

MINI-REVIEW

On the potential effect of circadian rhythms of cardiac troponins on the diagnosis of acute myocardial infarction

Aleksy Michailovich Chaulin^{1,*}, Dmitry V. Duplyakov¹

¹Department of Cardiology and Cardiovascular Surgery, Samara State Medical University, Chapaevskaya Str. 89, 443099 Samara, Russia

***Correspondence**

alekseymichailovich22976@gmail.com
(Aleksy Michailovich Chaulin)

Abstract

Methods for the determination of cardiac troponins have been significantly improved, facilitating further advancement of the therapeutic and diagnostic process of the cardiovascular diseases case management. In particular, acceleration of the acute myocardial infarction testing (early diagnostic algorithms: 0-1 h, 0-3 h) enabled earlier detection and choice of the optimal treatment tactics. At the same time, with the increased sensitivity in the laboratory test results interpretation, there emerged a necessity to take into account some additional factors that may affect the concentration of cardiac troponins in blood serum. Several recent studies have reported the existence of circadian rhythms in cardiac troponins. This article aims to discuss the possible mechanisms of how circadian rhythms of cardiac troponins develop and their influence on the diagnosis of acute myocardial infarction.

Keywords

Cardiac troponins; Cardiovascular diseases; Acute myocardial infarction; Circadian rhythms; High-sensitive analyses

1. Introduction

To date, cardiospecific troponin isoforms determined by high-sensitive methods (hs-cTnI and hs-cTnT) are the most preferred biomarkers in the detection of acute myocardial infarction (AMI) [1, 2]. Nevertheless, together with the sensitization (detecting ability) of these methods, a slight decrease in the specificity of hs-cTnI and hs-cTnT took place, which changed the concept of their diagnostic and prognostic value in terms of cardiovascular (CVD) and other diseases. Previously thought that cardiac troponins are strictly intracellular molecules, and their presence in biological fluids was considered as an important AMI pathological sign (diagnostic criterion), indicating cardiomyocyte death [3]. However, with the advent of new highly sensitive determination methods (hs-cTnI and hs-cTnT), these views have changed. So it was shown that modern highly sensitive methods of immunoassay could determine cardiac troponins for absolutely all healthy individuals, not only in blood [4] but also in other biological fluids, such as urine [5], saliva [6–8].

A decrease in specificity is expressed in the fact that hs-cTnI and hs-cTnT can increase under some other pathological conditions, that in a way affect the cardiovascular system (CVS) (sepsis, myocarditis, chronic kidney disease (CKD), use of cardiotoxic drugs (for example, chemotherapeutic agents) and others) (Fig. 1) [9–12], basically other than ischemia of the striated heart muscle, which requires clinicians to be more careful in interpreting overestimated and borderline results. Thus, hs-cTnI and hs-cTnT should be generally considered

specific biomarkers of myocardial injury, but not for any particular type, including the cardiac muscle ischemic necrosis. Moreover, the levels of hs-cTnI and hs-cTnT can increase several times even in obviously harmless conditions such as physical exertion and psychoemotional stress [13, 14]. Therefore, the final diagnosis of AMI, in no case should be based only on the results of laboratory tests.

However the decrease in specificity is not such a profound drawback as evidenced by the rapidly increasing demand for modern highly sensitive research methods. According to a recent study, many healthcare facilities have almost completely switched to the new methods (hs-cTnI and hs-cTnT) in routine clinical practice for AMI diagnosis [15].

Today there are a large number of manufacturers of high-sensitive test systems, different in analytical (quality) characteristics. For practical use, only those high-sensitive immunoassays are suitable that meet two key criteria: 1) the coefficient of variation (CV%), intended to estimate serial measurements scatter in one sample, should not exceed 10% ($CV\% \leq 10\%$) when troponin concentration is within the 99th percentile (accepted as the upper limit of the norm); 2) the level of troponins in the range from the limit of detection (LoD) to the level of the 99th percentile should be determined in more than 50% of the examined individuals from two populations, including at least 300 women and men, respectively. Given these requirements, the accurate determination of low troponin levels, comprising only a few ng/L in healthy individuals, is challenging [16].

