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# Myocardial Ischemia and Infarction Related to the Highly Sensitive Cardiac Troponin after Noncardiac Surgery: A Review

**Célio Gomes de Amorim*, Nicolas Alves Rocha, Tainá Mendes Bertolin, Tassiana Cristina Souza Dias, Maria José Carvalho Carmona and Ludhmila Abrahão Hajjar**

*Department of Anesthesiology, Federal University of Uberlandia, Minas Gerais, Brazil*

***Corresponding author:** Célio Gomes de Amorim, Department of Anesthesiology, Federal University of Uberlandia, Minas Gerais, Brazil, Tel: 55-34-99106-6935; E-mail: celioamorim@uol.com.br

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**Abstract**

Although Acute Myocardial Infarct (AMI) from its classic symptomatology added or not to electrocardiographic changes is a significant cause of perioperative associated mortality, when it is only plotted from the enzymatic curve, recent data points towards the existence of similar mortality. Considered as a biological marker of a more recent generation, the high sensitivity cardiac troponin (hs-cTnT) analysis may give clues on whether a rupture of the oxygen ($O_2$) is occurring or not offer and demand balance, without any association with other manifestations, which opens a gap to be investigated, when the diagnostic search after myocardial ischemia (MI), something that is not done unless the patient is under high risk or has a confirmed history of Coronary Artery Disease (CAD). This review explores the possible associated factors when analyzing the risks of AMI and MI in the perioperative period.

**Keywords:** Acute myocardial infarction; Myocardial ischemia; Perioperative period; Myocardial biomarkers; 30-day Mortality; Myocardial injury

**Abbreviations:** ACS: Acute Coronary Syndrome; AMI: Acute Myocardial Infarction; CAD: Coronary Artery Disease; CHF: Congestive Heart Failure; CM: Cardiomyopathy; CT: Computed Tomography; PCI: Percutaneous Coronary Intervention; PE: Pulmonary Embolism; STMI ST-Segment Elevation Myocardial Infarction.

## Introduction

Acute Myocardial Infarct (AMI) is a worldwide important cause of both disabilities and death, whose evidence can be easily seen in any available scientific evaluation used as a reference on this theme [1-3]. When hospitalization is motivated by any clinical condition and the treatment necessarily requires a surgical therapy, characterizing the perioperative period, AMI must be considered as being equally critical, something that deserves an additional exploration to understand better the underlying mechanisms.

## The Magnitude of the Problem

In the perioperative period, variables such as age, gender, triggered inflammatory activity, kind and duration of surgery, comorbidities, and habits, can interact with each other producing a clinical context that, by itself, tends to an adverse and deleterious evolution, considering the several kinds of possible complications [4]. Among these, under the statistical point of view, the occurrence of AMI has emerged as a preponderant event, because of its lethality [5]. Although the 30-day mortality in individuals submitted to noncardiac surgery (Vascular Reasons 1.6%, Cardiorespiratory Arrest 0.5% and Cerebrovascular Events 0.7%) has been considered a great public health problem, AMI, when diagnosed taking into account the symptomatology, the enzymatic change, and/or the electrocardiographic changes, represents about 5% an expressively more significant incidence [5].

On one hand, as a consequence of some insult, enough to trigger myocyte cell degeneration, the imbalance between oxygen offer and demand may not clearly reflect, up to a certain moment of evolution, the repercussions of clinical context that will subsequently characterize AMI [6]. On the other hand, such sequence of events at this moment already results in a serious condition called myocardial ischemia (MI) [6,7]. From these considerations, the major issue is that the perioperative MI may have a presentation, characterized by a set of signs and symptoms which are not clinically visible enough to the point of allowing the application of the third definition of AMI [3]. As a consequence, now under a preventive point of view, this is alarming, because the low frequency routine of seeking for an early diagnostic of MI, in subjects who underwent medium and major surgeries, making the MI probabilistic inferential diagnose becomes underestimated, evidently distorting the statistical analyses of post-operative outcome, like mortality for example [7]. In this way, emerging evidences show up to 60% of incidence increase of adverse events, when only the product of the imbalance between offer and demand of oxygen is analyzed, instead of searching under a clinical setting in which the AMI third definition is characterized [6-8]. Researchers have studied the possible reasons that justify the observed discrepancy between the incidence of classically diagnosed AMI and that characterized as MI, both of which related to the perioperative period, that being the scope of the present discussion.

