, but the association is more accurately predicted when intensity-duration is considered as a combined variable.

Conclusion

This systematic review supports the general notion that prolonged strenuous exercise as well as short duration high intensity exercise results in increased circulating concentrations of cardiac troponins. Both exercise duration and intensity are important factors related to this response. However, greater cTn elevations are seen after exercises at higher intensity-levels and exercise intensity seems be a more dominating factor influencing the cTn response.

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1- Introduction

1.2- Cardiac troponins and assays

According to the Universal Definition of Myocardial infarction, circulating concentrations of cardiac troponins (cTn) above the 99th percentile is an obligate criterion for the clinical diagnosis of acute myocardial infarction (AMI) (1). The mechanisms behind AMI-related cTn increase are pathological and caused by irreversible myocyte death after prolonged cardiac ischemia (2,3). In the absence of AMI, circulating concentration of cTn in blood in healthy individuals are normally low (< 14 ng/L), but concentrations may increase in response to cardiomyocyte damage such as ischemia as well as non-ischemic events, for instance severe infection or after physical activity (4).

Over the last decade, there have been improvements in the sensitivity of cardiac troponin immunoassays. The International Federation of Clinical Chemistry (IFCC) defines current high-sensitivity cardiac troponin (hs-cTn) assays as assays that reliably are able to detect cTn levels below the 99th percentile and above the limit of detection (LoD) in at least 50% of healthy subjects (5,6). Furthermore, hs- cTn assays have a low analytic coefficient of variation (<10%) at the 99th percentile and hs-cTn assays can detect both low and high circulating cTn concentrations (6) Clinically this means that we can detect and measure circulating cTn in a high proportion of asymptomatic individuals free of cardiovascular disease (7–9).

Myocardial injury is defined as elevated cTn levels above the 99th percentile upper reference limit (URL) in a healthy population (10). The injury is considered acute if cTn values show a rise and/or fall between serial samplings (5,11). This this is typically seen in patients with ongoing acute myocardial infarction (AMI) and is often caused by plaque rupture or thrombi-embolisms resulting in obstruction of coronary arteries and necrosis (12). Chronic and stable elevations of cardiac troponins is on the other hand often associated with chronic myocardial injury, and is more commonly observed in patients with stable coronary artery disease, heart failure or renal failure (4,13,14). Despite acute or chronically elevated levels of cardiac troponins, the URL of the 99th percentile have potential to vary within populations (12). Differences in sex, age and ethnicity are factors that may affect the URL for the different cTn assays (10). The URL is for instance higher in men and older patients compared with women

and a younger population (8,12). Therefore sex-specific 99th percentile URLs are recommended for the hs-cTn assays (2).

1.3- Troponin protein- complex

Cardiac troponins are intracellular protein complexes in the contractile apparatus of cardiac and skeletal muscle. Within the cardiac muscle, cTn facilitates the contraction of cardiomyocytes (15). Troponin consists of 3 subunits (I, T and C). Troponin T is responsible for attaching tropomyosin on thin filaments. Subunit C binds calcium, which leads to a conformational change of the cTn complex that allows contraction of cardiomyocytes. Subunit I inhibits actomyosin ATPase (3,16). Troponin I and T from cardiac muscle is immunologically distinct from isoforms in skeletal muscle, permitting their use as a specific clinical biomarkers for myocardial injury (4,15,17).

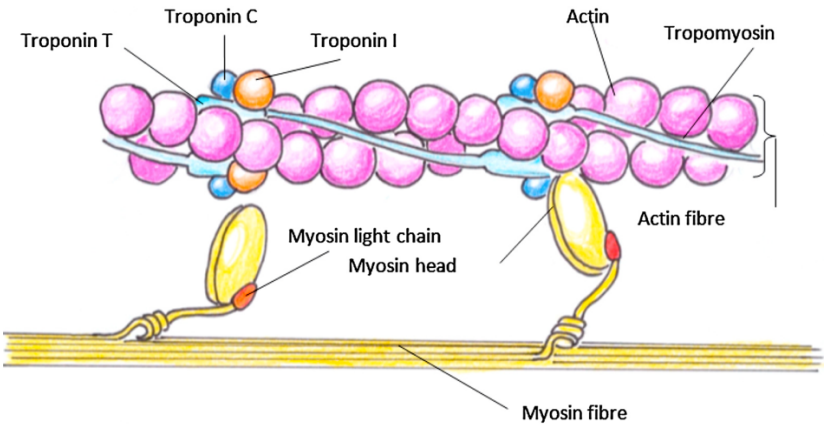


Figure 1 Troponin-tropomyosin protein complex (18)

1.4- Exercise and cardiac troponins

As awareness about the importance of a healthy lifestyle grows, there has been a noticeable surge in interest towards regular exercise and physical activity (19,20). The growing number of people participating in mass endurance events such as marathon runs, reflects that there is an increasing need to understand how such physical activity affect cardiac health (21). In response to this, several studies have examined the association between exercise and cTn response. In previous studies, exercise-induced cTn elevations has been evaluated in small study samples and within different types of physical activity (9).

Frequent moderate physical activity improves our general health on many levels (22,23). When it comes to long-term cardiac benefits of exercise, physical activity improves

cardiovascular function, reduces the risk of cardiovascular death and events, and promotes longevity (3). The World Health Organization (WHO) advises adults to engage in at least 150 to 300 minutes of moderate-intensity exercise weekly, as a preventative measure against cardiovascular disease (24).

Despite the long-term benefits of regular physical activity, prolonged strenuous exercise might lead to elevation in cardiac troponins, even in people without cardiovascular disease. Several studies on this topic have shown that healthy individuals can have cTn concentrations post exercise above the upper reference limit (URL), indicating myocardial injury. This is most frequently seen after prolonged exercise, such as completing a marathon. More surprisingly, this is also observed after short term high-intensity exercise (9). Consequently, this may cause clinical confusion and rise the discussion of whether exercise-induced cTn increase is a physiological or a patho-physiological mechanism.

