

# Cardiac troponin release following coronary artery bypass grafting: mechanisms and clinical implications

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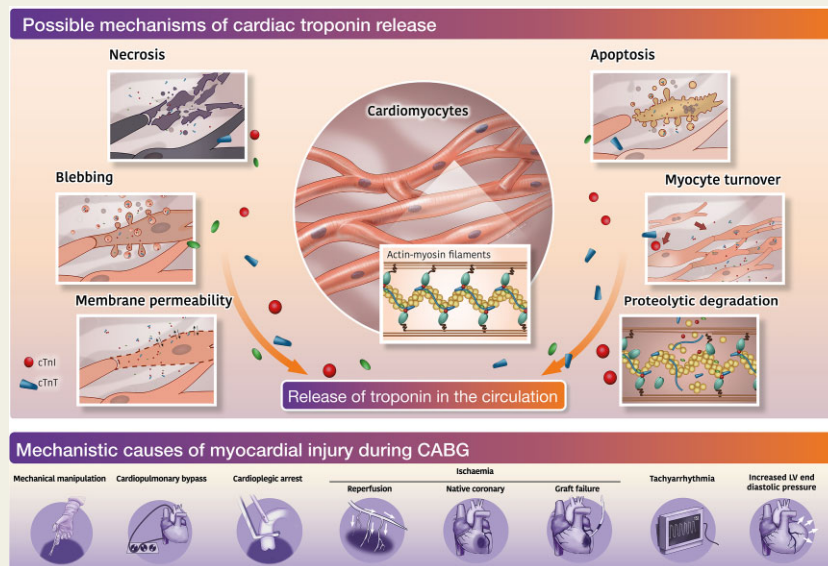
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## Graphical Abstract



Possible mechanisms of cardiac troponin release and their mechanistic causes in patients undergoing CABG (Barry van Varik, Pulse Medical Art). CABG, coronary artery bypass grafting; cTnI, cardiac troponin I; cTnT, cardiac troponin T; LV, left ventricular.

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## Abstract

The use of biomarkers is undisputed in the diagnosis of primary myocardial infarction (MI), but their value for identifying MI is less well studied in the postoperative phase following coronary artery bypass grafting (CABG). To identify patients with periprocedural MI (PMI), several conflicting definitions of PMI have been proposed, relying either on cardiac troponin (cTn) or the MB isoenzyme of creatine kinase, with or without supporting evidence of ischaemia. However, CABG inherently induces the release of cardiac biomarkers, as reflected by significant cTn concentrations in patients with uncomplicated postoperative courses. Still, the underlying (patho)physiological release mechanisms of cTn are incompletely understood, complicating adequate interpretation of postoperative increases in cTn concentrations. Therefore, the aim of the current review is to present these potential underlying mechanisms of cTn release in general, and following CABG in particular (*Graphical Abstract*). Based on these mechanisms, dissimilarities in the release of cTnI and cTnT are discussed, with potentially important implications for clinical practice. Consequently, currently proposed cTn biomarker cut-offs by the prevailing definitions of PMI might warrant re-assessment, with differentiation in cut-offs for the separate available assays and surgical strategies. To resolve these issues, future prospective studies are warranted to determine the prognostic influence of biomarker release in general and PMI in particular.

## Keywords

Cardiac troponin • Coronary artery bypass grafting • Cardiac surgery • Myocardial infarction • Periprocedural myocardial infarction

## Introduction

Biomarkers are the cornerstone of the diagnosis of primary myocardial infarction (MI), but their clinical significance following coronary artery bypass grafting (CABG) is less well understood. Indeed, CABG inherently induces the release of cardiac biomarkers, as reflected by significant cardiac troponin (cTn) concentrations in patients with uncomplicated postoperative courses.<sup>1</sup> Although the serial postoperative measurement of cTn is recommended by most contemporary consensus statements,<sup>2</sup> the underlying CABG-related release mechanisms of cTn are insufficiently studied, and only partly known to the clinician.

Therefore, in the present review, we aim to provide an overview of the potential release mechanism and evaluate the clinical applicability of cTn in the perioperative setting following CABG.

## Heterogeneity in definitions of periprocedural myocardial infarction

Several definitions of periprocedural MI (PMI) exist, which were developed to retrospectively identify patients with a relevant PMI following surgery, to improve patient care and quality assessment, and to use in clinical trials. The most prevailing definitions comprise the fourth universal definition of MI (UDMI-4),<sup>2</sup> the definition proposed by the Society for Cardiovascular Angiography and Interventions (SCAI),<sup>3</sup> and the definition as stated by the second Academic Research Consortium (ARC-2).<sup>4</sup>

These definitions exhibit some overlap but differ regarding important issues: the use of solitary biomarker cut-offs for diagnosing PMI, and a difference in the preference for specific biomarkers. The definitions and their conflicting conceptions are summarized in *Table 1*. Of note, these differing definitions significantly affect the clinical practice and endpoints of major clinical studies evaluating the outcome of CABG surgery.<sup>5–7</sup>

Especially regarding the use of solitary (*peak*) biomarker cut-offs, these definitions contradict.<sup>3,4,8</sup> When using solitary biomarker cut-offs, contemporary studies have demonstrated these cut-offs to be far too conservative.<sup>9</sup> Of note, for cTn, data on isolated cut-offs in CABG patients are scarce and most of the recommendations are based

on patients undergoing percutaneous coronary interventions. Moreover, the relationship between a 70-fold cTn increase and long-term survival was even doubtful.<sup>10</sup> Also, these definitions differ in terms of preoperative biomarker availability.<sup>2,3</sup> Therefore, the aforementioned multiplications of reference values only apply when the preoperative (baseline) concentration is below the upper reference limit (URL).<sup>2</sup> When baseline concentrations are in the supranormal range, relative increases can be used (>20% increase). Of note, these should always be in conjunction with a cTn concentration of >10× URL and supportive electrocardiogram (ECG) and/or imaging findings.<sup>2</sup>

The current definitions of PMI do not provide recommendations for patients operated on in an acute setting, with ongoing MI. Still, this comprises a relative minority of patients undergoing CABG (only 3.3% of CABG procedures are classified as emergent<sup>11</sup>).

In a contemporary, real-world analysis, 90.9% of patients undergoing CABG fulfilled the MI-5 criteria in terms of available values to be analysed using the UDMI-4, 97.7% by the SCAI definition, and 91.4% by the ARC-2 criteria.<sup>12</sup>

## The rationale for perioperative biomarker measurements

By convention, periprocedural biomarker measurements should aim to (i) identify patients suffering from a PMI and set a timely indication for diagnosis and re-intervention, and (ii) monitor the extent of myocardial injury over a longer period to assess the patient's prognosis. It should be noted that these objectives might seem to overlap, but this is not always the case. Indeed, the term *prognosis* is open to multiple interpretations, as it might relate to major adverse events,<sup>12</sup> 30-day mortality,<sup>9</sup> and/or longer term survival.<sup>13</sup> Given this variability, it may actually be not feasible to equate diagnosis with prognosis.