Special attention should be paid to the possibility of using

TABLE 1. hs-cTnI levels used for CVD risk stratification [16]

CVD developing risk	hs-cTnI concentration in women	hs-cTnI concentration in men
Low	< 4 ng/L	< 6 ng/L
Moderate	4-10 ng/L	6-12 ng/L
High	> 10 ng/L	> 12 ng/L

hs-cTnI and hs-cTnT to assess the CVD development risk in a healthy population. Thus, according to a large study involving 9005 people, exceeding hs-cTnI levels (> 10 ng/L for women and > 12 ng/L for men) were associated with a high risk of CVD developing in the long term, while at lower levels of hs-cTnI, the risk of CVD developing significantly decreased (Table 1) [16, 17].

The use of highly sensitive determination methods encourages consideration of various factors that can affect the research result. The latter, as shown by recent studies, include circadian rhythms, the effect, and the possible underlying mechanisms of which are discussed in this review.

2. Circadian rhythms of cardiac troponins

Circadian (circadian or diurnal) rhythms are understood as cyclical fluctuations in the intensity of various kinds of biological processes and body functions associated with the alternation of day and night. Along with the biorhythms that determine the performance of the organism functions (for example, the rhythm of sleep/wakefulness, blood pressure (BP) fluctuations, heart rate (HR), etc.), there exist so-called regulatory biorhythms, in particular, circadian rhythms of hormone secretion [18, 19]. To date, it has been established that most hormones (metabolism regulators) and metabolites, affected by the aforesaid regulators, have diurnal concentration variations, which should be considered in a study (selecting the time of biomaterial sampling) and interpreting the results.

With the advent of high-sensitive methods for cardiac troponin determination, it was noted that the concentration of hs-cTnT in the blood can also express a circadian rhythm [20–22]. K Aakre and colleagues studied weekly and 90-minute biological variations in hs-cTnT (Roche Diagnostics) and hs-cTnI (Abbott Diagnostics) levels in CKD hemodialysis-dependent ($n = 19$) and healthy patients ($n = 20$). Blood sampling from chronic kidney disease patients took place when no hemodialysis was performed. It was found that over a 6 hour period (from the moment of the first blood draw at 8:30 am to the last at 2:30 pm), the hs-cTnT and hs-cTnI concentrations gradually decreased [21].

In a clinical study, Klinkenberg *et al.* conducted a standardized assessment of intra-day, diurnal, and weekly biological changes in hs-cTnT levels (Roche Diagnostics) [22]. To examine these circadian variations in hs-cTnT concentration, the authors conducted 2 separate studies. The target of the research included type 2 diabetes mellitus patients without acute CVD. In the first study, blood sampling ($n = 23$) was performed through a venous catheter installed in the anterior ulnar veins 5 minutes before each standard meal (breakfast-8-30, lunch-12-30, dinner-17-00), 90 and 150 minutes after each meal. Thus,

each patient delivered 9 bioassays [22].

In a second study, to assess the diurnal variation, the researchers performed hourly hs-cTnT measurements in 7 patients, starting at 8-30 am (before breakfast) and completing at 9-30 am the next day. Thus, 25 measurements were made for each patient during this period of time. Patients followed a standard daily routine (diet and sleep), and night blood draws were performed without sleep disturbance. According to the results obtained, the researchers found that hs-cTnT concentrations do not vary by chance, but express certain tendencies: the maximum concentration was observed in the morning (8-30), while the hs-cTnT level decreased during the day, and in the evening (19-30) a smooth increase resumed. Thus, the concentration of hs-cTnT at time 8-30 a.m. significantly exceeded the evening values: median = 11.8 ng/L (interquartile interval: 9.3 to 15.2 ng/L) versus median = 8.6 ng/L [interquartile interval: 6.7 to 10.8 ng/L]; $P < 0.001$, respectively. It is estimated that, on average, the hs-cTnT level decreased by 24% over this period of time [22]. It is noteworthy that a similar pattern in the form of a gradual decrease during the day was previously noted for another marker (cardiac enzyme), namely, creatine kinase [23].