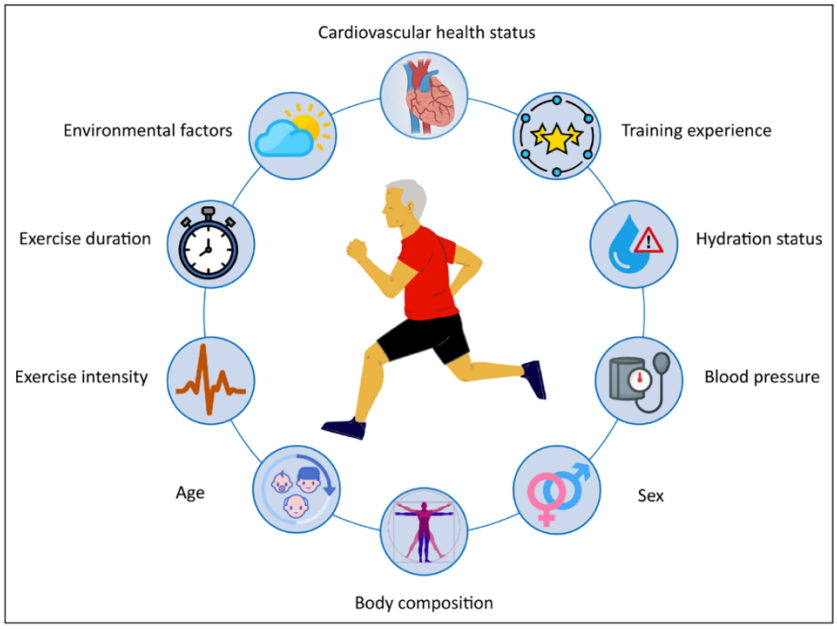


Figure 2 Different factors with potential impact on post-exercise cTn elevations (3).

Several factors may influence exercise-induced cTn levels. Some of the proposed factors of influence are age, gender, exercise intensity and duration as well as training experience (15). However, exercise intensity and duration are among the most studied factors. When jogging is compared to walking, studies show greater concentration of cardiac troponin among joggers, suggesting that the magnitude of cTn response is more significantly associated with intensity, rather than duration of physical activity (25). Another factor of influence is potentially the

type or form of physical activity, most studies have examined this in marathon runners, but it is unclear whether the cardiac troponin increase is as pronounced after other forms of exercise (22,26).

1.5- Mechanisms for exercise-induced cTn elevations

Over the last decades, different pathophysiological mechanisms have been proposed to explain the cTn response following exercise (22,27,28). In older articles, cardiomyocyte injury has frequently been mentioned as an explanation of exercise-induced cTn levels (26). More recent, proposed mechanisms include the theory of altered membrane permeability due to exercise-induced cardiomyocyte stress, leading to passive diffusion of smaller cTn fragments from the cell's cytosol into the extracellular space and bloodstream (3) It has also been suggested that the cTn elevations may be a result of the general inflammatory process occurring during exercise. Other potential theories include cardiomyocyte apoptosis or necrosis (26). However, this is yet to be fully understood.

1.6- Aim

The aim of this paper is to review existing literature on exercise-induced cTn increase in healthy individuals and to get a better understanding on how exercise intensity and duration may affect the cardiac troponin response. I will also review cTn response in relation to different exercise modes by including sports such as running, cycling, and swimming. Accordingly, the main research questions addressed in this thesis are:

What are the main findings on exercise-induced cTn elevations? How does exercise duration and intensity influence this response? Lastly, what are the clinical implications on exercise-induced cTn concentrations?

2- Method

2.1- Study design

To get a better understanding on how exercise duration and intensity influence the postexercise cTn response in healthy people, I chose a systematic review without meta-analysis as study design. The aim was to summarize existing literature on this topic, furthermore, to determine what factors of influence that appears to have the strongest impact on exercise-induced cTn elevations. The main factors of influence studied in this systematic review are exercise duration and intensity within different modes of exercise.

The search was limited by time and language. Only articles published between 2012-2023 were included, and all articles had to be in either English, Norwegian, Swedish, or Danish. Most studies included both men and women, therefore the search was not limited by gender. Furthermore, studies were limited to adults, including existing studies on people from 18-70 years of age. The reason for excluding all articles considering children and adolescents was because I did not want youth to be a potential interfering factor that would add complexity or the interpretation.

Table 1: Inclusion and exclusion criteria

inclusion	**Exclusion**
Humans	Animals
Adults (18-70 years)	Children, adolescents, and elderly > 70 years
Articles published between 2012-2023	Articles published before 2012
Norwegian, Swedish, Danish, or English language	Other languages
All nationalities	
Primary research articles	Reviews, editorials, letters, and conference abstract
Exposed to physical exercise	Not exposed to physical exercise
Exercise intensity, duration, swimming, running, marathon	Other sports (soccer, Triathlon, and ultramarathons)
Cardiac troponins	Other cardiac biomarkers
Cardiovascular healthy	Cardiovascular disease and/or other disease/illness

To ensure that exercise-induced cTn elevations was studied on the chosen population, only studies on cardiovascular healthy individuals were included, meaning that studies on people with cardiovascular disease were excluded (atherosclerosis, previous myocardial infarction, heart failure and arrythmias). Studies comparing exercise-induced cTn response after different

illnesses such as COVID-19 and cancer were also excluded. A complete overview of inclusion and exclusion criteria are shown in table 1.

2.2- Collection of data and search strategy

In preparation for the search, I used a variant of the PICO-form. P stands for *population,* I for *intervention*, C for *comparison* and O stans for *outcome* (29). Comparison was left out of the PICO-form, due to my topic of interest being how *exercise* affect cardiac troponin response. The population consists of apparently healthy individuals free from cardiovascular disease. The intervention is exercise (intensity and duration), and the outcome is cardiac troponin concentrations post exercise. Table 2 shows this PICO-form.

Table 2: PICO-form

p	I	C	O
Healthy, without cardiovascular disease	Exercise (Intensity, duration)		Cardiac troponins

I started out doing two independent systematic searches in Embase, which is a broad medical research database from Elsevier to which the UiO-library has access. Embase contains all articles that can be found in MEDLINE, as well as additional articles not found in MEDLINE or PubMed (30). The initial idea was to use articles from the two independent searches in different parts of this review. In the first search I reviewed articles regarding cTn response in relation to exercise intensity and duration, resulting in 77 articles. In the second search, I reviewed articles comparing the cTn response after marathon runs and swimming, resulting in zero articles. Because this second search conducted zero articles, I replaced marathon runs with running to see if this would provide more articles. However, this alteration only resulted in 7 articles. Concerned that this search method provided me with limited material, I decided to discard this initial search method and ended up doing only one search which included both intensity/duration and swimming/marathon. This final systematic search was conducted 21/11-23 using the Embase database as shown in figure 3.