As demonstrated by Thielmann and colleagues,<sup>14</sup> the kinetics of biomarker release are different following graft-related vs. non-graft-related PMI. Therefore, biomarker measurements should preferably aid in identifying patients with (graft-related) PMI in a very early phase to allow for timely intervention. Although the general recommendation is to intervene within 12 h of ischaemia onset, some studies have suggested a

**Table 1** Contemporary definitions of periprocedural myocardial infarction

	UDMI-4 <sup>2</sup>	SCAI <sup>3</sup>	ARC-2 <sup>4</sup>
Preferred biomarker	cTn	1. CK-MB 2. cTn (in the absence of CK-MB)	cTn
Definition incorporating isolated biomarker concentrations (yes/no)	–	+	+
Isolated biomarker cut-offs	NA	1. > 10× URL 2. > 70× URL	>70× URL
Biomarker cut-offs warranting supporting evidence	>10× URL	1. > 5× URL 2. > 35× URL	>35× URL
<b>Supporting evidence</b>			
ECG <sup>a</sup>	+	+	+
RWMA on imaging	+	–	+
Angiographic findings	+	–	+

ARC-2, Second Academic Research Consortium; ECG, electrocardiography; LBBB, left bundle branch block; NA, not applicable; RWMA, regional wall motion abnormalities; SCAI, Society for Cardiovascular Angiography and Interventions; UDMI-4, fourth universal definition of myocardial infarction; URL, upper reference limit.

<sup>a</sup>New Q-waves (UDMI, ARC-2) and/or LBBB (SCAI).

beneficial effect of delayed revascularization in terms of infarct size reduction and prevention of electrical instability.<sup>15</sup>

Biomarker measurements are the cornerstone of the diagnosis of PMI, but supporting evidence might be crucial.<sup>12,16</sup> These supporting findings comprise either ECG or imaging findings. Especially in studies evaluating postoperative cTn values with delayed enhancement cardiac magnetic resonance (DE-CMR) follow up, the amount of myocardial injury identified by DE-CMR was correlated with peak cTn and predictive of adverse prognosis.<sup>17,18</sup> Furthermore, higher cTn concentrations were associated with transmural (graft-related) infarction.<sup>19</sup> Still, in the direct postoperative phase, DE-CMR is less feasible given the prolonged supine position of the patient.

Although the requirement for supporting findings is a widely debated topic, and recent pivotal studies have refuted an association of isolated peak biomarker release-based definitions and impaired prognosis,<sup>12,16</sup> the need for supporting ECG and imaging evidence is beyond the scope of the current review.

## Biomarkers previously used for the diagnosis of periprocedural myocardial infarction

Historically, lactate dehydrogenase, myoglobin, and creatine kinase (CK) have been used to diagnose (P)MI. However, as these biomarkers are non-cardiac specific, a search for more specific markers has ensued. This search resulted in the identification of the MB isoenzyme of CK (CK-MB), and eventually in the cardiac-specific cTn as the most appropriate biomarkers for myocardial cell damage.<sup>8,20</sup> Both markers are significantly related to long-term prognosis following CABG, as

demonstrated by Domanski *et al.*<sup>13</sup>, in an elaborate meta-analysis. Still, as underlined by the contradicting definitions of PMI, there is a lack of consensus.

Creatine kinase is a cytosolic enzyme expressed in various metabolizing tissues and cell types and is involved in intracellular energy transportation. It consists of four iso-enzymes: CK-BB (primarily found in the lung and brain), mitochondrial-CK, CK-MM (primarily found in skeletal muscle), and CK-MB, primarily encountered in cardiac tissue.<sup>21</sup> The largest proportion of CK in the heart is CK-MM—CK-MB comprises between 5% and 30% of total cardiac CK, while only traces of CK-MB are found in skeletal muscle. Consequently, in cases of myocardial cell necrosis, both CK and CK-MB can be detected, but they are *not* cardiac-specific. While both enzymes are also found in skeletal muscle, the mere detection of CK-MB (84 kDa) does not exclusively reflect myocardial damage and needs to be interpreted relative to the total amount of CK released. Moreover, in patients undergoing cardiac surgery, skeletal muscle injury occurs secondary to the surgical incisions irrespective of myocardial injury. This might result in significant amounts of detectable CK-MB in the circulation. This skeletal muscle-related release can be confounding in several instances in CABG patients, especially with the use of bilateral internal thoracic artery grafts.<sup>22</sup> As CK-MB is exclusively cytosolic,<sup>23</sup> its release from the necrotic cardiomyocyte is acute after membrane disintegration. Furthermore, its levels return to baseline quite quickly.<sup>24</sup> Although some institutions and studies still exclusively use CK-MB to monitor the extent of perioperative myocardial injury, the general conception is that cTn is superior due to its cardiac specificity.<sup>2,25,26</sup>

## The use of cardiac troponin for diagnosis of periprocedural myocardial infarction

Cardiac troponin is a complex of three regulatory proteins two of which are cardiac specific (cTnI, cTnT) and one of which is non-specific C (TnC), and has a regulatory function in myocardial cell contraction and relaxation. cTnI (24 kDa<sup>27</sup>) *inhibits* the activity of actomyosin ATPase in the absence of Ca<sup>2+</sup>, preventing actin–myosin interactions and cross-bridge formation. cTnT (40 kDa<sup>28</sup>) binds *tropomyosin* and serves as the mechanical link anchoring the other cTn subunits to the thin filament.<sup>29,30</sup> As skeletal muscle troponin differs from both cTnI and cTnT in terms of amino acid composition, immunological techniques have allowed the development of immunoassays. These immunoassays use cTn-specific monoclonal antibodies to detect circulating cTn.<sup>31</sup> Advancements in the past decades have resulted in the introduction of high-sensitivity cTn assays, enabling the detection of cTn down to the femtomolar level.<sup>32</sup>

Several hypotheses exist, of which the most historical one perceives that cTn was primarily bound to myofibrils (structural cell components) and, to a far lesser degree, was located unbound in the cytosol.<sup>24</sup> This conception was used to explain the release curve of cTn: a fast release from the cytosol (the 'early releasable pool') and a slow, steady release secondary to necrosis and structural degeneration (the 'structural pool'). However, this conception has been disputed using results from more contemporary studies.<sup>33</sup> The latter data indicated that the specific cTn release characteristics might be caused by slow washout and local tissue degradation. In their model, Starnberg and colleagues<sup>33</sup> proposed cTn release to result from myofibril degeneration and washout of reversibly bound cTn (i.e. to *tropomyosin*). In that study, the presence of 'free' cTn in the cytosol was also refuted, and at least redefined as an 'early releasable pool'. The authors found the artificial extraction efficiency of cTn to differ significantly using different serum

extraction volumes, while even limited serum extraction volumes resulted in equally efficient extraction of other typical cytoplasmic cardiac damage biomarkers, such as CK-MB and myoglobin.<sup>33</sup> These findings imply a non-cytoplasmic cTn localization. Both models are used to explain sustained cTn elevation days after the event due to ongoing release secondary to infarct evolution.<sup>34</sup> Either way, both hypotheses rely on release curve characteristics and comparisons with other cytosolic biomarkers, emphasizing the need for future studies to address this critical topic. Still, it must be mentioned that all of these mechanisms and hypotheses are based on artificial experimental conditions, which might not resemble actual events in the ischaemic environment of the human heart.

