

## High-sensitivity cardiac troponins in health and disease

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### Cardiac troponins and myocardial infarction

#### *Acute myocardial infarction*

Acute myocardial infarction (AMI) is characterized by cardiomyocyte death due to prolonged ischemia (1). The initial step in the development of AMI is an imbalance between the oxygen demand of the myocardium and the oxygen supply by the coronary arteries, which is generally the result of a coronary occlusion (2, 3). Early identification of patients is of critical importance to initiate medical treatment and management. A clinical assessment of myocardial ischemia, consisting of an electrocardiogram and detailed evaluation of chest discomfort, is indispensable in the diagnostic workup of AMI. While these clinical tools have insufficient accuracy of their own, the biochemical hallmark of the diagnostic workup of AMI is the measurement of cardiac troponins (cTn) in blood (1-7).

#### *(Patho-)physiology of cardiac troponins*

cTn are components of the thin filament of the contractile apparatus of cardiomyocytes and fulfill a critical role in the regulation of excitation-contraction coupling in the heart (Figure 1). The troponin complex is composed of three protein subunits; cardiac troponin I (cTnI), cardiac troponin T (cTnT) and troponin C (TnC). cTn are compartmented in the cardiomyocyte as structurally bound to actin filaments, with possibly a small proportion (3 - 8%) existing as unbound protein in the cytosol (9-11). Whereas cardiac and skeletal muscle share the TnC isoform, cTnI and cTnT have unique cardiac isoforms (12). This makes both cTnI and cTnT suitable for diagnostic use in cardiac pathology.

Following an AMI, there is a distinct release kinetics of cTn into the circulation (Figure 2). The cTnT release curve is typical biphasic; with an early steep rise in concentrations, followed by a high peak and gradual decrease over several days after the onset of myocardial ischemia (13-14). It has been hypothesized that the initial increase of cTnT results from the release of the cytosolic pool. Subsequently, the second prolonged elevation has been suggested to result from

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the breakdown of the contractile apparatus (9, 10, 15). In contrast to cTnT, cTnI concentrations generally decrease more rapidly after reaching peak concentrations, resulting in a monophasic pattern. The exact reason for this different release kinetics is unknown, although cTnT differs from cTnI with respect to a higher molecular weight and higher fraction of unbound cTnT (16). Hence, in conjunction with typical clinical symptoms of myocardial ischemia, detection of elevated circulating cTnI or cTnT above the 99<sup>th</sup> percentile of a healthy reference population confirm a diagnosis of AMI.

#### *High-sensitivity cardiac troponin assays*

Recent advances in assay technology have led to an enhancement in the analytical performance of the troponin assays and therefore an improved ability to detect very low circulating levels of cTn with a higher precision. Therefore, these so-called (high-) sensitivity assays are therefore able to detect cTn in healthy individuals from the general population, enabling a precise determination of the 99<sup>th</sup> percentile cut-off value for the diagnosis of AMI (17). cTnT assays are only produced by a single manufacturer (Roche Diagnostics), due to intellectual property restriction. This is in contrast to cTnI, where more than twenty assays are nowadays commercially available

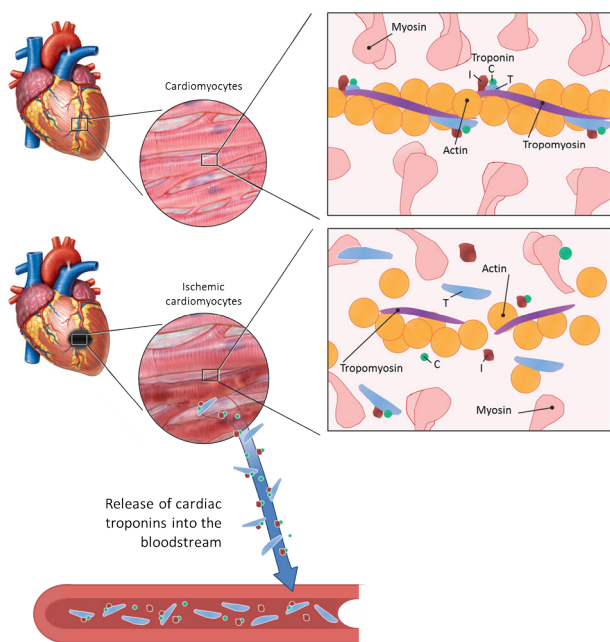
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**Figure 1.** Release of cardiac troponins following ischemic cardiac injury. A. Physiology of the healthy myocardium. The cTn complex, consisting of troponin C (TnC), cardiac troponin T (cTnT) and I (cTnI) is structurally bound to the actin filament. A small proportion of cTn possibly exists as unbound protein in the cytosol. B. Following myocardial damage, cTn are released into the bloodstream.