Figure 3: search strategy

Database(s): **Embase Classic+Embase** 1947 to 2023 November 29

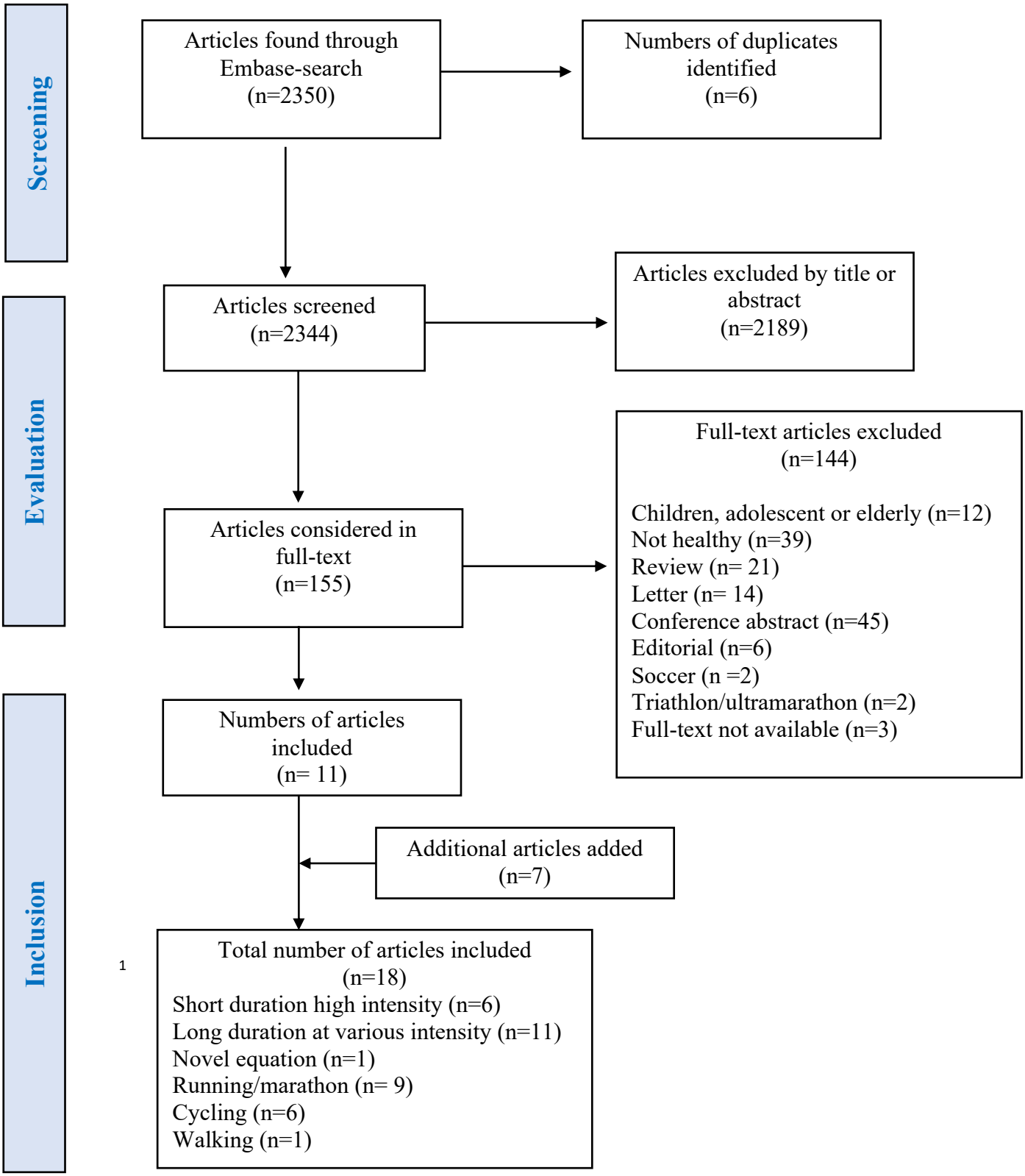
Search Strategy:

#	Searches	Results
1	exp Troponin/	87955
2	troponin t.tw.	16462
3	1 or 2	88946
4	exercise/ or running/ or jogging/ or marathon running/ or swimming/ or exercise intensity/	443793
5	Endurance Training/	9533
6	Athletes/	62071
7	(exercise* or running or marathon or swimming).tw.	613396
8	4 or 5 or 6 or 7	783607
9	3 and 8	3335
10	limit 9 to (english language or norwegian or swedish or danish)	3275
11	limit 10 to yr="2012 -Current"	2592
12	limit 11 to humans	2357

I searched for human studies, using both subject headings (Emtree-words) and text-words (tw) found in titles and abstracts as shown in figure 3. I combined subject headings and text-words using AND/OR, resulting in 2350 articles. An overview the complete search is shown in figure. Note that figure 3 was produced eight days after I did the search and additional seven articles have been published in the meantime, these articles are not included in this systematic review. Based on screening the headlines and abstracts of 2350 articles, I excluded a total of 2189 articles. These articles were excluded due to not fitting my topic of interest, as they either addressed cardiac troponin levels in response to illness, cardiovascular risk or used a different biomarker than cTn. The remaining 155 articles were all considered in full text.

Based on 155 articles, I then excluded articles that did not involve cardiovascular healthy individuals (n= 39), articles that included subjects < 18 years and subjects > 70 years (n=12). Furthermore, I excluded articles regarding other sport-activities such as soccer, ultramarathons, and triathlons (n=4). Articles other than original research articles, such as editorials or review papers, were also excluded (n=86). After excluding a total of 144 articles, I ended up with 11 articles. To further increase the number of relevant articles included in this review, I systematically reviewed the articles conducted with the first search method that was discarded and added 7 articles fitting my inclusions criteria. Accordingly, a total of 18 articles were included in this systematic review. A complete overview of this is shown in figure 4.

Figure 4: flow diagram



[1]

[1] The description of articles included in *figure 4* does not add up with the total number of articles included. This is further explained under *results*.

3- Results

Exercise-induced cTn elevations is the topic for discussion in all 18 articles included in this review. All articles besides one, observed significantly increased concentrations of cardiac troponin after exercise (31). 17 articles addressed different factors influencing cTn response after exercise and one article proposed a novel equation for future measures on exercise intensity (32). Regarding the factors of influence, 6 articles discussed how short duration exercises (maximum 92 minutes) at different intensities affect post exercise cTn concentrations (31,33–37). The remaining 11 articles examined how exercises at longer duration affect the cTn response (38–48). All studies were approved by their local ethics committee (31,33–48).

Different modes of exercises were also discussed. A total of 9 articles used running as their exercise intervention (33,34,37–43), whereas another 6 articles viewed spinning/cycling races (31,35,44–47) and one article studied walkers (48). Lastly, one article compared running, cycling and swimming (36). Difference in exercise modes were not found to impact post-exercise cardiac troponin elevations in a statistically significant way when compared in this article (36).

3.1- Factors of influence

Articles included in this systematic review demonstrated that prolonged strenuous exercise results in elevated levels of cardiac troponins post exercise (38–42). Furthermore, additional findings indicate that short duration high intensity exercise also result in increased cTn levels (25,33–35). Studies have addressed different contributing factors such as intensity, duration, age, exercise modes, blood pressure and previous training experience (38,39). However, the main findings show that both intensity and duration are important predictors for post-exercise cTn elevations.