## Physiopathology of Ischemia

Since the 1970's, a judicious look has been given to factors associated with the myocardial ischemia and the subsequent reperfusion period, called 'reperfusion injury', this one taking place in a discussion that, although interesting, will not be addressed here, only illustrated, because it is related to protection strategies [9]. In turn, the deleterious intracellular process may initiate as a consequence of the

reduced oxygen blood supply, which is not necessarily solely related to a classical occlusion of the coronary artery [9]. Additional circumstances that cause imbalance between offer and demand of oxygen to the cell can also lead to ultra-structural changes, enough to characterize a condition that can be considered as 'ischemic like' [10]. Since they can be as tiny as possible to cause a rupture of the physiologic cell functions, some degree of changing in intracellular transduction as a consequence must necessarily occur, as well as a break in the phosphorylation process, which are products of such reactions may lead to an impaired cell membrane function [11-13]. On the other hand, in more significant ischemic conditions, it is possible to identify several kinds of reactions that will integrate a deleterious sequence of events, characterizing the necrosis and apoptosis processes in its worse possible presentation, which can be exemplified by an artery occlusion, especially when the time elapsed is greater than 20-30 min [14,15]. Theoretically, all the rest of possible conditions will be located among these extreme situations. To illustrate, Figure 1 demonstrates the fine equilibrium that should be maintained, objecting to offer adequate conditions to cell function, as well as the critical points where the balance can be distorted [14-16].

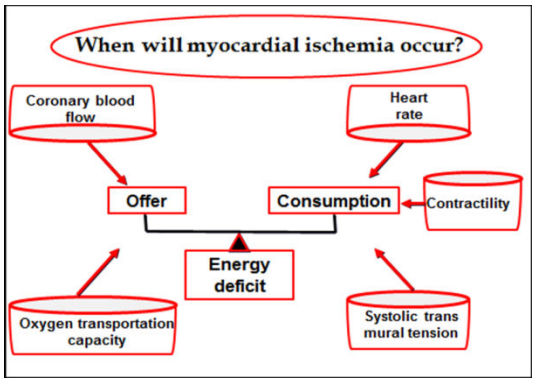



**Figure 1:** Scenario that characterizes the equilibrium between oxygen offer and demand.

Since established as a consequence of a anaerobic cell respiration, a rise in cytosolic lactate concentration and a fall in pH profile can be found, characterizing an acidotic atmosphere, which deflagrates a sodium and calcium overload, such process related to repolarization disturbance, with effect on cell contraction (Figure 2) [14]. The schematic sequence is presented in Figure 2.

As said before, a combination of characteristics observed in the perioperative period compound a pull of variables that need to be studied, when the objective is to analyze the late adverse outcomes [17]. Although it doesn't appear, the clinical aspects are closely linked to cell membrane function. The greater the insult acting as cause of energetic deficit, for whatever reason, the greater will be the accumulation of intracellular toxic substances, the greater the damage to cell membranes and the more exuberant the clinical context tend to be [14,16,17].

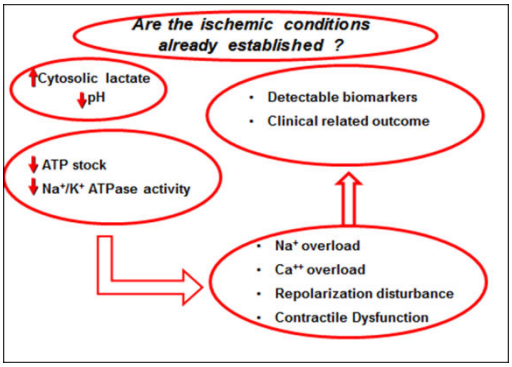



**Figure 2:** Scenario where a rupture of equilibrium between oxygen offer and demand has occurred [14].

In turn, Figure 3 shows the sequence of mechanisms related to ischemic and reperfusion periods, aiming to illustrate the harmful process that occurs in both of them, which has been the subject of intense study for many years [16].

