Review article

The combined measurement of high-sensitivity cardiac troponins and natriuretic peptides: a useful tool for clinicians?

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An enormous amount of experimental and clinical evidence has clearly shown that the measurement of cardio-specific biomarkers is able to significantly and independently improve the diagnostic accuracy and risk stratification in cardiovascular diseases. Furthermore, many recent studies have reported that the measurement of cardio-specific biomarkers has a positive impact also on the management and outcome of patients with cardiovascular diseases. Considering the significant and independent information associated with cardio-specific biomarkers, several studies have recently reported that the combined dosage of natriuretic peptides and cardiac troponins may be convenient not only for the diagnosis, prognosis, and treatment of heart disease, but also for general screening of the population for individuals with high cardiovascular risk. Due to the higher cost of cardio-specific biomarkers compared with other laboratory tests, the clinical adequacy of the combined measurement of natriuretic peptides and cardiac troponins must be carefully evaluated. Consequently, an increase in the clinical use of a laboratory test should be based not only on the favorable pathophysiological characteristics of a biomarker, but also on the high performance of the methods used for biomarker dosing. The purpose of this review is to discuss the clinical relevance and the possible cost efficiency of the combined dosage of natriuretic peptides and cardiac troponins in some clinical conditions, in particular those most frequently observed in patients with critical illnesses admitted to the emergency room.

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Introduction

In the last 20 years the measurements of cardio-specific biomarkers, such as cardiac troponins I (cTnI) and T (cTnT) and of cardiac natriuretic peptides (CNPs) [especially the active hormone brain natriuretic peptide (BNP) and the inactive N-terminal pro-BNP (NT-proBNP)], have progressively acquired more and more clinical relevance in the diagnosis, in the prognostic stratification, and also in the guide to the treatment of patients with cardiovascular diseases.[1] In fact, all the most recent international guidelines recommend the use of CNPs as first choice markers in the diagnosis and follow-up of patients with heart failure.[2,3] Furthermore, in 2018, the document Fourth Universal Definition of Myocardial Infarction[4] established that cTnI and cTnT (cTns) are the biomarkers of choice for the evaluation of myocardial damage and the diagnosis of myocardial infarction MI. Therefore, the use of CNPs is universally considered appropriate in the diagnosis and follow-up of patients with heart failure,[2,3] whereas that of troponins in the differential diagnosis of acute coronary syndromes (ACS).[4–6]

However, the measurement of cTns should not be considered as a test (YES/NO) for the differential diagnosis of ACS, as also the measurement of CNPs should not be interpreted exclusively with a test for diagnosis (YES/NO) of heart failure. The indication for a broad spectrum use in all patients with cardiovascular diseases of the measurement of cardio-specific biomarkers arises from considerations that concern both their biochemical characteristics and their pathophysiological properties,[6–9] as well as the high analytical performance of immunometric methods that are currently used for their measurement.[1,8,10–13]

The immunometric assay methods for cardio-specific biomarkers have changed over the last 10 years not only the diagnostic algorithm of the differential diagnosis of the most important heart diseases, such as acute MI (AMI) and heart failure, but are also changing the

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classification, risk stratification, and follow-up of patients with cardiovascular diseases. As always happens with the most important scientific discoveries, the new evidence, acquired with the use of cardio-specific biomarkers, has provided answers to some fundamental pathophysiological and clinical questions, but they have also opened up new avenues for experimental and clinical research. In particular, cardio-specific biomarkers are able to detect in the general population those individuals at higher risk of an accelerated progression to a symptomatic heart failure.[7–9,12,14] It is clear that this possibility opens up new perspectives not only from the point of view of prevention, but also of clinical and therapeutic interventions capable of influencing the natural history of heart disease itself.[8,9,14] However, these new applications of cardio-specific biomarkers involve a broadening of the spectrum of pathophysiological and clinical conditions, in which the measurement of CNPs and/or cTns should be considered appropriate, including perhaps the screening of cardiovascular risk in the general population.

In this review the authors discuss the relevance and clinical efficiency of the combined measurement of the two cardio-specific biomarkers especially in some of the most frequent and serious clinical conditions found in patients admitted to the Emergency Department (ED) in critical conditions.