To estimate exercise intensity, several studies have used heart rate (HR) and study subjects were placed with HR-monitors tracking the HR during exercise (31,34,44). However, the studies have used different HR-variables to address exercise intensity. Some studies used peak HR expressed as % of peak HR (31,36) whereas other studies used mean HR (40,45,48), expressed as % of $HR_{\%MAX}$ (33,37,40). In addition to different ways of expressing exercise intensity, different HR-monitors have also been used. Some studies gave the same HR-monitor

to all participants (31,33,36,37,40,46,48), whereas two studies allowed participants to have different HR-monitors and data variability from different brands were not considered (38,44).

Studies included in this systematic review show different findings on the association between intensity and duration of exercise and the elevation of cTn concentrations (33,34,37,38,40,44–46). Regarding exercise intensity, four studies observed a positive correlation between exercise intensity and exercise-induced cTn concentrations (33,37–39), whereas three studies found no significant association between exercise intensity and cTn response (31,40,42). In terms of exercise duration, one study observed an inverse relationship between exercise duration and cTn concentrations (44), whereas a positive correlation (40) or no significant association was observed in different studies (38).

In addition to this, one Norwegian study by Bjørkavoll-Bergseth et al. successfully analyzed exercise intensity and duration as a combined variable (45). This was done by calculating the duration of time spent above certain HR-thresholds (140, 150 and 160 bpm) following the race. They observed that only duration (time spent) with an HR>150 bpm correlated significantly with the exercise- induced cTn response, whereas single measures such as mean HR and mean HR%max did not (45). This study is highlighted because it underscores the importance of addressing intensity-duration domain as one predicting factor for exercise-induced cTn elevations.

A relationship between other influencing factors has also been addressed, besides exercise intensity and duration. Firstly, previous training experience was not associated with exercise induced cTn elevations in five studies (33,39,40,42,44) but found to be negatively correlated in one study (43). When previous training experience was evaluated as a potential factor impacting the cTn response, studies used self-reported methods to measure exercise experience (38,40,43,44) and further linear regression analysis to assess this relationship (40,43,44). Despite self-reported data on training experience being a limitation, this is also an understandable strategy. Other objectively methods measuring exercise habits and experience require researchers to follow the subjects over a long period of time, which is a rather time-consuming method.

Secondly, an inverse correlation between age and cTn elevations was found in two articles (40,41), as well as no correlation in a different study (42). In larger sample sizes, Kleiven et

al. found age to be inversely associated with the cTnI response at 3h post-race, but positively correlated at baseline and at 24h post-race (44). Supporting the findings 3h post-race, Eijsvogels et al. identified an inverse relationship between age and cTnI values immediately post-race ($p < 0.05$) (40). Despite conflicting data regarding training experience and age, exercise intensity and duration is the main topic for this review and further investigation besides this is yet to be reviewed.

3.2-cTn-assays

The included studies have measured circulating concentrations of cardiac troponins with different immunoassays. Most of the studies have used 5th generations of high-sensitivity immunoassays (33,34,36–47), whereas other studies have used contemporary 4th generation assays or conventional assays for analyzing cTn levels (31,43). In addition, two studies compared high-sensitivity assays with contemporary and conventional cTn assays and both observed greater cTn elevations in high-sensitivity assays (41,42). Lastly, one study did not elaborate what assay was being used (48).

Studies measuring high-sensitivity troponin T (hs-cTnT) have used immunoassays from Roche Diagnostics with overall 99th percentile of 14 ng/L (33–39,41,44,45,47). Measurements of high-sensitivity troponin I concentrations are done with assays from Abbott Diagnostics and Siemens Healthcare Diagnostics (33,37,40,41,44–47). Upper reference limits (URL) are based on the 99th percentiles of respectively 26 ng/L for the Abbott and 40 ng/L for the Siemens assay (33,37,40,41,44–47).

In addition to using different generations of assays, studies have also measured different cTn subunits (cTnI and cTnT). Five studies compared hs-cTnT assays with hs-cTnI assays (33,37,44,45,47). The main findings are that the URL is exceeded in a higher percentage of subjects when using the hs-cTnT assay compared with the hs-cTnI assay (33,37,37,44,47). The percentage of participants exceeding the assay-specific 99th percentile were 61% (hs-cTnT) and 13% (hs-cTnI) in a small study population (33). Similar findings were observed in a larger study, with respectively 95% (hs-cTnT) and 84% (hs-cTnI) fulfilling the biomarker criteria for myocardial infarction (44).

3.3- Mechanisms for exercise-induced cTn elevations

The mechanisms behind exercise induced cTn elevations are heavily debated (40,44,47,48). Besides summarizing and referring to previously proposed mechanisms, three of the articles included supports the theory of exercise-induced cTn elevations being a physiological phenomenon (36,40,44). However, studies in this systematic review provided insight into factors influencing the cTn response, hence novel findings regarding the underlying mechanisms exercise-induced cTn elevations are not found in the studies included (34,35,38,39,43,44,47,48). As a result, the mechanisms of this response as well as the clinical implications remains unknown.

Main findings are represented in the table below

Author	**Publication**	**Sample size**	**Exposure**	**Type of exercise**	**Cardiac biomarker and assay**	**Results**
George et al. (31)	2014	18 healthy male students. Mean age 23± 2 year.	Two cycling sessions of short duration (30s) high intensity.	Cycling.	cTnI (Chiron Diagnostics). Samples were collected before, right after and 24 h after exercise.	Short duration (30s) high intensity cycling sessions did not result in statistically or clinically significant cTnI increase post-exercise.
Nguyen et al. (33)	2023	24 healthy volunteers. Age between 18-50 years old.	3 X 60-min treadmill running sessions at various intensities (LIT, MIT and HIT).	Running.	TnI (Hs-cTnI, Abbott and Siemens) and TnT (hs- cTnT, Roche Diagnostics). Measurements prior, 2, 4 and 6 h after HIT and after 4h after MIT and LIT.	Only high-intensity (HIT), but not moderate (MIT) or low-intensity (LIT) resulted in a statistically significant cTn increase. Troponin concentrations correlated with HR% (intensity measure) during exercise ($p<0.0001$). 13% (hs-cTnI) and 61% (hs-cTnT) of the subjects had cTn concentrations exceeding the assay specific 99th percentile. There was no significant correlation between cTn concentrations post-exercise and self-reported exercise habits (hours pr week) ($p > 0.07$).
Weippert et al. (34)	2016	13 healthy males. Age 26.2 ± 2.9 years.	Two different running sessions: 60 min continuous running at moderate intensity (MCT) and two series of repeated sprint sessions (12 x 30s) (RST).	Running.	TnT (hs-cTnT, 5th generation Roche). Measurements before, 1 and 4 hours after exercise sessions.	Significantly elevated cTnT levels were only seen after RST and not after MCT. 5/13 subjects exceeding the 99th percentile at 4h post RST. A significant relationship between % peak HR and cTnT was also observed.