Another critical determinant of cTn release and kinetics is blood flow. Indeed, in patients with non-reperfused primary MIs, an early cTn peak was absent,<sup>24</sup> or appeared later with an attenuated peak,<sup>35,36</sup> when compared with reperfused primary MIs. Although these features are relatively well studied in primary MI, less is known regarding postoperative blood flow and cTn release, which might be affected by (temporary) coronary occlusion and completeness of revascularization.

Of note, definitions of PMI require the used biomarkers to be below the URL before surgery to adequately interpret postoperative concentrations.<sup>2–4</sup> As cTn is such a specific marker for cardiovascular disease and many of the patients undergoing CABG are subjected to such a risk profile, it is imperative to determine cTn concentrations immediately prior to surgery. These baseline concentrations may be age<sup>37</sup> and sex dependent,<sup>38</sup> but they can also be increased in patients with renal disease.<sup>39</sup> Moreover, as an important number of patients undergo CABG semi-electively after an acute coronary syndrome,<sup>40</sup> baseline cTn concentrations might still be increased preoperatively.<sup>1</sup> Also, a specific disease group of patients with skeletal muscle disorders might exhibit increased cTnT concentrations that are not attributable to cardiac disease.<sup>41</sup>

As a final remark, it is important to note that the various proposed cut-off concentrations of cTnI and cTnT for relevant periprocedural myocardial injury were based on differing diagnostic and prognostic timespans. For example, in the important position paper by the ESC Joint Working Groups on Cardiovascular Surgery and Cellular Biology of the Heart,<sup>26</sup> many studies were incorporated that assessed the association between cTn and post-CABG mortality quite differently. Indeed, the diagnostic timespans ranged between measurements taken only during the first day, to daily measurements for a week. Moreover, these studies' prognostic windows ranged from major adverse events to in-hospital mortality and 6-year survival.<sup>26</sup> Likewise, in the recently published Vascular Events in Surgery Patients Cohort Evaluation (VISION) Cardiac Surgery study, only adverse events and 30-day mortality were assessed, resulting in a proposed cut-off concentration of 218× URL.<sup>9</sup> Inherently, these dissimilarities in timing also result in varying cut-off concentrations, as the accrual of (i) more patients or (ii) more events (i.e. longer follow up) might result in more sensitive and 'lower' cut-off concentrations, compared to a shorter term assessment.

## Possible mechanisms of cardiac troponin release

In the early days following the introduction of cTn, it was perceived that cTn release was exclusively caused by cardiomyocyte necrosis, and the amount of cTn release was therefore an accurate reflection of the degree of necrosis.<sup>20,42</sup> However, many contemporary studies observed

significant increases in cTn concentrations in the absence of overt myocardial cell death,<sup>43–45</sup> which warranted reconsideration of this conception. Indeed, accumulating evidence suggests that cTn is released through different pathways, with varying extents of myocardial cell damage. As postulated by White in 2011, who proposed a pathophysiological classification for these various pathways, these mechanisms comprise necrosis, apoptosis, physiological myocyte turnover, proteolytic degradation, increased cell membrane permeability, and the formation and release of membranous blebs (Table 2, Figure 1).<sup>46</sup>

Indeed, the most obvious cause of cTn release is necrosis, which, in most instances, is caused by a prolonged period of ischaemia. Necrosis is characterized by sarcolemmal disruption and subsequent release of intracellular proteins (such as cTn) into the extracellular space, systemically detectable upon reperfusion.<sup>47,54</sup> This unrestrained release of intracellular content then causes the typical necrosis-associated local inflammation. Although this type of cell death was considered to be exclusively accidental, chaotic, and unregulated, this limited concept was refuted by Degterev and colleagues<sup>55</sup> in the early 2000s. They proposed an additional necrosis-like cell death mechanism. In their elegant study, the authors observed a tumour necrosis factor- $\alpha$ -regulated, but non-apoptotic, cell death pathway with necrotic cell death morphology, and coined the term *necroptosis*. Although incompletely understood, these mechanisms seem to be induced by either the *death receptor pathway* or the *mitochondrial necrosis pathway*.<sup>56</sup> In these cases of excessive myocardial cell injury, the presence of sufficient adenosine triphosphate (ATP) seems to be the deciding factor in whether the cell proceeds to an unregulated death (in the absence of ATP), or a programmed death (in the presence of sufficient ATP).<sup>47</sup>

A more commonly known form of regulated cell death is *apoptosis*. Regardless of the pathway (i.e. *intrinsic* vs. *extrinsic* or *cell surface receptor* vs. *mitochondrial*), apoptosis is mediated by the activation of specific cysteine proteases, known as caspases.<sup>56</sup> Of note, apoptosis is characterized by the preservation of cell membrane integrity and consequent phagocytosis by macrophages. This protective feature prevents the aforementioned local inflammation process associated with necrosis. Therefore, release of cTn might only be observed if a primarily apoptotic process transitions into necrosis, secondary to potential interconnections between the various apoptosis and necrosis pathways.<sup>56,57</sup>

Another widely debated topic is the presence of physiological cardiomyocyte turnover. Previously, the heart was regarded as an organ residing in a postmitotic state. However, recent observations have suggested that cardiomyocyte turnover occurs in the absence of disease or physiological stress. Still, this process occurs at a low rate of 0%–1% of myocytes,<sup>48</sup> and is most likely sex and age dependent.<sup>58</sup> Therefore, physiological turnover seems to contribute only marginally to cTn release in general, and even less in patients undergoing CABG.

Interestingly, myocardial cell damage can cause several of these mechanisms to occur concurrently. One other mechanism is the proteolytic degradation of cTn, which might take place within the cell or in circulation by various proteases. Indeed, extracellular degradation has been observed in blood circulation,<sup>50</sup> and even *in vitro* in blood tubes by thrombin activation.<sup>51</sup> Intracellularly, injury-induced calcium influx can activate calpain or caspase-3, known to result in proteolytic cleavage of cTn intracellularly,<sup>49</sup> in a variety of proteolytic fragments.<sup>28,59</sup>

Differences in cell membrane permeability may also predispose to cTn release in various conditions. Among others, the permeability of the membrane is modulated by *integrins* (transmembrane glycoprotein receptors linking the extracellular matrix to the cytoskeleton).<sup>60</sup> In an interesting *in vitro* experiment, Hessel et al.<sup>61</sup> demonstrated viable cardiomyocytes to release cTn by applying mechanical stress and stretch