Cardio-specific markers: analytical characteristics and pathophysiological relevance

Both cTns and CNPs are present in cardiomyocytes and in circulation in different iso-forms. Although the mAbs, used for cTns and CNPs measurement, currently show a high affinity for specific epitopes of respective biomarkers, nevertheless they also present various interferences with other proteins, peptides, or different molecules present in the plasma of both healthy subjects and patients with cardiovascular diseases. Furthermore, it is very difficult to develop immunometric systems for biological substances that have plasma concentrations in healthy subjects around a few ng/l such as cTns and CNPs. It is therefore important to analyze the quality specifications of the immunometric methods for cardio-specific biomarkers, because both the accuracy and the clinical interpretation of the measurement depend on analytical characteristics and performances of the cTns and CNPs methods.

Quality specifications of high-sensitivity methods for cardiac troponins

The document published in 2018 by the scientific societies AACC (American Association for Clinical Chemistry) and IFCC (International Federation of Clinical Chemistry)[6] establishes two fundamental criteria to define a method for the measurement of high-sensitivity cardiac troponins (hs-cTn). The first criterion establishes that the 99th percentile of the distribution of cTnI or cTnT values in the reference population (99th percentile upper reference limit) must be measured with an error (expressed as variation coefficient) of 10% or less.[6] The second, more restrictive, criterion establishes that a high-sensitivity method must measure the concentrations of cTnI and cTnT with values above the limit of sensitivity (Limit of Detection, LoD) of the method in at least 50% of individuals of a reference population consisting of at least 300 apparently healthy women and men.[6] In practice, considering that women generally show lower values of cTnI and cTnT than men, this criterion requires that a high-sensitivity cTn method (hs-cTn) should be able to provide measurable values of the marker in a population of at least 300 apparently healthy adult women.[6] Theoretical considerations[8] and experimental evidence in animals and humans[15–18] indicate that the value of the 99th percentile upper reference limit (URL) corresponds to the amount of cTn present in about 40 mg of myocardial tissue (approximately 0.015% of the total myocardial mass). In agreement with these studies,[8,15–18] a plausible hypothesis could be that the cTn circulating levels in apparently healthy adult normal subjects should be considered as an index of the physiological renewal of myocardial tissue. The estimation of 99th percentile URL value of cTn is influenced not only by the demographic characteristics of the reference population (sex, age, and probably ethnicity), but also (and perhaps above all) by the inclusion/exclusion criteria adopted for assessment of health status of 'apparently healthy' volunteers enrolled in clinical studies.[12,18–20] Many clinical studies have recently shown that some individuals, apparently free of cardiac disease, with cTn values near to the 99th percentile URL value, are at higher cardiovascular risk and for progression to heart failure and earlier mortality rate.[14] There are many clinical, cardiac, and extra-cardiac conditions, which are capable of producing myocardial damage without clinical evidence of acute myocardial ischemia[4,14,15] (Table 1). In some of these clinical conditions, the combined measurement of CNPs and cTns may facilitate the differential diagnosis of cardiac disease in patients admitted to the ED.

Quality specifications and clinical relevance of assay methods for brain natriuretic peptide/N-terminal pro-brain natriuretic peptide

The CNPs measurement presents analytical difficulties as these peptides, especially the active molecules ANP (atrial natriuretic peptide) and BNP (brain natriuretic peptide), circulate in the blood in a few ng/l concentration, so extremely sensitive immunometric methods are needed to distinguish peptides respectively present in healthy subjects from those characteristics of patients with mild heart failure.[1,7,11] Furthermore, CNPs belonging to the same family (ANP or BNP), which derive from the same precursor (i.e., proANP and proBNP), are very

Table 1 Pathophysiological mechanisms related to myocardial injury, according to the Fourth Universal Definition of Myocardial Infarction[4]

Myocardial injury related to acute myocardial ischemia
(Type 1 AMI)
Atherosclerotic plaque disruption with thrombosis
Myocardial injury related to acute myocardial ischemia because of oxygen supply/ demand imbalance
(Type 2 AMI)
Reduced myocardial perfusion
Coronary artery spasm, microvascular dysfunction
Coronary embolism
Coronary artery dissection
Sustained bradyarrhythmia
Hypothension and/or shock
Respiratory failure
Severe anemia
Increased myocardial oxygen demand
Sustained tachyarrhythmia
Severe arterial systemic hypertension
Other causes of myocardial injury
Related to cardiac diseases
Heart failure
Myocarditis
Cardiomyopathies
Takotsubo syndrome
Coronary revascularization procedures
Cardiac interventions and cardiac surgery
Catheter ablation
Cardiac defibrillation procedure
Cardiac trauma
Related to noncardiac and systemic diseases
Inflammatory diseases and sepsis
Chronic renal disease
Ischemic and hemorrhagic stroke
Pulmonary diseases (massive pulmonary embolism, pulmonary hypertension)
Cardiac involvement in systemic infiltrative diseases (e.g., amyloidosis, sarcoidosis, sclerosis)
Cardiotoxic chemotherapeutic agents (e.g. anthracyclines, alkylating agents, antimetabolites) and drug abuse (e.g. cocaine)
Severe diseases (e.g. patients admitted to ICU)
Strenuous physical exercise (marathon, long-lasting cycling races, endurance races)