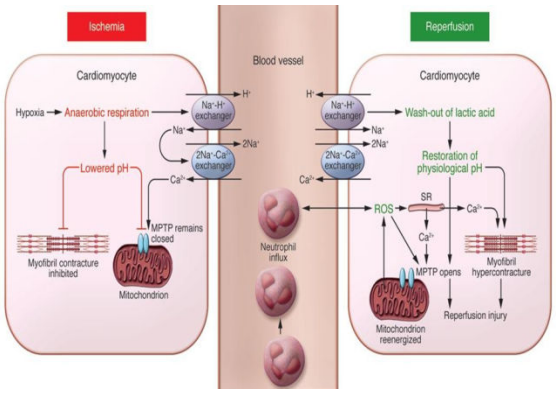



**Figure 3:** Scenario illustrating both ischemic and reperfusion periods [16].

## Cardiac Biomarkers

Since such conditions of imbalance have been created, as seen, even when the cell membrane disruption has not yet occurred, something that, consequently, allows quantum maintenance on both sides of the membrane, Troponin may be found in the circulation, although in a minimal plasmatic level [18]. Protein that regulates the calcium-induced actin-myosin coupling, consists of a complex formed by three subunits, i.e., Troponin C, Troponin I (TnI) and Troponin T (TnT), the last two being specific isoforms related to the contraction of the cardiac muscle cell [19]. The cytosolic pool, proportionally compared to total intracellular amount, was measured and described as 6 to 8%, for TnT, while for TnI it resulted in around 2.8%, in normal physiologic conditions [20]. Individuals with Stable Coronary Disease, presenting no clinical nor electrocardiographic manifestation, when submitted to stressing conditions, as they occur, for instance during stress tests, by both physical exercise and pharmacological infusion (ECO Stress), can show a cell liberation pattern of the mentioned subunits (TnI and TnT), which can be detectable by dosage assays [18].

In terms of mechanisms used for an early diagnostic, the presence of an enzymatic curve, in both troponin (Tn) and creatine phosphokinase, fraction MB (CK-MB), have been used, not only for diagnostic condition, but also as a predictive value [7]. However, it was possible to make such association only from few years ago to now, because of the sensitivity and specificity pattern of the method, which was improved after the development of highly sensitive cardiac TnT (hs-cTnT) measurement [21,22]. In this way, recent evidence shows that hs- cTnT measurement is associated with lower rate of both cardiac stress testing and coronary angiography use, lower time of emergency room discharge, as well as lower cost of hospital internment [21]. On the other hand, the percentage of surgery indication does not change, which could be a representative proof of method limitation. Thus, its use as an imbalance marker of the oxygen offer and demand relationship, in both perioperative period and other settings, appears to be an option that may favourably affect the post-operative outcome, owing to a better feasibility of an early diagnostic, possibly a shorter hospital internment period [23].

However, it is important to highlight that, as any method, other conditions besides MI or AMI may trigger a changed enzymatic curve, which demands control in the application of this technique, mainly when it is applied to curves that generate, at maximum, moderate elevations [16,22-25]. This way, it is needed to consider whether the changes are a consequence of a Hypertensive Crisis, or Pulmonary Thromboembolism, Sepsis, Cardiac Arrhythmia, Cerebrovascular Accident (CVA), Takotsubo Cardiomyopathy, Congestive Heart Failure (CHF), Acute Kidney Injury or Decompensated Valvulopathy [16,23].

When considering conditions within which a major part of patients come, to be submitted to medium and major surgeries, mainly when these are of an emergency or urgency nature, adding everything involving the perioperative variables, including psychological stress, we may say that there is a parallel with the stress provoked by tests applied for cardiovascular risk stratification [18]. However, if in perioperative period the process is not stopped, as it is can during the stress test, it will now occur in a more advanced stages of cell degeneration, which is certainly compromising [7,18]. Even when it is not possible to see symptomatology and suggestive electrocardiographic changes, by themselves, the surgical and anesthetic trauma, with the consequent release of inflammatory mediators, as well as bleeding, acute pain, and the presence of hemodynamic instability periods, are conditions more than enough to trigger an imbalance between offer and demand, consequently starting the deleterious process described, characterized by the enzymatic change [6]. In addition, still in the perioperative period, if not suitably identified, in individuals exposed to some degree of risk, the conduction strategies as a consequence will not obviously consider the potentially unfavourable outcome in course. Thus, if the cardiovascular adverse event happens, in the conditions as already mentioned, although it can be triggered by a minimal insult, within the spectrum of what can be considered as MI, it will certainly have an impact on both morbidity and mortality, if compared with AMI, as it has been suggested by the scientific literature and discussed in the sequence [5,17].