Duttaroy et al. (35)	2012	13 healthy, well-trained men and woman. Mean age 31.	A single bout of 60 min high-intensity spinning session.	Cycling.	TnT (hs-cTnT, Roche). Measured before, 1 and 24h post exercise.	cTnT concentrations significantly increased 1h following exercise and two subjects had concentrations above the URL. Concentrations declined back to baseline 24h post exercise.
Li et al. (37)	2020	12 healthy runners (11 males and 1 female). Mean age 23.5 ± 5.5 years.	Two exercise tests in random order: Intermitted running trial (90%vVO2 max for 2 min, followed by 50% vVO2max for 2 min, repeated for 92 min) and continuous running for 92 min (70%vVO2max).	Running	TnI (hs-cTnI, Abbott) and TnT (hs-cTnT, Roche). Measurements before, immediately after, 2,3,24 and 48h post exercise.	Both exercises conducted elevated cTn concentrations. Respectively 11 (intermittent) and 10 (continuous) subjects had concentrations exceeding the URL No significant difference in the cTn response for intermittent and continuous exercise at similar mean heart rates. However, a positive correlation between intensity (average HR of 160 bpm) and cTn elevations was found for the intermittent exercise and not for the continuous.
Richardson et al. (38)	2018	52 healthy marathon runners. Mean age 39± 11 years.	Brighton marathon (9th April 2017).	Maratho n.	TnT (hs-cTnT,5th generation Roche). Measured before and immediately after finishing.	All runners showed post-race cTnT values above the URL. Exercise intensity was positively correlated with post-race cTnT elevations and subjects with the highest HR during the race also displayed the greatest troponin T increase. Exercise duration was not related to cTnT.
Jörres et al (48).	2021	43 athletes (25 male and 18 female). Mean age 34.6 ± 8.8 years.	100 km- walking march (Mammut march), expected to complete the distance within 24h (mean calculated speed of 4.17 km/h).	Walking march.	TnT (assay use is not explained). Measurements taken before, and at 30,70 and 100km checkpoints.	low-intensity exercise over a long duration does not result in cTnT elevations above the URL. However, subjects with a greater mean HR during the race, showed significantly higher cTnT levels. Suggesting that intensity might be a more important factor of influence, compared with duration.
Legaz-Arrese et al. (36)	2015	15 healthy amateur male triathletes at the age of 35±9 years.	Compared the cTnT response after 60 min of swimming, running, and cycling in well trained triathletes.	Running, cycling, and swimmin g.	TnT (hs-cTnT, Roche Diagnostics). Sample measures collected before, 5 min after and 1,3,6,12 and 24 post exercise.	All independent exercises resulted in cTnT elevations post exercise and concentrations returned to baseline 24h post-exercise. Exercise mode did not impact the cTnT concentrations and there was no significant difference in the percentage of subjects with values exceeding the URL for the different modes of exercises.

Kleiven et al. (44)	2019	1002 healthy cyclist. (782 men and 220 woman). Median age were 46.8 years old.	91-km mountain bike race	Cycling race.	TnI (hs-cTnI, Abbott) and TnT (hs-cTnT, Roche). Measured before race, at 3 and 24h post-race.	In both assays, cTn levels increased from baseline to 3h post-race. The URL was reached in 92% (hs-cTnT assay) and 84% (hs-cTnI assay). Declining concentrations were seen 24h post-race. Statistical analysis found higher systolic blood pressure at baseline and shorter race duration to be independent predictors of cTn increase after exercise. Observed an inverse correlation between race duration and cTn values and the duration of high intensity exercise was found to be a significant determinant for exercised induced cTn increase. No association between mean HR and post-exercise cTn levels were found.
Bjørkavoll-Bergseth et al. (45)	2020	177 healthy cyclists (31 woman and 146 men). Average age were 44 years old.	91-km mountain bike race.	Cycling race.	TnI (hs-cTnI, Abbott) and TnT (hs-cTnT, Roche). Measurements2 4h before, 3 and 24h post-race.	TnI and TnT concentrations increase in all participants after exercise. Peak concentrations were observed 3h post-race. Time spent at a certain intensity (HR-threshold of 140-150 bpm) was found to be an important predictor for the exercise-induced cTn response. The duration of exercise spent with HR above 150 bpm correlated significantly to the cTn response, whereas single measures of mean HR and HR%max did not.
Mehta et al.(43)	2012	A total of 52 healthy runners were split in two. HIGH T-E group (n=27) and LOW T-E group (n=25).	Subjects were separated in two groups based on training experience (HIGH-T-E and LOW T-E). Both groups completed the London Marathon.	Maratho n.	TnI (Ultra assay, Siemens Healthcare Diagnostics). Measurements were collected before and right after the marathon run.	Training experience (average miles run per week over the last three years) was negatively associated with post-race cTnI concentrations: the cTnI response post-marathon was significantly greater in subjects with less training-experience (LOW T-E group), when compared to HIGH T-E group. In total 52% of the participants had cTnI rise above the URL (33% in the HIGH-T-E group and 60% in the LOW-T-E group).

Skadberg et al.(47)	2018	97 healthy recreational cyclists of both genders.	91-km mountain bike race	Cycling race.	TnI (hs-cTnI, 5th generation Abbott Diagnostics) and TnT (hs-cTnT, 5th generation Roche Cobas e602). Measurements drawn before, immediately after, 3 and 24 h post-race	Increased cTn concentrations were seen for both assays after race. Peak concentrations were observed immediately after the race for hs-TnT, and after 3h for the hs-TnI assay. In both assays, cTn concentrations exceeded the URL, but this was most frequent seen with the cTnT assay (95%). The largest cTn increase was observed in women.
Martínez-Navarro et al. (39)	2020	98 healthy participants (83 men and 15 woman). Mean age were 38.72 ±3.63 years.	Valencia Fundacion Trinidad Alfonso EDP marathon in 2016.	Marathon run.	TnT (Hs-cTnT, Roche Diagnostics). Measurements were collected before and immediately after race and at 24, 48, 96, 144 and 192h post-race.	cTnT concentrations increased in all participants post marathon.73 subjects (95%) had concentrations above the URL. The magnitude of the TnT response was positively correlated with mean HR. Runners who performed the marathon with a higher intensity level, also showed greater post-race cTnT values. A significant association between self-reported training history and post-race TnT values was not observed.
Eijsvogels et al. (40)	2015	92 healthy, moderate-highly trained individuals	Participated in a marathon at a self-selected speed	Eindhoven Marathon run in 2010.	TnI (Centaur TnI-Ultra, Siemens Healthcare Diagnostics). Measures drawn before and right after the race.	cTnI concentrations increased significantly after the marathon with 65% of the subjects demonstrating cTnI levels above the URL. Based on regression analysis, younger age (β= –0.27) and longer exercise duration (β=0.23) was found to be significant predictors of higher post-race values ($p<0.05$). This was not observed for exercise intensity nor previous marathon participation.
Niemelä et al.(41)	2016	10 healthy individuals. Mean age was 27 ±13 years.	Marathon run (n=4) and half-marathon run (n=6)	Marathon run	TnI (Hs-cTnI, 5th generation Abbott) and TnT (hs-cTnT 5th generation and conventional 4th generation assays by Roche Diagnostics). Samples were collected before, at 3 and 48h post-race.	cTn elevations were larger after marathon, when compared with the half-marathon group. Greater concentrations were also observed with the high sensitivity assays compared to the conventional assay. Younger age is suggested as a factor of influence: The largest cTn elevations were observed in young participants (< 30 years) and concentrations were highest in those < 20 years of age.