Another work of L. Klinkenberg and colleagues was devoted to circadian rhythms hs-cTnT and hs-cTnI. The authors found hs-cTnT circadian rhythms characterized by higher concentrations in the morning (about 16.2 ng/L at 8-30 am) and lower levels in the evening (about 12.1 at 7-30 pm). Besides, individuals with the highest hs-cTnT concentrations demonstrated the largest amplitude of daily fluctuations, as evidenced by the close correlation between the hs-cTnT concentration in the morning and the range of individual changes in hs-cTnT values over a 25-hour period ($r = 0.70$; $P < 0.001$) [24]. However, unlike hs-cTnT, hs-cTnI showed no typical statistically significant differences in values during the day.

The results obtained by L. Klinkenberg are in good agreement with the data of N. Linden *et al.*, who described an interesting clinical case [25]. Significant circadian variations in hs-cTnT concentration were found in an elderly patient with severe chronic kidney disease (estimated glomerular filtration rate = 14 mL/min/1.73 m²). Determination of hs-cTnT and hs-cTnI in the blood was carried out hourly for 25 hours (from 8-30 am the previous day and until 8-30 am the next day). The initial concentration of hs-cTnT in CKD patient (147.7 ng/L), in contrast to the initial concentration of hs-cTnI (10.3 ng/L), was more than 10 times higher than the values of the 99th-percentile (14 ng/L). The levels of hs-cTnT, in contrast to hs-cTnI, were “chronically” increased throughout the measurement period (several times exceeding the values of the 99th-percentile) (Fig. 2). The hs-cTnT concentrations in CKD a patient showed a circadian rhythm corresponding to the cosine model according to the cosine rhythmometry method