## Biomarker associated with signs, symptoms and electrocardiographic finds

Regarding the clinical setting whereby it is possible to observe the presence of enzymatic curve of biomarkers, an important study analyzing a heterogeneous population of 457 individuals presenting symptoms of acute coronary syndrome (ACS) was developed in 2009, a time when the sensitivity and specificity patterns of cTnI and cTnT were becoming to be considered as having unsatisfactory ROC (Receiver Operator Characteristic Curve) measurements [16]. An area under the ROC curve of 0.83 was found, with a clinical specificity of 89%, showing a substantially more robust assay, compared to first-generation assays. Although at that time the value of the new assay of cTnI had been exposed, it was observed that 49 of the 67 individuals that had enzymatic increased concentration, at initial presentation, weren't diagnosed with AMI. Also, the clinical symptomatology presented at admission was constituted by: chest pain (63%); other typical symptoms (shortness of breath, nausea and vomiting, sweating, epigastric pain, abdominal pain, neck or shoulder pain-15%); syncope (7%); tachycardia or bradycardia (5%); altered mental status (2%); gastrointestinal bleeding (2%); and hypoxia (2%) [16]. At the same time, while other differential diagnostics were established, the prognostic value of the cardiac biomarkers was beginning to be constructed by other research, to attempt the new era, imputed by such conceptual ideal ROC area [26]. So, such analysis at that time exposed the gaps built by the changes related to the sensitivity and specificity of the smallest values of the new assays, leading consequently to a necessary redefinition of what until a few years before had been created, i.e., the AMI criteria [26]. In this way, an interesting original observational research was made taking into account surgical procedures, aiming to observe what could be the characteristics of perioperative myocardial infarction, if analyzed considering these gaps already questioned [5]. The groups considered were those as being symptomatic (with ischemic symptoms), asymptomatic (without ischemic symptoms) or as having an elevated cardiac biomarker or enzyme [5]. The authors observed a 30-day mortality of 12%, extracted from a population of 5% who had perioperative myocardial infarction, compared with the individuals who had not (Figure 4). Regarding the main characteristics found, distinct patterns of evolution among the groups were observed and, as a consequence, different profiles of cumulative hazard rations for mortality [5]. The additional information relates to the group that presented only an altered pattern of curve, in cardiac biomarker or enzyme, which, as having been clearly demonstrated, an important impact on outcome did not meet the established criteria for the definition of myocardial infarction. Furthermore, surprisingly, in 64.6% of symptomatic individuals, as well as 79.3% of the asymptomatic, and 61.8% of those who presented only biomarker or enzymatic profile, the critical adverse event was observed within 48 h after surgical procedure, something that has become a critical point to be addressed by scientific community up to present.

Leaning on these observations, following in the same way, in 2012, a Joint Task Committee established the Third definition of Myocardial Infarction, whose concepts required to diagnose conditions related to the Symptomatology and to the pattern of enzymatic changes, among others, demonstrating a certain refinement of such criteria. Figure 5 shows the new pattern of diagnose adopted since that task force, which is still used today.