with different analytical characteristics (18, 19). The analytical characteristics of the troponin assays used throughout this thesis are summarized in table 1.

To classify troponin assays according to their analytical performance, Apple et. al. proposed a two criteria 'scorecard' (20). Based on the recommendation of the current universal definition of AMI to measure the 99<sup>th</sup> percentile value with an optimal imprecision, assays are designated as 'not acceptable' (coefficient of variation [CV] >20%), 'clinically usable' (CV >10 - ≤20%) or 'guideline acceptable' (CV ≤10%). In addition, four assay levels are defined according to the percentage of healthy reference individuals who have a measurable cTn value: 'level 1' (contemporary, <50%), 'level 2' (first generation high-sensitivity [hs], 50 - 75%), 'level 3' (second generation hs, 75 - 95%), and 'level 4' (third generation hs, >95%). For example, both the hs-cTnT assay of Roche Diagnostics and hs-cTnI assay of Abbott Diagnostics are designated as 'level 4 guideline acceptable assays' (17,20).

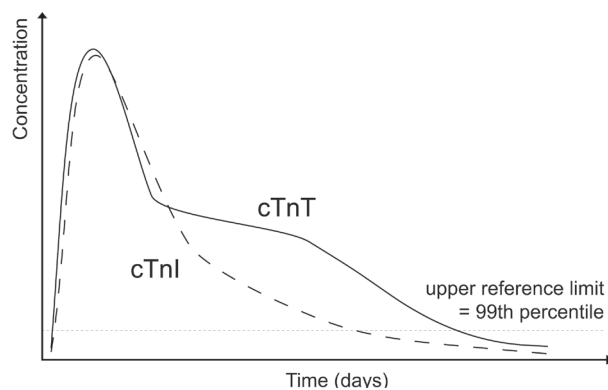
**Table 1.** Analytical characteristics of the troponin assays used throughout this thesis.

Troponin	Manufacturer	LoB <sup>a</sup> , ng/L	LoD <sup>b</sup> , ng/L	99 <sup>th</sup> percentile, ng/L	10% CV, ng/L
hs-cTnT	Roche Diagnostics	3.0	5.0	14.0	13.0
hs-cTnI	Abbott Diagnostics	0.7 - 1.3	1.1 - 1.9	26.2	4.7
s-cTnI	Beckman Coulter	<10.0	10.0	40.0	40.0

<sup>a</sup> The highest concentration that can be observed (with a 95% probability) for a sample that does not contain the analyte of interest.

<sup>b</sup> The lowest concentration of an analyte that can be detected (with a 95% probability).

LoB; limit of blank, LoD; limit of detection, CV; coefficient of variation, s-cTnI; sensitive cardiac troponin I.

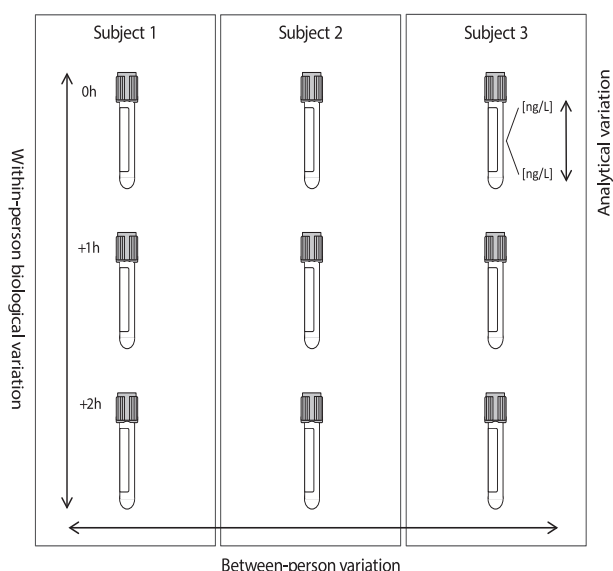


**Figure 2.** Release curve of cardiac troponins after the onset of symptoms of myocardial ischemia. In general, cTnI and cTnT display a monophasic and biphasic release curve, respectively. This figure was used with permission of Creative Commons (14).