AMI, acute myocardial infarction; ICU, intensive care unit.

similar to each other.[1,7,11] For this reason, in recent years immunometric methods have been developed that use mAbs and chemiluminescence detection for the measurement of both active and inactive CNPs.[1,7,11,21–23]

From a pathophysiological point of view, the main limitation of immunoassay methods for BNP is the interference due to the precursor peptide proBNP, which has lower biological activity than BNP.[11] Another limitation of CNPs measurement is that the active peptides (ANP and BNP) are quickly degraded by proteolytic enzymes, so to limit peptide degradation it is recommended to use plasma with EDTA (an inhibitor of some plasma proteases), and it is also preferable to transport the sampling tubes on ice and centrifuge them at 4–8 °C and perform the assay as soon as possible.[11] The inactive NT-proBNP is more stable and can be used as a matrix, both serum and EDTA or heparinized plasma.[11]

Circulating levels of BNP and NT-proBNP are higher in women than in men of the same age.[11,24,25] This sex-dependent difference is due to the stimulating action of women's steroid hormones and, conversely, to the inhibitory action of men's steroid hormones on CNPs production by cardiomyocytes.[24,25] The difference in concentration between the sexes tends to decrease progressively after the age of menopause.[24,25] The BNP and NT-proBNP assay methods have a wide working range (the values found in heart failure patients can be up to 100 times higher than normal values).[11,26] This difference in values allows distinguishing healthy subjects not only from patients in the earliest stages of the disease (functional class NYHA I or II), but also from subjects who have some structural cardiac alterations, without heart failure symptoms (stage B of the natural history of the disease).[26,27] The circulating levels of CNPs are increased in practically all heart diseases and also in many other systemic pathological conditions in which there is an activation of the neuro-immune-hormonal system (Table 2). Some additional pathophysiological considerations are necessary for a correct interpretation of results obtained with immunometric methods in heart failure patients, especially with the introduction of a new pharmacological combination called ARNI (Angiotensin Receptor-Neprilysin Inhibitors). In patients who respond positively to treatment with ARNI, there is a significant reduction in circulating levels of inactive peptide NT-proBNP and cTns already in the first weeks of treatment. However, if patients respond to treatment with a sustained improvement in the clinical condition, after a few weeks the BNP levels also tend to decrease in parallel to those of the inactive NT-proBNP peptide and cTns.[11]

Table 2 Brain natriuretic peptide/N-terminal pro-brain natriuretic peptide levels in some clinical conditions

Clinical conditions	Circulating levels
(A) Cardiovascular diseases	
Heart failure	Greatly increased
AMI	Increased
Hypertensive cardiomyopathy	Increased
(B) Pulmonary diseases	
Acute dyspnea	Increased
Pulmonary embolism	Greatly increased
Chronic obstructive pulmonary disease	Increased
(C) Endocrine-metabolic diseases	
Hyperthyroidism	Increased
Hypothyroidism	Decreased
Cushing syndrome	Increased
Hyperaldosteronism (primitive or secondary)	Increased
Diabetes mellitus	Normal or increased
(D) Liver cirrhosis with ascites	Increased
(E) Acute or chronic renal insufficiency	Increased or greatly increased
(F) Paraneoplastic syndromes	Normal or increased
(G) Ischemic or hemorrhagic stroke	Increased

AMI, acute myocardial infarction.

Combined measure of cardio-specific biomarkers is a valuable resource for the clinician: some examples related to specific clinical conditions

In the next paragraphs some clinical conditions that are frequently found in patients admitted to the ED, which may present high values of both cTns and CNPs, will be treated. In particular, we will discuss the working hypothesis that the combined measurement of both cardio-

specific biomarkers can help clinicians in the differential diagnosis between these conditions and other cardiac and noncardiac pathologies.