**Table 2** Possible mechanisms of cardiac troponin release described in literature<sup>a</sup>

Mechanism	Extent of injury	Explanation
Necrosis	Late phase of cell death	Commonly initiated by prolonged ischaemia or ischaemia-reperfusion injury, through either the <i>death receptor necrosis</i> or <i>mitochondrial necrosis</i> pathway, accompanied by a typical release of intracellular molecules to the interstitium, resulting in a local inflammatory response. Conventionally, necrosis was perceived to be unregulated and chaotic, but tumour necrosis factor- $\alpha$ programmed forms (known as necroptosis) exist as well. <sup>47</sup>
Apoptosis	Early phase of cell death	Programmed cell death can be initiated by <i>cell surface death receptors</i> (extrinsic pathway) or the <i>mitochondric pathway</i> (intrinsic pathway), associated with different forms of caspase activation. In general, apoptotic cells fragment into apoptotic bodies, preserving membrane integrity and part of cell functionalities until undergoing removal through phagocytosis, <sup>47</sup> but early defragmentation might also result in secondary necrosis (necroptosis).
Cardiomyocyte turnover	No cell injury	Although the cardiomyocyte was previously perceived to reside in a postmitotic state, recent studies have demonstrated evidence of age-dependent cardiomyocyte renewal. <sup>48</sup> This mechanism seems of little importance in patients undergoing CABG.
Proteolytic degradation	Later phase of cell injury/death, and after release into circulation	Secondary to myocardial cell injury, increased cytoplasmic calcium concentrations can activate calpain or caspase-3, known to result in proteolytic cleavage of troponins intracellularly. <sup>49</sup> These degraded forms of troponin proteins can in turn be released to the interstitial space due to an increase in membrane permeability or 'blebbing'. Also, further degradation of troponins might take place in the (extra cardiac) blood circulation, <sup>50</sup> and <i>in vitro</i> in blood tubes by thrombin activation. <sup>51</sup>
Increased membrane permeability	Early phase of cell injury/death	Increased cellular wall permeability (or cell wounds) secondary to myocardial injury (or other causes), in absence of necrosis, might lead to 'leakage' of cTn from the early releasable pool. <sup>52</sup>
Blebbing	Later phase of cell injury/death	Release of subcellular structures containing cytoplasmic content, during the early phase of (temporary) ischaemia, still reversible, but soon followed by apoptosis, and maybe necroptosis. <sup>53</sup> After bleb rupture, these proteins can be released to the systemic circulation.

Adapted from White<sup>46</sup> and Park *et al.*<sup>27</sup>

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass.

<sup>a</sup>It should be noted that these different mechanisms of myocardial cell death may be interconnected and several of the proposed mechanisms might be induced by one single stimulus.

to the cell, mediated by integrins. Of note, a related hypothesis suggests that temporarily increased membrane permeability is caused by injury-induced *cell wounds*. This mechanism might be reversed by a process called *cell wound repair*, which is incompletely understood.<sup>62</sup>

Finally, Hickman and colleagues<sup>63</sup> proposed the occurrence of blebbing in 2010. This hypothesis is derived from the observation of bleb formation in ischaemic hepatocytes,<sup>64</sup> but its occurrence is yet to be confirmed in cardiomyocytes.<sup>27</sup> In such a process, the myocardial cell is in a preapoptotic stage secondary to injury and sheds membranous blebs containing intracellular content in response to oxidative stress.

Although there is abundant circumstantial and experimental evidence of the abovementioned processes, it should be mentioned that the vast majority of these mechanisms are yet to be confirmed clinically. Furthermore, it is likely that these processes do not take place separately, but rather simultaneously at multiple levels with interconnecting pathways.

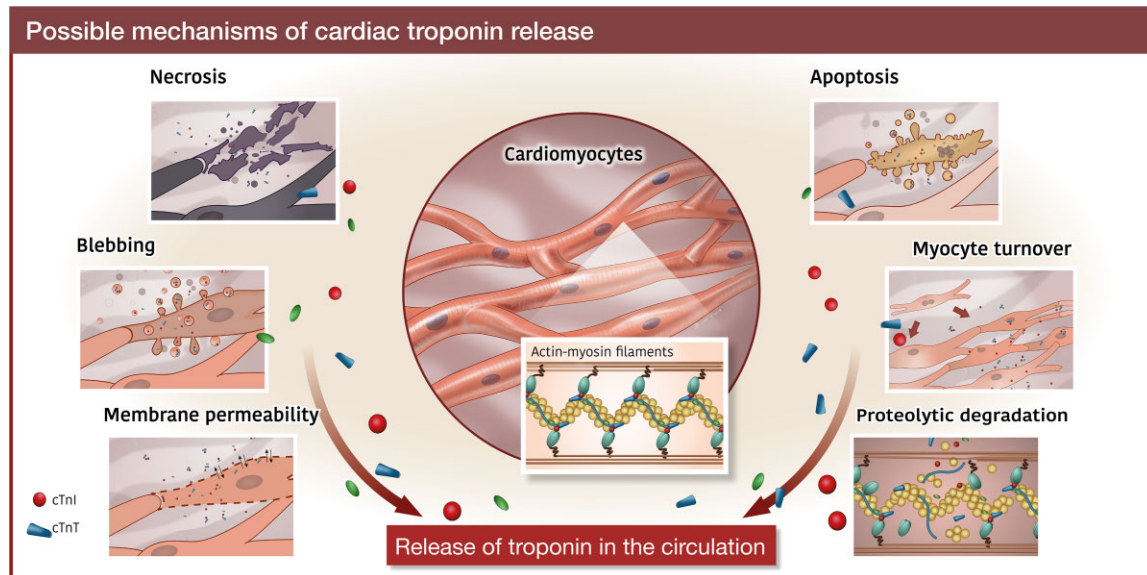
## Mechanistic causes of myocardial injury during coronary artery bypass grafting

In general, cardiac surgical procedures comprise many features that might induce myocardial injury, especially when involving surgery to the

coronary arteries, such as CABG. Although there is little clinical evidence on the degree of injury and consequent cTn release regarding these various aspects, some preliminary conclusions can be derived from experimental studies, which will be highlighted in the following section.

### Mechanical manipulation

In the majority of cases, CABG is performed with the support of a cardiopulmonary bypass (CPB) circuit during the cardioplegic arrest.<sup>65</sup> For cannulation of the CPB circuit, atrial and ascending aortic sutures and incisions are required, subjecting cardiac tissue to injury. In the remaining instances, CABG is performed on a beating heart without CPB support, known as off-pump CABG (OPCAB). Still, both strategies require extensive mechanical manipulation of the heart, especially when the lateral and inferior wall coronaries are targeted. Inevitably, this manipulation induces some myocardial cell damage. Additionally, the epicardial coronary vessels are prepared from their surrounding tissue and incised for graft anastomosis. This hypothetically results in minor cell damage as well, especially in the instance of an intramyocardial coronary trajectory. As this direct mechanical injury most probably leads to some cell damage, cTn release might be secondary to necrosis, apoptosis, or a combination of both (Table 3).