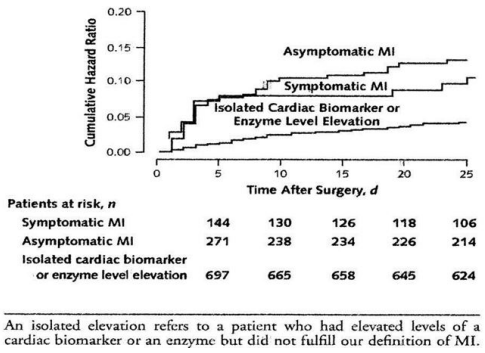


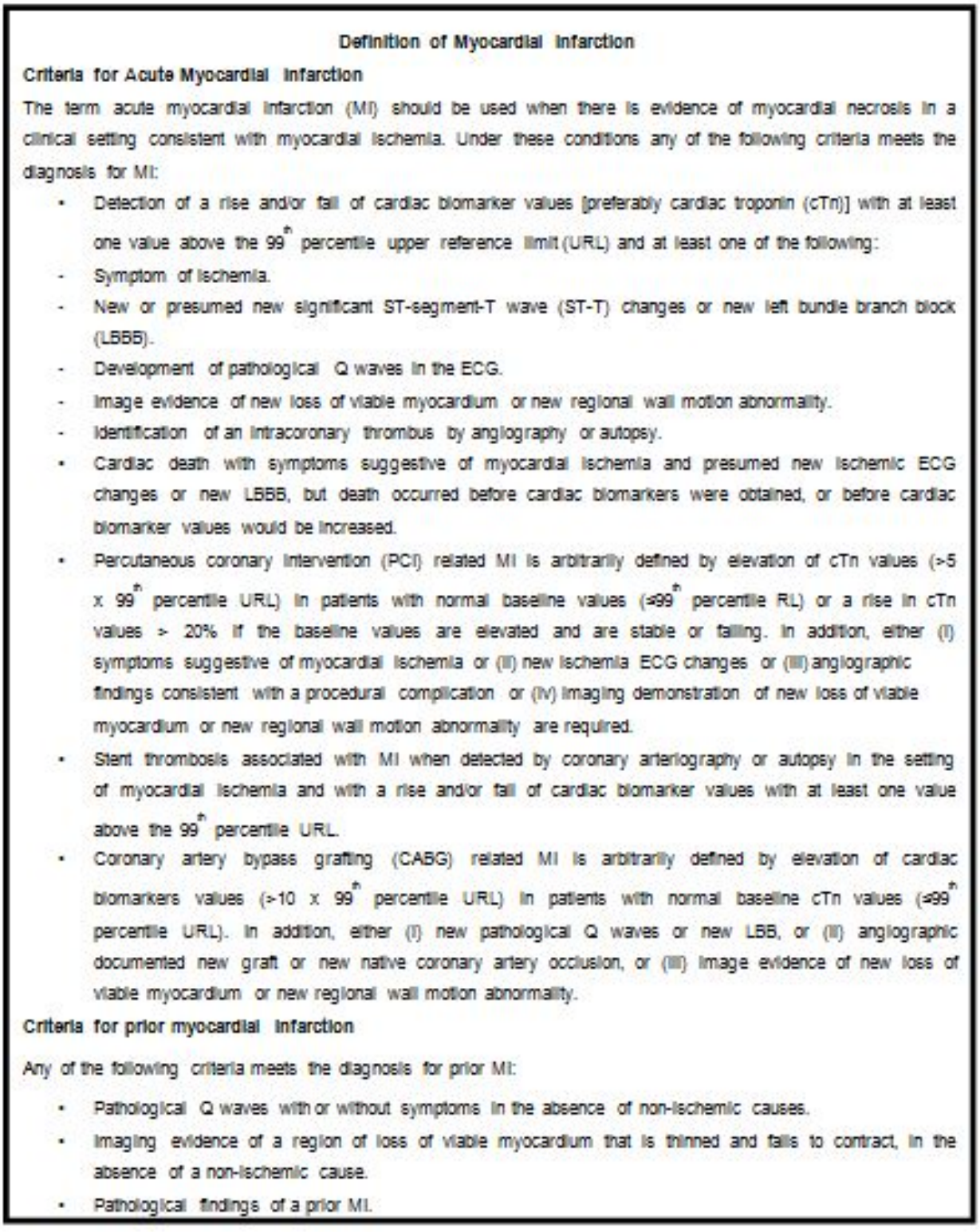

**Figure 4:** Cumulative hazard rations for mortality among patients who had symptomatic or asymptomatic myocardial infarction or an isolated elevation of a cardiac biomarker or enzyme after surgery [5].

However, what was seen in the following scientific scenario, related to combination of the enzymatic presentation with both, electrocardiographic pattern and symptomatology, was a changing as to the look of the prognostic value of enzymatic profile, and this because some authors observed clinically the effects of such information over the outcome [5,17,23]. For example, when a total of 15,133 individuals was analyzed undergoing noncardiac surgery, in a Cohort study, the peak TnT value of 0.02 ng/mL was identified in 11.6% of them, and it was observed that values situated between 0.02 and 0,29 ng/mL showed a higher impact on mortality than what was supposed to be expected [17]. Figure 6 shows the association between TnT observed peak values and their effect on 30-day mortality. At the same time, in this research, considering the effect on prognostic relevance, TnT values showed a population attributable risk of 41.8%, the largest value. However, under the clinical point of view, the signals and symptoms were not taken into account, aiming to better elucidate their relationship with the laboratory aspects of what was found, in terms of peak values.