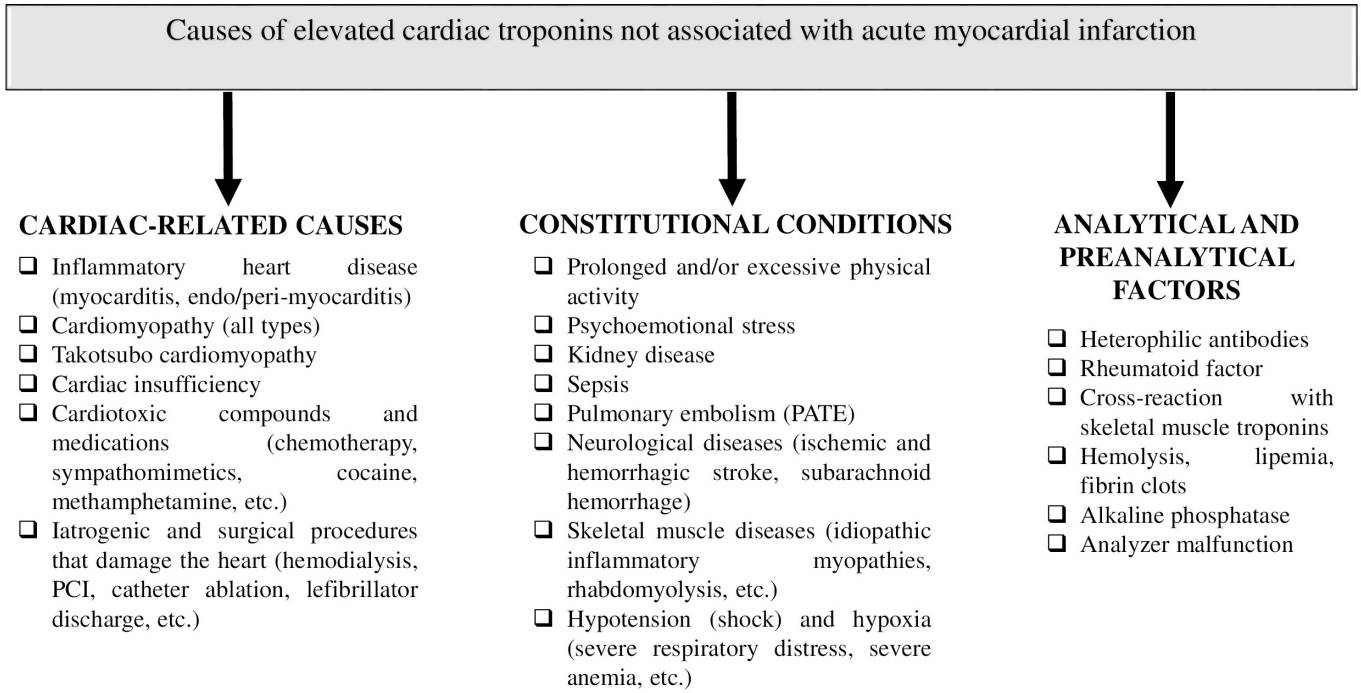


FIGURE 1. Ultimate reasons for hs-cTnI и hs-cTnT increase, apart from AMI according to [8, 9] amended and revised.

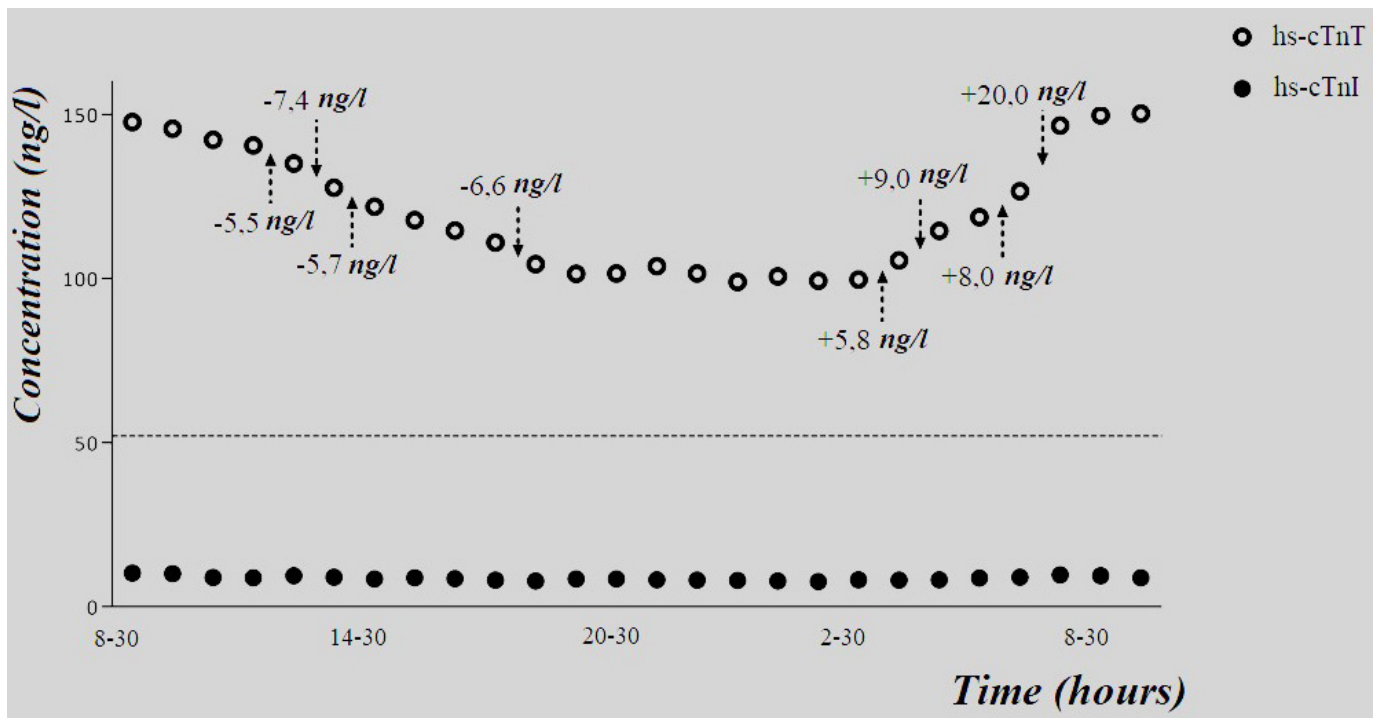


FIGURE 2. Circadian fluctuations in concentration of hs-cTnT and hs-cTnI, as per [25] amended and revised. Notes. The hs-cTnT concentration curve shows one-hour changes that exceed the 1-hour delta-changes according to the recommended ESC 1-hour algorithms. The dashed line marks the hs-cTnT level (52 ng/L) for the quick exclusion of AMI without ST-segment elevation following the current diagnostic algorithms recommended by ESC [2].