**Figure 1** An overview of possible mechanisms of cardiac troponin release (Barry van Varik, Pulse Medical Art).

## Cardiopulmonary bypass

The myocardial interstitial fluid balance is dependent on the coronary microvascular exchange rate and the fluid removal rate by lymphatic vessels. In turn, the cardiac lymphatic system is primarily driven mechanically by ventricular contractions.<sup>79,80</sup> However, during cardiac surgery, after the initiation of CPB, cardiac function is steadily taken over by the CPB circuit, resulting in diminished pulsatility. When cardioplegic arrest is induced by administration of the cardioplegic solution, the heart is emptied, ceased, and paused in diastole. In addition to the absence of the driving force of the lymphatic system, the non-pulsatile blood flow increases the duration of transmicrovascular flow.<sup>81</sup> This might result in an increased cellular wall permeability secondary to oedema, accumulation of waste products and cytokines, and activation of humoral and cellular mediators.<sup>81,82</sup> Inherently, the rate at which any molecule or protein is liberated from the cell depends on its intracellular location, molecular weight and folding, its electrical charge, and local blood and lymphatic flow.<sup>27</sup> Irrespective of the free or reversibly bound location of cTn in the cardiomyocyte,<sup>24,33</sup> a reduction in microvascular wall integrity could lead to the leakage of smaller sized proteins, such as cTn [24 kDa (cTnI) and 40 kDa (cTnT)] compared with CK-MB (87 kDa)<sup>83</sup>. In this scenario, significant CK-MB release might only be observed in the case of irreversible cell damage, necrosis, and complete cell-wall disintegration. Although these findings could be considered in line with clinical observations,<sup>84,85</sup> it should be emphasized that these mechanisms remain speculative. Still, this conception would also explain the important difference in cTn release patterns between patients undergoing conventional CABG or OPCAB. After the latter procedure, significantly lower cTn concentrations are observed in the post-operative phase (Figure 2A, based on cTnT).<sup>1</sup> Of note, in an interesting study evaluating the presence of cTn in cardiac lymph fluid, the importance of the cardiac lymphatic system was underlined.<sup>87</sup> In their porcine model, Vazquez-Jimenez and colleagues selectively cannulated the cardiac lymphatic trunk and observed significantly increased cTn concentrations in lymph compared with coronary sinus blood (up to 50 times) after aortic declamping and weaning of CPB. Although human

data on this matter are scarce and statements regarding this topic are only hypothesis generating, these findings seem to highlight the possibility of CPB-related release mechanisms and alternative release routing by the lymphatic system.

## Cardioplegic arrest

To achieve cardioplegic arrest, the ascending aorta is cross clamped, and for cardioprotection during arrest, the cardioplegic solution is administered. This can be done antegradely through the aortic root, retrogradely in the coronary sinus, or using a combination of these routes. Of note, various cardioplegic solutions (blood or crystalloid based) are used in the field. These can be administered at different temperatures (cold, tepid, warm), with different electrolyte concentrations (intra- or extracellular) at different intervals (single shot, intermittently). All of these features are known to have some effect on perioperative myocardial injury.<sup>88</sup> For a certain amount of time (depending on the cardioplegic solution used), the heart is optimally protected against the adverse effects of arrest, as it reduces myocardial oxygen demand by putting the myocardial cells in a refractory state.<sup>89</sup> Several studies and meta-analyses have addressed differences in outcomes between cardioplegia regimens. Although some of these are suggestive of a superior short-term effect of blood cardioplegia,<sup>90</sup> no differences in long-term outcomes in terms of survival or cardiac function were observed.<sup>91</sup> Still, when the distribution of cardioplegic solution is suboptimal (a common pitfall in retrograde administration, or in the case of occluded coronaries or aortic valve regurgitation<sup>92</sup>), or an excessive amount of time passes, (ir)reversible cell damage (i.e. PMI) might occur (Table 3).

## Ischaemia-reperfusion injury

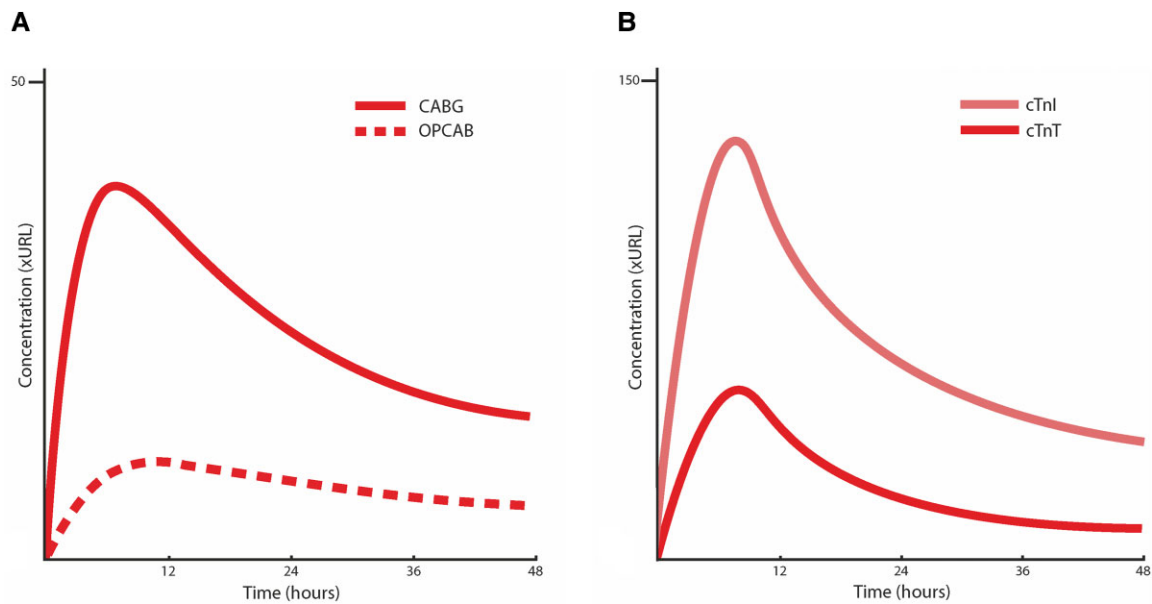
Ischaemia-reperfusion injury (IRI) is among the most studied phenomena in cardiac surgery. After temporary ischaemia, reactive oxygen species, such as peroxides (i.e. H<sub>2</sub>O<sub>2</sub>) and superoxides, are generated, from which different oxygen radicals can be cleaved.<sup>93</sup> Consequently, these

**Table 3** Possible mechanistic causes of periprocedural cardiac troponin release in CABG patients and in the context of their studied settings