Nonetheless, as a sequence, another group of researchers put in check the third definition of myocardial infarction, taking into account the discrepancy observed between symptomatology (with or without association to electrocardiographic findings) and the smallest possible enzymatic curve obtained, which, as a consequence, was exerting effect on the postoperative mortality [3], because AMI was being considered only a 'myocardial necrosis in a clinical setting consistent with acute myocardial ischemia' [7]. So, since then, the authors have proposed that Myocardial Injury after Noncardiac Surgery (MINS) may be applied; aiming to contemplate such missing data, rather than using the previous definition put into practice, about myocardial infarction, but that may be useful, at the same time, as a complementary concept [7]. Considered as 'myocardial injury caused by ischemia (that may or may not result in necrosis), this has prognostic relevance and occurs during or within 30 days after noncardiac surgery', the authors suggest, in fact, a 'broader' definition. In such cohort including 15,065 individuals submitted to a nocardiac surgery, a TnT peak plasma concentration as small as 0.04 ng/mL or greater 'with or separately without an ischemic feature', was considered as independent predictors of 30-day mortality. Taking into account the referred peaks as a consequence of myocardial ischemia, the authors reported MINS diagnostic with an incidence of 8%, and a population-attributable risk of 34% (95% CI, 26.6-41.5), the largest value found. Surprisingly, in those individuals characterized as having MINS, 84.2% didn't experience an ischemic symptom, relevant information, considering the perioperative period. As complementary information, only in 48.2% of the individuals, with MINS diagnostic, it was possible to observe ischemic symptoms in according to third universal definition. Furthermore, an impressive percentage of 9.8%, representing the 30-day mortality in cases of MINS, was a value incredibly similar to the cases in which MINS occurred with ischemic feature (13.5%), which is, in other words, 'classically' diagnosed as myocardial infarction [7].

## Perioperative Conduct and Perspectives

Several variables are associated with perioperative period and exert some degree of attributable risk. Perioperative instability, tachycardia, bradycardia, diabetes, hypertension, peripheral vasculopathy, can trigger an imbalance between supply and demand, which, even being small, as seen, may induce to an imperceptible but deleterious myocyte dysfunction [7,23]. Considering the aspects related to management, either during the anesthesia or in the immediate care, in the postoperative period, undoubtedly, critical moments that require extreme attention, one must act proactively with a view to maintaining microcirculatory perfusion at all costs [27]. However, it is not so easy to reach this objective, once the postoperative routine conduct is already extensively well established in the intensive care unit, and, even that, the mortality rates of MI and AMI are still quite similar, as it is possible to observe [5,7]. In this way, if, on the one hand, such behaviour is an obligation for the practitioners of perioperative medicine, on the other, at the same time, it becomes a challenge. Especially in urgent and emergent surgical procedures, in which innumerable variables act producing a tendency to progressively worsen the cellular energy deficit, a careful look at a clinical scenario is essential. For example, the elapsed time until surgical procedure, the triggered inflammatory response, bleeding, body temperature, surgical time, in case of cardiac surgery, the characteristics related to bypass conditions, and others, need to be considered as a pivotal point of a sequence of events, which will potentially deflagrate MI [28,29]. However, even when a conduct is adequately adopted, it may not necessarily result in an immediate response, something that, unfortunately, certainly acts as deleterious mechanisms. Anyway, the 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery [27], and the 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease [2], list a range of guidelines, which certainly help in driving and in prevention of adverse outcome.



**Definition of Myocardial Infarction**

**Criteria for Acute Myocardial Infarction**

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and at least one of the following:
  - Symptom of ischemia.
  - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Image evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile RL) or a rise in cTn values > 20% if the baseline values are elevated and are stable or falling. In addition, either (I) symptoms suggestive of myocardial ischemia or (II) new ischemia ECG changes or (III) angiographic findings consistent with a procedural complication or (IV) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary arteriography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarkers values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (I) new pathological Q waves or new LBB, or (II) angiographic documented new graft or new native coronary artery occlusion, or (III) image evidence of new loss of viable myocardium or new regional wall motion abnormality.

**Criteria for prior myocardial infarction**

Any of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause.
- Pathological findings of a prior MI.