### Diagnosis of myocardial infarction by high-sensitivity troponin assays

Several large clinical trials have demonstrated that the advent of the high-sensitivity troponin assays has resulted in an increase in the diagnostic accuracy at the time of patient presentation to the emergency department (21,22). This superior performance of hs-cTnI and hs-cTnT in comparison to the contemporary assays is the result of an improved diagnostic sensitivity. These assays allow therefore a rapid rule-in of AMI and reduce morbidity and mortality through early initiation of evidence-based treatment and management (23).

However, the improved sensitivity for AMI has come at a cost of specificity. Although elevated circulating hs-cTn indicate myocardial injury, cTn are not exclusively released as a result of ischemic cardiomyocyte death (13). Any acute or chronic condition that injures cardiomyocytes may lead to measurable and/or elevations of circulating hs-cTn (8,13,24). Acute conditions that for example can elevate hs-cTn include acute decompensated heart failure, pulmonary embolism, sepsis, endocarditis and stroke (25-29). In addition, persistent low-level elevations in hs-cTn are frequently measured among patients with chronic conditions such as chronic heart failure, stable coronary artery disease, type 2 diabetes mellitus and chronic kidney disease (30-33). While hs-cTnI and hs-cTnT are not specific for any particular mechanism of myocardial injury, solitary elevations of



**Figure 3.** Design of biological variation studies. Biological variation studies are based on the collection of series of blood samples from several individuals to calculate between-person variation, within-person biological variation and analytical variation.

hs-cTn with levels exceeding the 99th percentile limit are not distinctive between cTn release resulting from an acute or chronic event. Therefore, the current universal definition of AMI is based on the detection of a rise and/or fall of cTn (cTnI or cTnT) above the 99th percentile of a healthy reference population together with evidence of ischemia either by clinical symptoms, electrocardiographic findings or imaging techniques (1).

### Serial testing of cardiac troponins

The critical tool in the diagnostic workup of AMI is serial testing and the assessment of kinetic changes in hs-cTn. The detection of a rise and/or fall of hs-cTn in the definition of AMI is based on the assumption that concentrations of hs-cTn tend not to change acutely in individuals with chronic conditions (1). The universal definition of AMI however does not provide a substantiated guidance regarding the magnitude of the change required to discriminate between AMI-induced cTn release and other causes of circulating cTn (1). In the past few years, several biological variation studies have been published addressing this unmet clinical need. These studies are generally based upon healthy subjects and collected series of blood samples at standardized time intervals while minimizing pre-analytical variation (34). Subsequently, aliquots are stored appropriately and hs-cTn are measured in duplicate fashion in a single analytical run. The variance constituents of this dataset can be calculated accordingly and are composed of analytical variation ( $CV_A$ ), biological variation or within-person variation ( $CV_i$ ) and between-person variation ( $CV_G$ ) (Figure 3). This design enables to derive so-called reference change values (RCV), according to the formula:  $RCV = \sqrt{2} \cdot Z \cdot \sqrt{(CV_A^2 + CV_i^2)}$ , where Z is a constant, depending on the statistical probability (usually a Z-score of 1.96 for 95% probability) (35).

The statistically calculated threshold-value distinguishes 'true changes' from 'noise' or random physiological fluctuations. All conducted studies so far have measured the biological variation of hs-cTn over a short time window (4 - 6 h) and have been unable to verify the general, critical pre-condition of using RCV; that serial values of hs-cTn show true random variation without correlation between successive results (34,36-39).