Bjørkavoll-Bergseth et al. (46)	2021	59 healthy individuals (13 woman and 46 men). Mean age were 50 ± 9 years.	Results from 3 exercises were compared (T0, T1 and T2). T0: participants in 91-km mountain bike race in either 2013 or 2014. T1: cardio-pulmonary exercise test (CPX-test) and T2: 91-km mountain bike race in 2018.	Cycling	TnI (hs-cTnI, Abbott Diagnostics). Samples were collected prior to race, at 3 and 24h post-race for T0, T1 and T2	Elevated cTn concentrations were seen after T0, T1 and T2 with peaking values 3h post exercise. The largest post-exercise cTn increase was seen after the T0 race, second largest after the T2 race and the lowest levels was observed after the T1 test. Duration of high-intensity exercise and mean HR were higher in T2 compared with T1. T2 also showed higher post-exercise cTnI level than T1. Race duration was shorter, and intensity was higher in the T0 compared with T2. The exercise-induced cTn response is related to exercise duration and intensity. Longer duration of high-intensity exercise result in the largest cTnI increase.
Voets et al. (32)	2016	Presents a new mathematical model that address the relationship between exercise intensity and post-exercise cTnI response. The purpose with this model, is to aid in objectively quantifying exercise intensity, based on post-exercise assessment of cTnI. This is proposed to be a better estimate for exercise intensity compared with %HRmax.				
Lippi et al. (42)	2012	17 healthy trained males. Mean age 47 years old.	Preforming a 21 km, half marathon with a heart rate (HR) monitor.	Half-marathon run (21 km)	TnI (conventional AccuTnI and hs-AccuTnI, Beckman Coulter). Samples were collected before and immediately after, as well as 3,6 and 24h post-race.	cTnI concentrations significantly increased from baseline after completing a half-marathon. The increase was greater with the hs-TnI assay compared with the conventional TnI assay. Peak cTnI values were seen 6h post-race. At this time, 11 (hs-TnI assay) and two (TnI assay) subjects had concentrations exceeding the URL. Exercise intensity, age, training history were not associated with changes of hs-TnI.

4- Discussion

4.1- Sampling times

Studies included in this systematic review have measured cTn concentrations following exercise at multiple sampling times. Exercise induced cTn concentrations typically peak 3-6 hours post exercise (33,36,46) and declining concentrations are starting to show from 24h post exercise (33,44–46). However several studies failed to include blood-sampling at times where the cTn concentrations are suggested to peak (31,34,40,41), resulting in missing data on how concentrations changes over time post-exercise.

Three studies included five or more sampling times, investigating the rise and fall of cTn concentrations post exercise (36,37,42). Findings from multiple sampling times support that cTn concentrations peak somewhere between 3-6h post exercise (36,37,42). Despite the strength of including multiple sampling times, small sample sizes of less than 20 participants could be a major limitation in all three studies. However, managing multiple blood samples of five or more is technically easier to do on a small study group and would require far more resources if done on a larger population. It is therefore understandable that studies including a larger population, also have fewer sampling times post-exercise.

4.2- cTn-Assays

All studies included in this systematic review were published between 2012-2023 and during this period, new and improved generations of cTn assays were developed (14,15). While older studies have used the conventional cTn assays having a higher detection limit (31,35), other and more recent studies have used the contemporary 4th and the highly-sensitive 5th generation cTn assays with a lower detection limit (34,37,38,41). Partly because the hs-cTn assays are more sensitive and partly because of enhanced low-concentration precision, studies using high-sensitivity assays are more likely to show subjects exceeding the URL. Supporting this, Lippi et al. compared the conventional AccuTnI assay with the novel hs-AccuTnI assay and found that 65% of the subjects had values exceeding the 99th percentile of the URL with the hs-cTnI assay, compared to only 12% with the conventional cTnI assay (42).

As previously mentioned, studies observed that the URL was exceeded in a higher percentage of subjects when using high-sensitivity assays (hs-cTnT and hs-cTnI), but most frequently with the hs-cTnT assay (33,37,44,47). The reason for this is not clear, but it might be related to

differences in sampling times as well as different release patterns following exercise. Additionally, this may also be associated with the earlier peak of hs-cTnT (26,33,44,47). One study observed that hs-cTnT reached maximum concentrations immediately after exercise, whereas hs-cTnI peaked 3h post-exercise (47). Nevertheless, there is missing data on how concentrations decline for both hs-cTnT and hs-cTnI beyond 24h. Lastly, it should be mentioned that the 99th percentile URLs are defined by the manufacturers and varies among companies (49,50). As a consequence, the 99th percentile URLs are not established on the same healthy reference population. Variations in age distribution, sex, ethnicity and how the healthy reference population has been defined are analytic factors that may affect the assay-specific 99th percentile URLs (50).

4.3- Duration

Long duration exercises have previously been associated with increased cTn concentrations (40–42,51). This have been observed after both half-marathons and marathons (40–42). To further investigate how different race-duration impact the post-exercise troponin response, one study compared this response in six half-marathon four and marathon runners (41). Although, both races produced significantly increased cTn levels, the cTn increase was more profound in the group of marathon runners, purposing that a race of longer duration results in greater cTn elevations (41). However, this comparison lacks depth since both distances are considered as long duration races. In addition, the study subjects did not participate in both races and potential individual variations within the two groups were not considered. To further address the importance of different race duration, findings from short duration exercises needs to be addressed in a more precise study design investigating different distances for the same study population.