Primary prevention

Many studies, including three meta-analyses, have shown that cardiovascular risk tends to increase in apparently healthy subjects of both sexes, even for cTnI and cTnT values lower than the 99th percentile URL.[27–36] These studies also indicate that some individuals, apparently free of heart failure symptoms, who have cTnI and cTnT values above the interquartile range of the reference normal population, are at greater risk for cardiovascular events and also for progression to heart failure.[28–37] In particular, Willeit *et al.*[29] published a meta-analysis including 28 studies, involving 154 052 individulas. These authors reported that relative risks comparing the top versus the bottom troponin tertiles were 1.43 (1.31–1.56) for cardiovascular diseases (11 763 events), 1.67 (1.50–1.86) for fatal cardiovascular diseases (7775 events), 1.59 (1.38–1.83) for cardiac disease (7061 events), and 1.35 (1.23–1.48) for stroke (2526 events).[29] Neumann *et al.* showed that among 22 651 patients admitted to ED the prevalence of MI was 15.3%. Lower high-sensitivity troponin concentrations at presentation and smaller absolute changes during serial sampling were associated with a lower likelihood of MI and a lower short-term risk of cardiovascular events.[35] In the North-Trøndelag Health (HUNT) study,[36] authors evaluated the prognostic role of high-sensitivity troponin I (hs-TnI) assay in a cohort of the general population, including 9005 participants free from known cardiovascular disease at baseline, evaluated for a median follow-up period of 13.9 years. The addition of hs-TnI to established cardiovascular risk prediction models led to a net reclassification improvement of 0.35 [95% confidence interval (CI) 0.27–0.42] compared with the classical cardiovascular risk factors.[36] It is important to note that the tertile with the highest risk showed a cutoff value of 10 ng/l for women and 12 ng/l for men (99th percentile URL value: for women 15.6 ng/l, for men 34.2 ng/l).[36] Therefore, the results of these studies demonstrated that the combined mortality and cardiovascular risk significantly increases even for hs-cTnI values much below the 99th percentile URL values, divided for sex.[28–37] In particular, a central role must be played by the measurement of CNPs in the screening of high-risk patients that should be carried out by family doctors and also by some specialists (such as diabetologists) at the general population level, as recommended by a recent document of the HFA (Heart Failure Association) of the ESC (European Society of Cardiology).[27]

Acute coronary syndromes

In the last 20 years, the development of new generations of methods for the measurement of cTnI and cTnT, characterized by a progressive and continuous improvement of the analytical sensitivity, has drastically reduced the time of diagnosis in patients admitted to the ED with suspicion of ACS. If at the beginning of the 2000s it took more than 12–24 h for rule-in and rule-out of ACS-AMI, then in the years 2005–2007 we went to about 6–12 h, and currently with highly sensitive methods for cTnI and cTnT assay the ESC guidelines recommend 3-h diagnostic algorithms (or even less, especially for rule-out, in some specific cases).[5] Values of hs-cTn above the 99th percentile URL certainly indicate the presence of myocardial damage, but for the diagnosis of AMI it is necessary that the damage is acute and of ischemic origin.[4] There is a 'gray' zone that includes the values of hs-cTn, between the 99th percentile URL and about 2000 ng/l, in which the differential diagnosis between AMI and other causes of heart damage is more difficult. The probability that a patient with suspected ACS actually has an AMI progressively increases with biomarker values and becomes very high for hs-cTn values greater than 2000 ng/l.[5]

In one study, cTnT was measured in a random sample of 651 individuals (average age 65 years) admitted to ED triage without diseases considered able to produce significant myocardial damage.[38] Indeed, 36% individuals of this population aged at least 65 years had cTnT values more than the 99th percentile URL (i.e. 14 ng/l), compared with only 2% of those aged less than 65 years.[38] Irfan *et al.*[39] found 88 patients with acute chest pain and high cTnT values (15.4% of 572 consecutive patients admitted to ED), but without cardiac or noncardiac conditions that could explain the increase in cardiac-specific biomarkers.[39] The factors most frequently related to high cTnT values in these patients were in order of importance: advanced age, chronic renal failure and/or disease, hypertension, previous AMI.[39] More recently, Lee *et al.*[40] measured the hs-cTnI in 918 patients admitted consecutively to the ED without suspicion of ACS. High values of hs-cTnI were found in 114 (12.4%) patients, of whom only 2 (0.2%) had the final diagnosis of type 1 AMI, and another 3 (0.3%) the diagnosis of type 2 AMI, and finally for the remaining 109 patients (11.9%) the diagnosis of myocardial damage.[40] Elevated values of hs-cTnI were closely correlated with age, renal function, multiple comorbidities, and worse prognosis. Finally, other more recent studies have reported that the measurement of hs-cTnI in addition to standard risk scores was able to identify type 2 AMI patients compared with patients with myocardial injury,[41] and was also able to identify patients at higher risk of death and rehospitalization in patients with type 2 AMI.[42]