Mechanistic cause	Hypotheses or circumstantial evidence	Studied settings		
		<i>In vitro</i>	<i>In vivo</i> (animal)	<i>In vivo</i> (human)
Mechanical manipulation and cannulation	Intraoperative cTn concentrations increased before and after cannulation (0.87 vs. 1.12 µg/L) <sup>66</sup>	—	—	—
Cardiopulmonary bypass	Significantly lower cTnT concentrations in OPCAB patients vs. CABG patients <sup>67</sup>	—	CPB vs. non-use of CPB was associated with significantly increased cTnI degradation in an immature porcine model <sup>68</sup>	Intraoperative CS venous plasma measured cTnT concentrations increased during CPB <sup>69</sup>
Cardioplegic arrest	Significantly lower cTnT concentrations in OPCAB patients vs. CABG patients <sup>67</sup>	—	CS venous cTnT concentrations significantly increased during and after cardioplegic arrest (18 vs. 281 ng/min) in a porcine model <sup>70</sup>	—
Ischaemia-reperfusion injury	—	Markedly more cTnI degradation was observed during longer periods of ischaemia, in an isolated rat heart IRI model <sup>71</sup>	Significantly increased cTnI and cTnT concentrations following 5 min of ischaemia and subsequent reperfusion, in a porcine <sup>a</sup> model <sup>72</sup>	Cardioprotective effect of remote ischaemic preconditioning, in terms of IRI reduction, measured by cTnI in a randomized trial in CABG patients (266 vs. 321 ng/mL) <sup>73</sup>
Ischaemia: native coronary artery occlusion (brief or prolonged)	—	Significant increase of full-length cTnI following ischaemia and no reperfusion in an isolated rat heart model, and more cTnI degradation in reperfused <sup>a</sup> hearts <sup>49</sup>	Delayed release of cTnI exceeding the 99th percentile after 10 min of LAD occlusion in a porcine model (12 vs. 180 ng/L after 24 h <sup>3</sup> ) <sup>43</sup>	Significantly increased cTnI concentrations in patients requiring repeat revascularization compared with uncomplicated patients following CABG (36 800 vs. 2407 ng/L) <sup>16</sup>
Ischaemia: graft failure	—	—	—	Higher cTnI concentrations in post-CABG patients with graft-related PMI vs. non-graft-related PMI (39.5 vs. 19.7 ng/mL) <sup>14,74</sup>
Perioperative tachyarrhythmias	Markedly increased cTnI concentrations in patients with supraventricular tachycardia and normal coronary angiography (ranging between 0.11 and 2.47 ng/mL) <sup>75</sup>	Tachypacing induced cTn degradation in cultured atrial myocytes, and significantly more cTn degradation products were observed in atrial cells from AF patients compared with SR <sup>76</sup>	—	cTnT plasma concentrations measured in the CS significantly increased after rapid atrial pacing during coronary angiography in patients evaluated for microvascular dysfunction (6.8 vs. 15.6 pg/mL) <sup>77</sup>
Increased left ventricular diastolic pressure	Significantly higher CS cTnT concentrations in HF compared with non-HF patients during coronary angiography, correlating with LVEDP (13.1 vs. 6.1 ng/L) <sup>78</sup>	Integrin stimulation caused intact cTnI release in cultured human cardiomyocytes in absence of cell death as quantified by LDH <sup>61</sup>	Transient LVEDP increase resulted in significant cTnI release in a porcine model (16 vs. 856 ng/L), normalizing after 24 h, in absence of histological necrosis <sup>44</sup>	—

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; CS, coronary sinus; cTnI, cardiac troponin I; cTnT, cardiac troponin T; IRI, ischaemia-reperfusion injury; LAD, left anterior descending artery; LDH, lactate dehydrogenase; LVEDP, left ventricular end-diastolic pressure; PMI, periprocedural myocardial infarction; OPCAB, off-pump CABG.

<sup>a</sup>Brief period of ischaemia, < 20 min.



**Figure 2** Cardiac troponin release patterns following on- and off-pump coronary artery bypass grafting (A) and differences in cardiac troponin I and cardiac troponin T release following coronary artery bypass grafting (B). (A) Following coronary artery bypass grafting and off-pump coronary artery bypass grafting (based on data from Heuts et al.<sup>1</sup> and based on cardiac troponin T exclusively for assay comparability). (B) Cardiac troponin I vs. cardiac troponin T following coronary artery bypass grafting (based on Heuts et al.<sup>1</sup> and Denessen et al.<sup>86</sup>). Data in this figure were derived from a systematic review and meta-analysis of all available literature on postoperative high-sensitivity cardiac troponin T and I measurements following isolated coronary artery bypass grafting. Assays used for this analysis were Abbott Architect, Siemens Advia Centaur, Siemens Dimension Vista, Beckman Access2 (high-sensitivity cardiac troponin I), and Roche (high-sensitivity cardiac troponin T). All absolute concentrations of the individual studies per assay were corrected to the assay-specific upper reference limit before incorporating the data into the figure. CABG, coronary artery bypass grafting; cTnI, cardiac troponin I; cTnT, cardiac troponin T; OPCAB, off-pump coronary artery bypass grafting; URL, upper reference limit.

radicals might attack important cell structures such as the cell membrane, leading to cTn release.<sup>72</sup> These experimental findings were confirmed clinically (*ex-juvantibus*), when comparing periprocedural protocols such as anaesthesia regimens and ischaemic preconditioning strategies.<sup>73,94</sup> Indeed, when compared with the use of propofol, the use of volatile anaesthetics has been associated with a superior organ-protective effect, most probably by reducing post-CABG IRI in terms of cTn release and improving postischaemic recovery at the cellular level.<sup>95</sup>

### Ischaemia: native coronary artery injury

During CABG, the coronary artery is incised for sutured graft anastomosis. Due to technical failures, such as narrowing of the anastomosis or native coronary, or native coronary artery occlusion secondary to misplacing a suture to the opposite coronary intimal layer, coronary and anastomotic flow can be compromised, leading to ischaemia. In most instances, such technical errors are noticed intraoperatively due to difficulties in separating from CPB, ST-segment deviation on ECG, or abnormal echocardiographic findings. If recognized promptly during the operation, anastomotic revision can be performed in time, averting actual myocardial cell necrosis and excessive cTn release.

Other factors to take into account are native coronary artery occlusion of a non-bypassed vessel due to mechanical manipulation and/or distal coronary microembolization.<sup>14</sup> Importantly, as these are all potentially reversible causes, early diagnosis, even in the intensive care unit, is imperative.

### Ischaemia: graft failure

The spectrum of graft failure comprises graft occlusion, kinking, overstretching, or spasm. Injury of the grafts during harvesting might limit flow, and anastomosis proximal to coronary stenosis might compromise the efficacy of the graft due to competitive flow. All these mechanisms potentially lead to ischaemia, necrosis, and subsequent cTn release.<sup>14,74,96</sup> Still, graft failure does not necessarily result in ischaemia. This is reflected by the surprisingly high percentage of 17% of asymptomatic postsurgical patients with at least one occluded graft at discharge in a contemporary analysis of patients undergoing OPCAB.<sup>97</sup> Presumably, this also applies to patients undergoing on-pump CABG, as illustrated by the findings of Ueyama and colleagues (>7% pre-discharge vein-graft failure).<sup>98</sup>

### Perioperative tachyarrhythmia

Myocardial injury related to the surgical procedure is not limited to the intraoperative phase but is also considered procedure-related in the first 48 h following surgery.<sup>2</sup> Indeed, this means all postprocedural causes of haemodynamic instability and subsequent potential secondary ischaemia should be taken into consideration. Several causes of such an imbalance can be present after surgery, such as low cardiac output syndrome or tamponade,<sup>99</sup> but tachyarrhythmia is the most studied feature in the context of cTn release. Indeed, postoperative atrial fibrillation (AF) and flutter occur in 10%–33% of patients undergoing CABG.<sup>100</sup> Moreover, both in the experimental and clinical setting, tachyarrhythmia (most frequently induced by atrial pacing) has been shown to be associated with significant release of cTn.<sup>45,75,76,101</sup>