Surprising evidence from several studies have observed that exercising at short duration result in significant increased cTn concentrations post-exercise (25,35,36). This challenges the previous findings in half-marathon and marathon runners (41,42). Even though exercises of shorter-duration may have the potential to elicit elevated cTn levels, the intensity is often greater in these studies (25,33,35,36). In a study by Duttaroy et al, 1h cycling session was performed with mean intensity being 85% of estimated HRmax (35), translating to high intensity exercise level, and it becomes difficult to solely evaluate the impact of short duration alone. Additional limitations such as blood-samples drawn at different times and small sample sizes are seen in several studies on short-duration exercises (31,34,35,42).

Conflicting evidence on the relevance of race-duration are also seen in larger study populations. Two studies addressing this are by Eijsvogels et al. and Kleiven et al. (40,44). Eijsvogels and colleagues observed a positive relationship between race duration and cTnI levels after a marathon race (42 km) (40). This was further demonstrated in a linear regression analysis observing longer race duration to be an independent predictor for higher post-race cTn values ($p<0.05$), which strengthens the findings of longer race-duration to be a significant predictor for higher post-race cTnI levels. In contrast, an inverse relationship between race duration and cTn levels was presented in the study by Kleiven et al. in both bivariate and multiple regression models (44).

Exercise duration is accessible parameter that is often measured as exercise time (in hours) or race distance (33,35,38,40,41,44,48). To fully understand this parameter, researchers should consider that exercise time could depend on several other factors such as speed, intensity, training experience and exercise technics. These are factors associated with individual physical fitness level and have the potential to vary within the study population. The participants in the cycling study by Kleiven et al. consisted of athletes with a higher fitness level than the general population (44), whereas Eijsvogels et al. studied moderate to highly trained runners without making a comparison to the fitness level in the general population (40). The different findings on the relationship between race duration cTn elevations might be influenced by difference in exercise mode, individual fitness level and race-duration.

To investigate if different modes of exercise over similar durations would impact cTn elevations, one study from 2015 compared the hs-cTnT response after completing 60 minutes of running, cycling and swimming in a randomized order (36). Interestingly, cTn elevations were observed after all three exercises. Furthermore, they found no significant difference in hs-cTnT response relating to exercise mode ($p=0.102$) and there was little difference in the percentage of participants exceeding the URL within the three exercise modes (36). This study is interesting as it implies that different exercise modes at a high-intensity level over same durations are comparable. However, one study is not enough to conclude on this and it should be mentioned opposite findings have been observed in a previous meta-analysis from 2007 which is not included in this review (52). Despite the findings, the study from 2015 was based on a small heterogenous group consisting of fifteen young male triathlons, and results might

not be transferable to the general population. Further studies examining cTn response after different exercise modes over a fixed duration are needed to make further conclusions.

Studies addressing the relationship between race-duration and cTn elevations are conflicting. Despite a positive or inverse correlation between duration and cTn increase, marathon runs, half-marathon runs, cycling races and even shorter duration of exercise sessions have shown to induce a large cTn increase (36,40–42,44,47), indicating that race-duration might not be the only factor influencing post-exercise cTn concentrations.

4.4- Intensity

Mean and peak heart rate (HR) have been used as estimates for exercise intensity. However, HR is a fluctuating parameter with several other variables known to influence heart rate during exercise (32). This makes the interpretation of exercise intensity complex and difficult to estimate. Factor influencing HR could be age, gender, training history and race duration (32,44). In addition, these factors are also interfering with one another, and accordingly, HR may be an imperfect parameter for exercise intensity. As an example it has been observed that highly trained participants have a lower estimated HR (43,48) as well as younger age being related to fewer years of training experience (40). In an attempt to address the impact of exercise intensity in a more precisely method, Voets et al proposed a novel mathematical equation for determining the intensity of conducted exercise based on a cTnI assessment (32). However, this does not reply to changes in cTnT.

Studies have observed different findings examining whether the magnitude of post-marathon cTn elevation is related with race-intensity or not. Neither Lippi et al, or Eijsvogels and his associates observed exercise intensity to be a significant predictor of higher post-race cTnI levels (40,42). The first study lacks a complete explanation on how intensity was measured, which is a major limitation in itself (42). In the study by Eijsvogels et al, exercise intensity was measured as mean HR expressed as % of max predicted HR (40). However, only small variations in intensity (91 +- 5% of HRmax) was seen in participants and exercise intensity was therefore not included in the regression analysis for contributing factors of post-race cTnI levels (40). Both studies have limitations in either not explaining how exercise intensity was measured, or not including measurements of intensity in a statistic analysis.

Opposite findings were observed in the studies by Martínez-Navarro et al and Richardson et al. They found a direct correlation between cTn levels post-marathon and exercise intensity (38,39). Both studies used several measures for exercise intensity and included these measures in statistical analysis which strengthens their observations. Martínez-Navarro et al found Hs-cTnT increase to be directly correlated with marathon speed $\%V_{VT2}$, mean $HR_{\%VT2}$ and mean $HR_{\%MAX.}$(39), suggesting that runners preforming the marathon at higher relative intensity also showed greater cTnT concentrations. Supporting this, both mean HR ($r=0.50$, $p < 0.05$) but also peak HR ($r=0.68$, $p < 0.01$) was found to be strongly correlated with post-marathon cTnT levels in the study by Richardson et al (38). However, Richardson et al. only measured cTn concentrations immediately after the marathon, whereas Martínez-Navarro and colleagues proceeded with multiple sampling times. Despite differences in sampling times, both studies suggest that cTn concentrations post-marathon are associated with running at a greater intensity during the marathon (38,39).

Time spent exercising at a high intensity level have been addressed as an important factor contributing to elevated cTn levels after cycling races (45,46,53). In long distance cycling races, long duration of high intensity exercise have been suggested to induce the greatest cTnI elevations (45,46). Bjørkavoll-Bergseth et al. found that the combination of duration with elevated HR (above 150 bpm) was the best predictor of exercise-induced cTn concentrations, and in contrast to findings by Richardson and Martínez-Navarro et al, single variables measuring exercise intensity (mean HR and HR%max) did not (45). There is no doubt that determining the relationship between duration and intensity is complex and depending on several variables. However, the combination of both exercise duration and intensity (reflected as heart rate) seems to influence the troponin response post-exercise (38,39,44–46,53) and the best way to address this association might be when variables of intensity and duration are considered combined.

The influence of exercise intensity have also been discussed studying exercises of shorter duration (25,31,33–35). Consistent findings suggests that the elevations in cardiac troponins are greater after exercises of higher intensities (25,33–35,37). In two studies, intermittent running was suggested to produce a larger postexercise cTn increase when compared with continuous running for respectively 60 and 92 minutes (34,37). In the study by Li et al. the greatest cTn elevations were particularly observed after completing intermittent exercise with an average HR of 160 bpm, translating to a high-intensity level (37). Similar findings supporting

the theory of intensity driving the cTn response have also been observed in long-distance walkers. Participants who walked with a greater heart rate (HR> 106.5 bpm) showed significantly higher cTnT levels (p=0.02), however this was only observed in the first checkpoint sampling at the 30km distance (48).