Considering the document Fourth Universal Definition of Myocardial Infarction,[4] the most difficult task for the clinician is to distinguish between a possible diagnosis of AMI from all other causes of high hs-cTn. Indeed, the main clinical problem in the differential diagnosis of ACS is to identify among patients with high values of hs-cTn values only the patients (about 30% of the total) who actually have had AMI.[5] It is important to note that in

patients with ACS, admitted to ED with cTn below the 99th percentile URL, increased CNPs can offer incremental prognostic information for mortality and occurrence of heart failure.

Heart failure

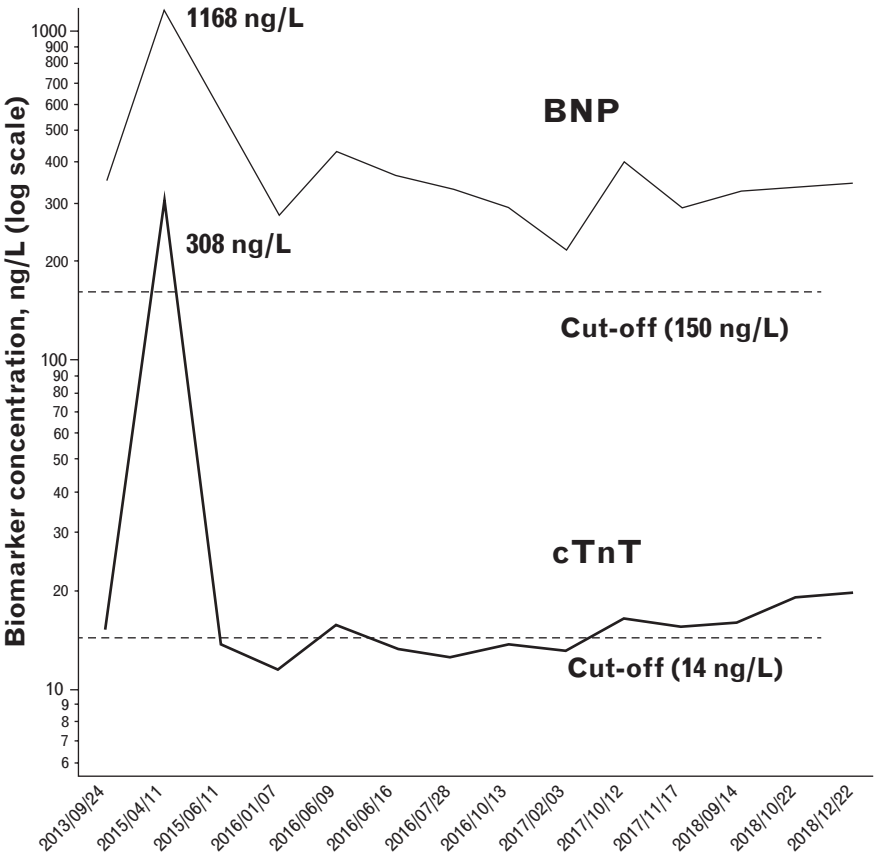
The cardio-specific biomarkers play an important role in patients with heart failure. The measurement of CNPs is recommended with the highest degree of evidence by all national[13] and international[2,3,27] guidelines both for diagnosis and prognostic stratification of patients with heart failure. On the other hand, the more frequent cause for high cTn values in patients, admitted to ED with age more than 65 years and with some comorbidities, is heart failure. In Fig. 1, the values of cTnT and BNP are reported in a patient (man of 60 years) who presented the first episode of acute heart failure in 2013. This patient was then monitored with cardio-specific biomarker measurement for a period of 5 years. Both the specific biomarkers dropped rapidly after the first heart failure episode, but then NT-proBNP remained above the cutoff value (i.e. 150 ng/l) about two times, whereas cTnT fluctuated around the 99th percentile URL value (i.e. 14 ng/l).