**Figure 5:** Third definition of Myocardial Infarction [3].

Going in the same direction, it seems equally important to identify individuals in whom postoperative monitoring is required, through the use of such assays, since more than 80% of cases, considered as having myocardial injury, may not be early diagnosed [7], which is also

equally harmful. In turn, if it is considered a high risk population to be included in such analysis, a routine screening will logically become imperative. For example, studying 625 individuals with either known coronary artery disease or multiple risk factors, submitted to major non- cardiac surgery, a research recently published found that (i) 98.5% of them had detectable preoperative hs-cTnT, with a median hs-cTnT of 12 ng/L [IQR 8.3,19.3], and 41% presented dosage above 99$^{th}$ percentile of the upper reference (URL) [30]; (ii) a percentage statistically significant showed a rise in the plasmatic levels postoperatively; and (iii) the preoperative values found were independent predictors of AMI and 3-year mortality.

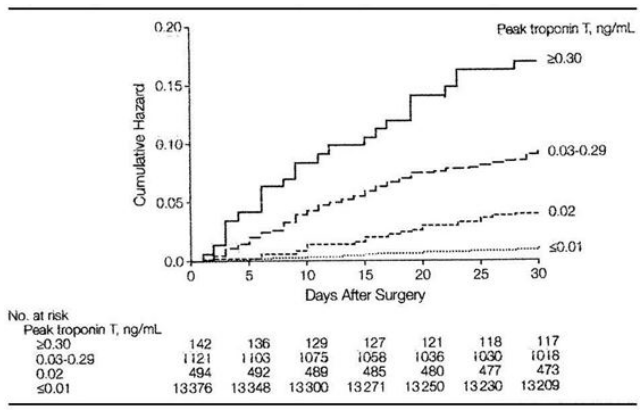



**Figure 6:** Cumulative hazard ratios for 30-day mortality among patients in whom the peak TnT values, after noncardiac surgery, were considered [17].

Although the authors bring an interesting discussion about absolute and relative hs-cTnT changes, called Δhs-cTnT, showing the necessity of its preoperative dosage, the study was made using a selected high risk population, not allowing the generalizability, considering the philosophical thinking of 'Construct Validity'. Furthermore, the criteria used to diagnose AMI were based on Third Definition of AMI [3], which, although still extensively used, is under a recent criticism, if applied in perioperative period, as discussed previously.

Aiming to help thinking contextually, in Figure 7 it is possible to evaluate a flow chart that explores the possible diagnosis, associated with the adverse event.

Finally, in terms of perspectives, it seems that researchers have expanded their way of thinking, as they have identified an existing association of biomarkers with stable coronary artery disease (CAD) and congestive heart failure (CHF), related to long term discharge. Additional concepts were extracted from observations that, first, found the hs-cTnT discriminating the outcome related to CAD from the outcome deflagrated by CHF, around five years later, and, second, resulted from the association of hs-cTnT with both death and MI feature almost five years later, after an identifiable kind of profile, in terms of curve [32,33]. As another point of view to be established, a special attention has been given by our group, to the association of acceptable hemoglobin levels with respective enzymatic curve, aiming to see if the extracts of hemoglobin to be found exert any kind of effect on the enzymatic curve. After that, if any type of interaction can be observed the next step will be the search for the population attributable risk of such interaction.

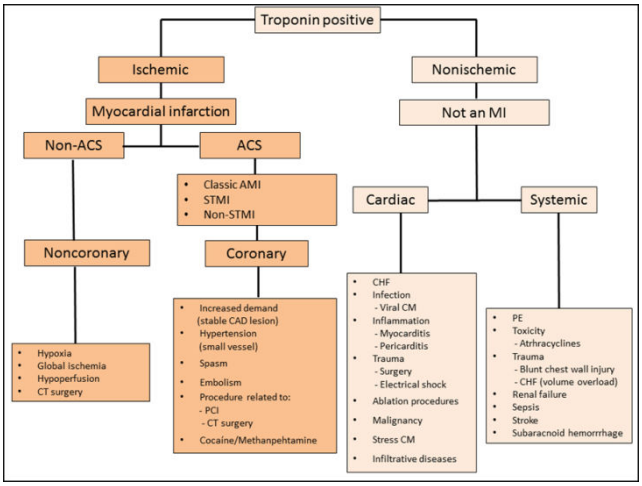



**Figure 7:** Diagnostic algorithm [31].

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