Although refractory tachyarrhythmia can lead to secondary ischaemia, it might also result in cTn release through proteolytic degradation in the absence of necrosis.<sup>76</sup> It is hypothesized that the AF-associated L-type calcium channel alterations result in calcium overload, which in turn activates calpain, with its known (cTn) proteolytic capacities.<sup>49,76</sup>

### Increased left ventricular end-diastolic pressure

More recently, myocardial cell stretch-induced cTn degradation has been proposed as an alternative mechanism explaining the observed cTn release in temporarily ischaemic isovolumetric isolated rat hearts.<sup>44</sup> Feng and colleagues<sup>102</sup> were the first to evaluate the possibility of stretch-induced cTn degradation secondary to an elevated preload in the absence of ischaemia, *in vitro*. Subsequently, Weil *et al.*,<sup>44</sup> in a porcine model mimicking acute volume and pressure overload, found transient increases in cTn release and myocyte apoptosis in the absence of ischaemia. This final mechanism might also play a role in patients undergoing cardiac surgery, as they are subjected to significant volume shifts associated with the use of CPB and excessive fluid resuscitation in the intensive care unit.<sup>103</sup>

In summary, even in uncomplicated CABG, cTn release is expected as mechanical manipulation, CPB, and cardioplegic arrest are inherently part of the procedure. In the case of such a truly uncomplicated procedure, a rapid incline and decline of cTn release should be observed, while more prolonged cTn release is to be expected in patients with more extensive myocardial injury, due to graft failure, native coronary problems, IRI, or perioperative haemodynamic instability. Indeed, this is confirmed by recent findings by Omran and colleagues.<sup>16</sup> In their elegant retrospective analysis of almost 5000 patients undergoing CABG with standardized postoperative high-sensitivity cTnI measurements, patients with an uneventful course reached a peak concentration of 90× URL, 8 h after surgery, after which a rapid decline was observed. Conversely, patients requiring revascularization due to PMI exhibited a bimodal cTnI curve, peaking 18 h after surgery for the first time (992× URL) and a second time after 25 h (1415× URL). This study, in conjunction with another analysis by Pözl *et al.*<sup>12</sup> proved currently applied isolated cTnI and cTnT cut-off concentrations (>70× URL) to be far too conservative. Moreover, these studies demonstrated that isolated cTn increases, even at excessively high levels, have little prognostic relevance in CABG patients.<sup>104</sup> Derived from this study and a previous meta-analysis by our group, it can be appreciated that cTnI seems to reach far higher concentrations than cTnT in the postoperative setting (Figure 2B),<sup>1,86</sup> urging re-appraisal of their specific cut-offs.

### Differences between cardiac troponin I and T for diagnosis of periprocedural myocardial infarction

Cardiac troponin I and T have convincingly proved to have equal diagnostic performance for diagnosing primary MI.<sup>2</sup> Nevertheless, although both are expected to be expressed in cardiac tissue to an equimolar amount, they are different proteins with individual biochemical characteristics and should therefore not be used interchangeably.<sup>2,105</sup> Indeed, clinical studies in primary MI patients illustrated important differences in their release pattern, clearance, and predictive value,<sup>106–108</sup> which will be discussed below.

In typical non-surgical patients with suspected primary MI, a biphasic release curve is observed for cTnT (especially in the case of reperfusion), while cTnI exhibits a more monophasic curve.<sup>106,107</sup> Also, cTnI reaches higher concentrations and returns faster to normal than

cTnT.<sup>108–110</sup> Conflicting evidence exists regarding the clinical importance of this difference in curves, as some studies have suggested that such a second hs-cTnT peak might be related to infarct size.<sup>111</sup> Still, others have refuted an association between the second peak and long-term prognosis.<sup>107,112</sup> It should be mentioned that these release curve differences have been insufficiently studied in CABG patients. Interestingly, some have attributed these differences to the conception that the early releasable cTnI pool is smaller than its counterpart,<sup>113</sup> while previous CABG studies also considered the role of renal and hepatic (dys)function.<sup>114,115</sup>

Of note, the forms of cTnT in patients with end-stage renal disease seem different from the cTnT forms found in patients with MI, implying different cTnT fragments to be released or degraded in acute and chronic phases of cardiovascular disease.<sup>116</sup> Also, Starnberg and colleagues<sup>117</sup> recently compared cTnI and cTnT kinetics and found cTnI to be released much faster than cTnT from damaged cardiac tissue, without a difference in clearance rate when cTn reaches the systemic circulation. A potential explanation for these observations could be a difference in degradation processes, which might occur more slowly for cTnT.<sup>117</sup> Furthermore, it is perceived that the cTn complex is also affected by the 'trapping effect', which applies directly to cTnT and only indirectly to cTnI.<sup>117</sup> In this model, in contrast to cTnI, cTnT re-binds directly to thin filaments,<sup>118</sup> while cTnI only binds to thin filaments indirectly via its interaction with cTnT.<sup>117,119</sup> It should be mentioned that this model is more or less based on circumstantial and indirect evidence.

In general, and as also recognized by expert groups, the release of cTnI following CABG seems more abundant compared with cTnT, even when corrected for its URLs.<sup>26</sup> In their consensus statement, Thielmann and colleagues<sup>26</sup> recommend further investigation (in terms of supporting evidence) when cTnI surpasses >20× URL, while this applies to cTnT at the peak of >7× URL. Still, the authors also recognize that further studies are needed to support evidence-based decision-making. For the diagnosis of PMI using solitary cut-offs, the expert group did not differentiate between cTnT and cTnI (both >70× URL), but an explanatory pathophysiological mechanism was not provided in that statement.

Finally, only one assay is available for measuring cTnT, while for cTnI, multiple assays are available on the commercial market. These various assays all determined a separate URL and exhibited significant differences—up to 10-fold—relative to each other, even in a universal sample bank.<sup>120</sup> The latter findings at least imply that if cTnI is used in a local laboratory, these results are not comparable with cTnI results from other assays or institutions, even when corrected for URL. Still, irrespective of the assay applied, it is inevitable that higher cTn concentrations or URL multiplications indicate more urgency and severity of disease.

These caveats are further complicated by the observation of different circulating cTnI and cTnT forms, from ternary T-I-C complexes to degraded forms,<sup>28,116</sup> limiting the possibilities of assay harmonization and comparability. Interestingly, our centre's studies illustrated that cTn forms in the acute phase of MI differentiate from chronic, stable conditions, opening new diagnostic possibilities that might be more specific for acute myocardial injury.<sup>28,116</sup>

### Future directions for biomarker evaluation in the postoperative setting

Based on the identified underlying mechanisms, several preliminary implications can be derived, which warrant confirmation in future studies. Most importantly, based on several clinical and experimental observations, one must consider that cTn elevations following CABG may not be viewed as direct and definite evidence of cardiac necrosis that

is of clinical importance. As such, the relationship between transient cTn peak elevations after cardiac surgery and prognosis is not unequivocal, and the current definitions of PMI might warrant reconsideration.<sup>121</sup> Given the presented considerations in the use of postoperative cTn measurements, one might question whether such measurements should actually be performed. It should be mentioned that PMI is a relatively rare complication and the overwhelming majority of procedures are uncomplicated. Therefore, as traditional postoperative diagnostic modalities, and especially traditional ECG findings such as ST-segment depression or T-wave inversion, are rather unspecific in this phase, relatively low cTn concentrations are definitely reassuring of an uncomplicated course due to cTn's superior specificity, providing the clinician with important information.