### Prognostic value of cardiac troponins

It is inevitably clear that elevated levels of hs-cTn are associated with an increased risk of developing cardiovascular events and all-cause or cardiovascular mortality, regardless of an acute or chronic setting of myocardial injury, such as acute chest pain, acute dyspnea, type 2 diabetes, stable coronary artery disease, and chronic kidney disease (32,33,40-42). In addition, the detection of hs-cTn in almost every individual of the general population has expanded the possible use of cTn from diagnostic care to risk stratification and prognostic medicine. It has become clear that even in the general population and when adjusted for traditional cardiovascular risk factors, hs-cTn are important predictors for an adverse outcome (43-45). Nevertheless, this prognostic value of hs-cTn in the general population has not been systematically assessed.

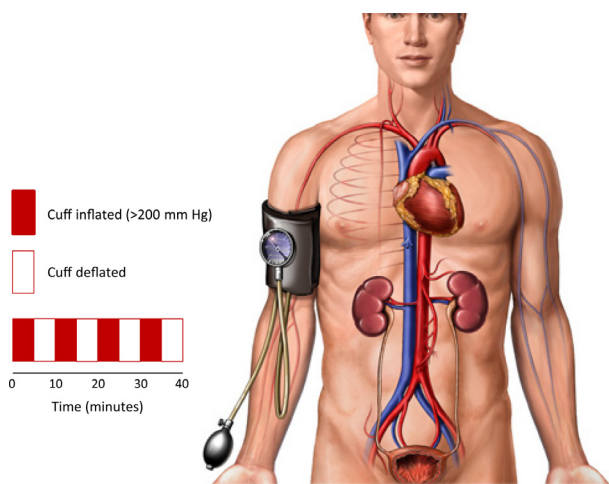
### Exercise-induced cardiac troponins release

#### *Elevation of cardiac troponins with endurance-type exercise*

Prolonged endurance-type exercise by recreational athletes, such as (half-)marathon running and cycling, has been associated with an acute impairment in cardiac function and release of cTn into the circulation (46-50). The kinetics of exercise-induced cTn release consists of an initial peak during exercise, followed by a second peak 3 - 6h upon cessation of exercise (51). Within 24 - 48h, circulating cTn decrease significantly and generally normalize to baseline concentrations (49,51-55). Post-exercise concentrations of hs-cTn can vary tremendously among athletes, ranging from concentrations below the diagnostic cut-off for AMI to more than ten times the 99th percentile limit (50). In an attempt to understand the heterogeneity of exercise-induced cTn release, several studies have examined possible predisposing factors, such as exercise modalities or athletes' characteristics. These studies have reported that the cTn response to exercise is strongly related to the intensity and the duration of the exercise and inversely associated with the training experience of the athlete (56-61).

#### *Potential mechanisms for exercise-induced troponin release*

Since it is well-known that regular exercise training reduces cardiovascular disease risk (62,63), it seems counter-intuitive to define circulating cTn as a result of irreversible cardiomyocyte injury. Nevertheless, there are no conclusive data supporting a pathological or



**Figure 4.** Remote ischemic preconditioning. The remote ischemic preconditioning stimulus consists of the inflation of a blood pressure cuff on an upper limb to induce transient ischemia, followed by cuff deflation.

physiological nature of cTn release in response to exercise (46). There are two prevailing hypotheses: the physiological concept is based on the assumption that exercise-induced cTn release reflects reversible cardiomyocyte injury, characterized by a change in cardiomyocyte permeability and subsequent release of the cytosolic cTn pool, followed by cardiomyocyte repair and resulting in myocardial hypertrophy (46). This is in contrast to the pathological model, which is based on the hypothesis that exercise-induced cTn release is the result of irreversible cardiomyocyte injury, followed by scarring and fibrotic replacement of the myocardium (46).

#### *Strategies to study troponin release in response to exercise*

Since intensive endurance-type exercise involves the integration of muscular, cardiovascular and neurological processes that function cooperatively to transfer energy into velocity and power (64), it is challenging to investigate *in vivo* contributing mechanisms responsible for the release of cTn associated with endurance-type exercise. Several components of the altered physiological environment of the cardiomyocyte during exercise have been suggested, such as an imbalance in oxygen supply and demand, elevations in reactive oxygen species and increased mechanical stress (65,66).