developed by W. Nelson *et al.* [26] ($R^2 = 0.90$) with 50.9 ng/L being a maximum change in concentration within 24 hours. In contrast, hs-cTnI levels remained practically unchanged over time with a maximum difference of just 2.6 ng/L over the course of a day and no visual match to the cosine model. Notably, the concentration of hs-cTnT exceeded not only the 99th-percentile baseline level, which is, incidentally, typical

for most chronic kidney disease patients [27] but also delta-changes used in modern 1- and 3-hour algorithms for AMI diagnostics, developed by experts from European Society of Cardiology (ESC) [2, 28, 29]. According to these algorithms, if the level of hs-cTnT (Roche diagnostics) is 52 ng/L upon admission to a hospital with suspected AMI, then AMI is diagnosed and the required amount of treatment is performed

according to the protocol without additional serial measurements. Also, the 1-hour delta changes (> 5 ng/L) used in the diagnosis of AMI by ESC for this test system were exceeded in the mentioned patient eight times a day (especially around noon and early morning). Thus, in contrast to the results of studies by L. Klinkenberg *et al.* [22, 24], the data of this study indicate that the natural circadian rhythms of hs-cTnT can directly affect the accuracy of AMI diagnosis when the rapid diagnostic algorithms recommended by the ESC are applied [23].

Despite several consistent results regarding the existence of hs-cTnT circadian rhythms, hs-cTnI determination methods do not record the same. Thus, K. Wildi *et al.*, studying the levels of hs-cTnI, used three analysis methods (Abbott Architect, Siemens Ultra, Beckman Accu) and did not reveal significant differences in morning and evening troponin I level in the same patients [30]. However, given the huge variety of existing methods for determining hs-cTnI, the presence of circadian changes in hs-cTnI cannot be completely ruled out in the study of blood serum by other immunoassays.

It is also worth noting an important drawback of the clinical studies conducted on the study of hs-cTnT circadian rhythms: a small sample of examined individuals, which limits the output clinical and diagnostic value. An important factor that seems to restrict the conduct of large studies on the hs-cTnT and hs-cTnI circadian rhythms is their cost. So, for example, to assess circadian rhythms (the hourly study of troponins) in 100 subjects, it is necessary to conduct about 2.5 thousand analyzes. Nevertheless, such large studies are urgently needed for reliable assessment of the circadian rhythm impact on the accuracy of early CVD detection (screening) and algorithms for the AMI diagnosis. The second important restriction in assessing the significance of the cardiac troponins circadian rhythms is a large number of manufacturers of high-sensitive test systems [31], possessing different analytical characteristics and, probably, the effect of circadian rhythms on the diagnostic value will differ depending on test system.

3. Possible mechanisms of the formation of circadian fluctuations in the concentration of cardiac troponins

Elucidation of the causes and mechanisms underlying the formation of circadian fluctuations in the levels of cardiac troponins is extremely important since it allows to definitively establishing whether it is necessary to take into account circadian variations in the concentrations of these cardiomarkers in routine clinical practice.

A relation to circadian changes in the physiology of the CVS and the hemostatic system is proposed as a possible explanation for the increased levels [32–37]. For example, Soviet and foreign scientists more than 50 years ago established that soon after awakening healthy patients demonstrate body temperature and blood pressure rise during the day, while in the evening when preparing for sleep a decrease in these parameters is contrarily noted [32, 33]. Later, the circadian rhythm was also described for several other indicators of CVS and the hemostatic system: heart rate (HR), the activity of the sympathetic nervous system, vascular resistance, renin-angiotensin-

aldosterone system, coagulation hemostasis enzymes activity, platelet aggregation, and activity of the fibrinolysis system [32–37]. All the above components exhibit peak activity in the morning hours, which is necessary for a normal healthy individual to maintain an optimal wakefulness period. It is noteworthy that the peak activity of these parameters also coincides with the maximum concentration of hs-cTnT during the day, which may indicate their possible effect on the release of cardiac troponin molecules from myocardial cells.