A possible explanation for observing greater postexercise cTn increase at higher intensities could be because the duration may be shorter, and participants are therefore able to proceed with a higher race speed. In the walking-march study, it possible that participants reached an exhaustion point following the 30-km distance, resulting in a lower walking speed for the remaining race-distance that may have been below the exertion level needed to generate elevated cTn concentrations (48). However, when runners are exposed to various intensities over a fix duration, it has been observed the cTn increase correlates with the highest intensities (33). Demonstrating that intensity may have a stronger potential impact on post-exercise cTn concentrations rather than duration. As a result the existence of a threshold for intensity-level needed to be achieved in order to produce elevated cTn levels have been proposed by several researches (37,45,54)

4.5- Clinical implications

The kinetics of cTn elevations seen after exercise differs from what is seen in patients with ongoing myocardial infarction (3,33,43). Exercise induced cTn elevations peak 3-4h post exercise and return to pre-exercise baseline concentrations within 24-72h post-exercise (39,41,42,55). In contrast, patients with acute myocardial infarction show peak cTn levels after 10h and concentrations remain elevated for 4-12 days depending on the size of the AMI (3,33,43). The early peak and rapid declining of cTn levels post exercise contrast with the later peaking and longer lasting elevations seen as a result of ongoing cell necrosis and fragmentation in patients with AMI (3,4). As a result, the mechanisms behind elevated cTn concentrations may be different in these two circumstances.

Even though mechanisms for post-exercise cTn elevations is yet to be discovered, the present biomarker criteria for myocardial injury do not distinguish between exercise-induced cTn elevations and elevations seen in response to acute myocardial infarction (47,56). Consequently, this could cause clinical confusing when athletes are admitted to medical clinics after exercise. It is therefore important that clinicians notice that induced cTn concentrations are frequently seen after both prolonged strenuous exercises as well as seen

after high intensity interval sessions. Supplementary studies investigating the mechanisms behind this increase needs further assessments to conclude that exercise induced cTn elevations are a benign response, rather than patho-physiological.

Cardiac troponins are proteins that can be degraded to smaller circulating primary and secondary fragments (15,57). Circulating cTnT fragments in patients with MI is proposed to be time-dependent with a greater percentage of fragments showing early release (13,58). Interestingly, recent findings have observed that the circulating cTn fragments seen in patients with acute myocardial infarction (AMI) differs from the fragments circulating in healthy individuals post-exercise (58). In patients with AMI the circulating cTnT fragments are found to be larger (primary 29 kDa and secondary fragments of 14-18 kDa), while only small secondary cTnT fragments (14-18-kDa) have been observed after exercise (15,57,58). Future use of analytical methods that can separate the cTn fragments by size could potentially be helpful for clinicals in discriminating between exercise-induced cTn elevations and elevations caused by AMI.

5- Limitations

Firstly, it must be mentioned that studies included in this systematic review are based on presumably healthy individuals with no history of cardiovascular events or risk factors (31,33–37,39–48). Their health status was evaluated by medical examinations and questioners on medical history (31,33,34,37–40,43–47). To further ensure that there were no obvious obstructive coronary artery disease (CAD), additional blood samples, blood pressure, ECG, and echocardiographic examination were done in some studies (33,34,39,43,44,46,47).

Even though examinations on health status were evaluated prior to exercise, these do not necessarily detect underlying conditions such as atherosclerosis, which also is believed to be associated with cardiovascular risk of events during and following exercise (56). Due to some subjects showing unexpectedly high cTn concentrations 24h post-race, one study proceeded with conventional invasive coronary angiography or coronary computer tomography (CT) angiography, detecting CAD in three participants (47). All three subjects were excluded after these findings. However, investigating this is rather invasive, it is an important discovery and there is no guarantee that remaining studies have included data from subjects at risk for cardiovascular disease.

Secondly, the study subjects are described as well trained, having training experience prior to participating in studies (34,35,37–42,44,48). In one study, participants were recruited from local triathlon clubs through open invitations, resulting in data on a rather homogenous group (36). However, similar bouts and types of exercise are likely to produce different cTn responses in different populations and the magnitude of changes in levels of cardiac troponins will vary within individuals depending on their fitness levels. Therefore, findings on exercise induced cTn elevations in this systematic review might not apply nor represent the general and more unfit population.

Thirdly, few studies have successfully explained the total variation in cTn response post exercise. Studies on small sample sizes have estimates of lower precision and does not address this individual variation (37,41). In larger sample sizes this is explained in statistical models (40,44,46). However, low predictive values with explaining variance of only 9,3% and 15-36% are seen in two studies (40,44). This Implies that factors included in current prediction models does not fully explain the post-exercise cTn increase, furthermore it emphasizes the possibility that unidentified individual factors play an important role. Future studies investigating these "unknown" factors are important for improved predictions and to better understand the cTn response following exercise.

6- Conclusion

Supporting evidence from various studies, involving both small and large study groups show that exercise have the potential to elicit increased concentrations of cardiac troponins in healthy individuals. In addition, some individual might show post-exercise cTn concentrations exceed the assay-specific URL, fulfilling the diagnostic biomarker criteria for myocardial infarction. This was observed after both prolonged and strenuous exercise, as well as after shorter duration high intensity exercises, regardless of different exercise modes. There are several potential factors that should be considered when reviewing data on exercise-induced cTn response such as study size, sampling times, assay use as well as studied factors of influence.

Although the relationship between post-exercise cTn elevations, and exercise duration and intensity are difficult to comprehend and depending on several variables, supporting evidence argue that both exercise duration and exercise intensity are important factors associated with

postexercise cTn elevations. However, this association might be best predicted when intensity and duration are addressed as combined variables. In addition, the magnitude of the cTn increase seems to be more associated with exercise intensity rather than duration, and a threshold for intensity-level creating this response have been suggested.

This systematic review concludes that transient elevations in cardiac troponin can be seen in presumably healthy asymptomatic individuals after exercise. Even though the mechanisms behind exercise-induced cTn elevations are not fully discovered nor elaborated in this review, the cTn kinetics are different from what we see in patients with acute myocardial infarction: post-exercise cTn concentrations peak earlier and return to baseline concentrations in few days without any apparent long-term adverse consequences. This might indicate that exercise induced cTn elevations does not elicit permanent damage and may reflect a potential physiological response rather than patho-physiological.

7-Literature

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