Conceptually, the diagnosis of relevant periprocedural myocardial injury or PMI is debateable as it has been based on studies assessing different prognostic timespans. Inherently, there is a substantial difference between the definition of an event and its prognostic significance. Therefore, we should not only strive to reach uniformity in the formulation of cut-off concentrations and a possible (re-)definition of PMI, but also on which prognostic event we deem important and at which time such relevant prognostic events should be assessed.

In addition, heterogeneity in surgical and interventional procedures exists, as not every CABG is the same, and one must expect different biomarker release patterns and peaks following CABG performed with the use of CPB and without,<sup>1</sup> perhaps even using different periprocedural protocols.<sup>122</sup>

Then, a uniform cut-off for cTnT and cTnI seems inappropriate and could perhaps be adapted to the specific cTn assay, as was proposed in the 0/1 h protocol for Type 1 MI.<sup>123</sup> In addition, as in Type 1 MI, not only the peak, but also the steepness of the release curve could be considered, potentially identifying patients with graft-related PMI in an earlier phase.<sup>14,123</sup>

Furthermore, irrespective of the use of cTnI or cTnT, supporting evidence in terms of ECG or imaging findings seems to be of utmost importance, while there is little diagnostic value of isolated biomarker increases in the acute phase.<sup>2,12,16,104</sup>

The terms *reversible* and *irreversible* myocardial injury require clarification, while they are being used in different settings with different meanings.<sup>124–126</sup> In an interesting opinion paper on primary MI patients, Jaffe and Wu<sup>124</sup> rightfully stated that even if cTn release is in part the consequence of reversible injury, clinically one does not need to make a differentiation between reversible and irreversible injury in non-surgical patients, as they both prove to influence prognosis. Moreover, the same authors concluded that in present-day practice, there is no room anymore for CK-MB.<sup>25</sup> While this certainly holds true for most clinical instances, CK-MB might still have some value in patients undergoing CABG. As current diagnostic MI-5 definitions based on cTn turned out to be far too conservative and would diagnose a significant proportion of CABG patients with PMI, CK-MB could still be considered concurrently. The acute assessment of (graft-related) PMI requiring prompt re-intervention based on a peak concentration, the proposed additional release mechanisms could cloud the assessment of actual cell necrosis, as the observed cTn peak in this scenario could be an accumulation of *reversible* and *irreversible* injury. In this surgical setting, cTn and CK-MB might still have the potential to be used together, at least until more applicable recommendations regarding the use of cTn cut-offs have been provided.

Then, derived from data of recent studies, the isolated peak concentration might be less associated with long-term prognosis in this setting,<sup>12,16</sup> while AUC measured over a longer period of time seems to have important diagnostic possibilities as it might be more reflective of this outcome.<sup>73</sup>

As mentioned previously, one must be cautious to use the term 'prognosis' in this context without uniformity, as it might apply to major adverse events, short-term mortality, or long-term survival. Also, one might argue that the complete revascularization provided by CABG attenuates or resolves the previously perceived impairment of prognosis of some irreversible loss of viable myocardium. The question then remains how much cell necrosis does affect prognosis and justifies re-intervention.

In summary, these relatively unexplored underlying mechanisms, and the inconsistent use of definitions of PMI, underline the need for clinical prospective studies to be conducted, evaluating the actual diagnostic accuracy of the different biomarkers in this unique postcardiac surgical setting.

## Limitations

Many of the statements and hypotheses provided in this overview originated from *in vitro* and animal studies, opinion papers, reviews, and expert consensus statements and should be interpreted in that context as hypothesis generating. Moreover, there is no available data describing these mechanisms in the actual ischaemic human heart. To corroborate the proposed mechanisms, future clinical studies are warranted to confirm the proposed mechanisms.

Throughout the years, the UDMIs have recommended using an assay's URL, for cardiac biomarkers based on the 99th percentile.<sup>2</sup> In contrast, the SCAI definition specifically advises using the upper limit of normal (ULN), while referring to the 97.5th percentile, which is more common for other non-cardiac biomarkers.<sup>3</sup> Since URL is equal to ULN, and to avoid further confusion, URL has consistently been used in the current review to indicate reference values. Furthermore, a significant amount of incorporated references and studies examined the relationship between outcomes and rather outdated cTn assays. As such, the results of these studies cannot necessarily be extrapolated to the current high-sensitivity assays, which have superior diagnostic accuracy and are able to detect concentrations below the URL.

Furthermore, the current review aimed to provide an overview of the potential cTn release mechanisms. However, due to the scarceness of post-CABG cTn data in relation to clinical endpoints and outcome, it was not possible to provide the reader with specific cTn cut-offs to apply in daily practice. Also, based on the available evidence, there remains important uncertainty regarding the relationship between isolated postoperative cTn concentration increases and long-term prognosis. To evaluate the actual relationship between postoperative cTn concentrations and long-term outcomes, future studies are warranted that incorporate serial cTn measurement, supportive diagnostic modalities, and long-term follow up.

The outcomes of graft-related PMI warranting re-intervention and long-term survival seem to overlap but are different, and one must be cautious to mistakenly use these terms interchangeably. It should also be noted that all of the above recommendations are based on data evaluating the biomarker release after *isolated* coronary bypass surgery. Patients undergoing other cardiac procedures in general, and procedures with the intent to induce myocardial damage, such as ablative surgery in particular, exhibit distinct release patterns and peaks.<sup>127</sup> As such, the current review only applies to CABG patients.

Finally, for reasons of assay comparability, cTn data for [Figure 2A](#) was exclusively based on studies evaluating the cTnT assay, as cTnT is measured by one assay (Roche Diagnostics, Basel, Switzerland) with a specific URL of 14 ng/L. Furthermore, cTnI data for [Figure 2B](#) were based on a recent meta-analysis and derived from different cTnI assays, but corrected for using the assay-specific URL.<sup>86</sup>

## Conclusion

The use of cTn is undisputed in primary MI, but its diagnostic accuracy is less well studied in the postoperative phase. As CABG inherently induces cardiac injury, the evaluation of this unique patient population can increase our understanding of cTn release mechanisms in general. Without a doubt, cTn is currently the most sensitive and specific cardiac biomarker, but its perioperative release dynamics after CABG in particular are not yet fully understood. Based on recent observations, current cTn cut-offs are too conservative and warrant re-assessment. Furthermore, as cTnI and cTnT are not interchangeable, their release should be weighed separately. However, to resolve these issues, future prospective studies are warranted to determine the actual prognostic influence of biomarker release following cardiac surgery.

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No new data were generated or analysed in support of this research.

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