Studies analyzing the effect of circadian rhythms on the severity and prognosis of AMI are quite interesting [38–42]. According to some data, circadian fluctuations of the sympathoadrenal system, clotting, and the endocrine system activity may coincide with circadian variations in the size of the necrotic focus in AMI, which also indirectly indicates the importance of these systems activity to the regulation of the degree of myocardial damage and the level of cardiomarkers in the blood serum. Thus, according to a retrospective study, the infarction size depends on the time of day: the largest size of the AMI zone is observed in patients admitted in the morning [38]. In another study by Arroyo Úcar *et al.* [39], patients with AMI symptoms were divided into two groups depending on the time of admission: 1) 0-12 hours; 2) 12-24 hours. Patients of the first (“morning”) group had a significantly higher concentration of cardiac troponin I compared with the second group (70.85 ± 16.38 versus 60.90 ± 22.92 ng/mL, respectively, $P = 0.003$), which indicates more severe AMI in the first group. And according to multivariate analysis, the onset of AMI in the time interval 0-12 hours turned out to be an independent predictor of the size of the infarction zone (odds ratio 1.133, 95% confidence interval 1.012-1.267, $P = 0.01$) [39].

Yu. Tsareva and colleagues reported on the existence of circadian rhythms of thyroid hormones and cortisol (in most patients morning concentrations are higher than in the evening hours), which is associated with a more severe clinical picture of CVD [19]. Thyroid hormones are known to potentiate the effect of catecholamines on the heart, increasing heart rate. An increase in heart rate, in turn, leads to a shortening of the myocardium relaxation period (diastole), when the myocardium blood filling happens. Reportedly, the heart rate is associated with the cardiac troponins level. Some researchers even reported the presence of a close correlation between heart rate and troponin T concentration [43]. Considering the work of Yu. Tsareva *et al.* (which states that cortisol concentrations are higher in the morning) [19] and the study by A Lazzarino *et al.* (where cortisol values are shown to be associated with hs-cTnT levels) [13], it can be assumed that cortisol is also one of the important factors contributing to circadian (diurnal) differences in hs-cTnT concentration in patients.

The reason for the differences in the existence of circadian rhythms hs-cTnT and hs-cTnI remains unclear. Although, it should be once again emphasized that due to the wide variety of methods for analyzing troponin I, the absence of circadian rhythms in the study by several methods (Abbott Architect, Siemens Ultra, Beckman Accu) [24, 25, 30] is not a reason to believe that the same will be typical for other immunoassays. More research is needed to finally shed light on the existence of clinically significant hs-cTnT and hs-cTnI circadian rhythms.

4. Conclusions

Thus, according to several recent studies, rhythmic daily fluctuations in concentration are peculiar of hs-cTnT: maximum values are observed in the morning, after which they gradually decrease during the day, and then again there is a gradual increase to morning values. According to some data, hs-cTnT circadian rhythms can have a significant impact on the accuracy of CVD early detection (screening) and even the diagnosis of AMI. Additional studies using larger samples are essential to more accurately assess the impact of hs-cTnT circadian rhythms on rapid algorithms for the AMI diagnosis. These studies will make it possible to finally decide whether, in addition to gender features of the 99th-percentile, it is worth introducing circadian features of the 99th-percentile and delta values of hs-cTnT depending on the time of patient admission.

The mechanisms underlying the formation of circadian fluctuations in the concentration of cardiac troponins are complicated in nature, including changes in the functioning of the cardiovascular system (increased heart rate, vascular resistance, blood pressure), hemostasis system (coagulation hemostasis enzymes activity, platelet aggregation, and fibrinolysis activity), as well as endocrine system (renin-angiotensin-aldosterone system, the activity of the thyroid gland and adrenal cortex).

AUTHOR CONTRIBUTIONS

Aleksey M. Chaulin and Dmitry V. Duplyakov designed the study. Aleksey M. Chaulin and Dmitry V. Duplyakov collected the data. Aleksey M. Chaulin analyzed the results and drafted the manuscript. Dmitry V. Duplyakov edited the manuscript.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

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