It has been demonstrated that exhaustive exercise results in the formation of reactive oxygen species in the myocardium (67,68). Furthermore, the significant association of oxidative stress markers with levels of cTn in these exercise animal models, has resulted in the hypothesis that oxidative stress contributes to cTn release in the setting of prolonged endurance-type exercise (69). Supporting endogenous antioxidant systems with additional doses of antioxidants could therefore provide an important strategy to examine the role of reactive oxygen species as an underlying biological mechanism for exercise-induced cTn release.

The contribution of an imbalance in oxygen supply and demand to cTn release following prolonged exercise can be studied by remote ischemic preconditioning (RIPC). RIPC is a powerful non-invasive cardio-protective strategy, whereby brief episodes of non-lethal ischemia followed by reperfusion of one tissue or organ leads to the protection of another visceral organ against an injurious ischemic insult (70-71). This intervention is safe, extremely simple and requires only a blood pressure cuff applied to the upper or lower limb. The RIPC stimulus is achieved by inflating the cuff to >200 mm Hg and then deflated after a predetermined period of time (typically 5 min) for four cycles (Figure 4). This strategy has been successfully translated to humans, and powerful cardiomyocyte protective effects have been reported in cardiac surgery and angioplasty, measured by post-surgery levels of hs-cTn and all-cause mortality (72-76). The exact nature of how challenging one vascular bed transduces to protection in another distant visceral organ is the subject of intense research. Two potential pathways have been postulated, a humoral pathway, involving a blood-borne mediator, and secondly a neuronal pathway (77,78). If an imbalance in oxygen supply and demand during prolonged endurance-type exercise contributes to cTn release, applying a RIPC stimulus would result in a decrease of post-exercise hs-cTn.

#### **Outline of this thesis**

Cardiac troponins (cTn) are currently the most sensitive markers for the detection of myocardial injury and are therefore the biochemical gold standard to diagnose acute myocardial infarction (AMI). Major analytical refinements in the troponin assays have resulted in more sensitive and precise information regarding circulating levels of cardiac troponin I (cTnI) and T (cTnT). This resulted in the detection of previously unnoticed levels of cTn in a wide spectrum of acute and chronic diseases, that are inevitably associated with adverse outcomes. The critical tool in the diagnostic workup of AMI is therefore serial testing and the assessment of kinetic changes of hs-cTn. On the other hand, the accurate detection of cTn in almost every healthy individual of the general population has expanded the possible use of cTn from acute cardiac care to risk stratification. The single exception where it is unclear whether cTn are linked to adverse outcomes is the release of cTn during and after endurance-type exercise.

The aim of the first chapters of this thesis is to improve the interpretation of serial hs-cTn measurements. **Chapter 2** challenges the critical assumption that hs-cTn fluctuate randomly in subjects with chronically elevated levels of hs-cTn. Specifically, this chapter shows that circulating hs-cTnT exhibits diurnal oscillation in male subjects with type 2 diabetes. **Chapter 3** validates that the diurnal hs-cTnT rhythm is a general phenomenon, independent of sex and glucose metabolism status. The clinical impact of the diurnal rhythm on the diagnostic accuracy of hs-cTnT for AMI is additionally described in this chapter. Furthermore,

this chapter evaluates whether (hs-)cTnI assays are equally affected by the clock time.

**Chapter 4** describes a systematic assessment of the prognostic value of hs-cTn in the general population. By a meta-regression analysis, this chapter aims to compare the prognostic performance of hs-cTnI and hs-cTnT.

The objective of the last chapters of this thesis is to study exercise-induced cTn release. In order to understand the heterogeneous release of cTn following an acute bout of endurance-type exercise, a highly standardized assessment of the reproducibility and predisposing factors of cycling-induced hs-cTnT levels are described in **Chapter 5**. The effect of two interventions on cTn release following prolonged exercise is evaluated in the following two chapters. **Chapter 6** describes the effect of antioxidant supplementation on exercise-induced hs-cTnT levels in cyclists. **Chapter 7** investigates the effect of remote ischemic preconditioning on the release kinetics of hs-cTnI and hs-cTnT following a 30 km running trial. **Chapter 8** contains a general discussion of the work presented in this thesis and directions for future research are provided.

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