Levels of hs-cTnI or cTnT just above the 99th percentile URL, which do not vary significantly over 3 h and are accompanied by BNP/NT-proBNP values with much higher values (more than three times) compared with decisional value of the method, strongly suggest the presence of both myocardial damage and heart failure. In contrast, a significant increase (or decrease) in hs-cTn levels throughout 3-h algorithm, accompanied by high levels in BNP (>80 ng/l) or NT-proBNP (1170 ng/l in men, and 2150 ng/l in women) suggests AMI with severe impairment of myocardial function.[43] In AMI patients, CNPs correlate positively with the area of necrosis and negatively with LVEF (left ventricular ejection fraction).[43,44] Another study reports that AMI patients who have NT-proBNP less than 1115 ng/l have a high probability of recovering cardiac function.[45] In contrast, AMI patients with cardiogenic shock have NT-proBNP more than 12 782 ng/l and a high risk of poor prognosis, despite coronary revascularization.[46]

Atrial arrhythmias

It is well known that atrial arrhythmias (especially atrial fibrillation and flutter) constitute a serious public health problem that is constantly increasing, so much so that it is

Fig. 1



Cardiac troponins T and brain natriuretic peptide values measured in a patient with heart failure with a 5-year follow-up.

considered one of the most common causes of admission to ED in Western countries.[47] Patients with atrial fibrillation have an average age of about 70 years; women are slightly prevalent (51–53%) and often have comorbidities, such as hypertension, heart failure, chronic kidney disease, heart valve alterations, chronic obstructive pulmonary disease, and diabetes mellitus.[47] Patients with atrial fibrillation frequently present with symptoms such as dyspnea, whereas acute heart failure is present in approximately 65% of cases.[27] Two recent systematic reviews with meta-analysis confirmed that atrial fibrillation is associated with the risk of developing both AMI (also in patients without coronary artery disease) and heart failure.[48,49] Patients with atrial fibrillation have elevated values of both CNPs (generally more than five times compared with the reference limits in acute episodes) and cTns (in about 10–15% of patients).[50–64] In particular, high levels of CNPs predict the risk of developing atrial fibrillation in the short term with better accuracy than clinical findings and classic markers of cardiovascular risk in the community.[54] More recently, cTnI and cTnT, measured with high-sensitivity methods were found to be independent predictors of acute atrial fibrillation episodes.[55–59,62–64]

Syncope

Syncope is generally defined as a transient loss of knowledge due to cerebral hypoperfusion and characterized by rapid onset and spontaneous and complete recovery.[65,66] The prevalence of syncope in patients admitted to ED varies from 0.8 to 2.4%.[65] The 2018 ESC guidelines classify syncope into three groups according to the possible pathophysiological mechanism: mediated by nerve reflexes, due to orthostatic hypotension, or cardiac causes.[66] Patients with cardiac causes of syncope are more frequently elderly (>60 years), men and with a history of heart disease. Risk of death or adverse events is much higher in patients with syncope of cardiac origin rather than those noncardiac diseases.[65,66] As regards risk stratification, in 2015 a meta-analysis (11 studies, including 4246 patients) evaluated the prognostic accuracy of both CNPs (1353 patients) and cTn measured with nonhigh sensitivity (2693 patients) or high-sensitivity (819 patients) methods.[67] This meta-analysis showed that both CNPs and hs-cTn have a good degree of prognostic accuracy in patients admitted to ED with syncope.[67] Regarding the differential diagnosis of syncope, CNPs and hs-cTn values were reported significantly higher in patients with cardiac rather than noncardiac causes of syncope.[68] Furthermore, the combined assay of CNPs and hs-cTn significantly increase the diagnostic performance of laboratory tests with an Area Under the Curve ROC value (AUC 0.81) superior to that obtained with the most common clinical scores used for cardiovascular risk evaluation.[68]

Pulmonary embolism

Pulmonary embolism is considered the third most frequent cardiovascular disease with an annual incidence of approximately 39–115 per 100 000 inhabitants.[69] The 2019 ESC guidelines recommend an initial stratification of patients with acute pulmonary embolism for determining the appropriate therapeutic management approach.[69] The use of cardio-specific biomarkers in patients with acute pulmonary embolism is recommended by international guidelines especially for the evaluation of the risk of early death.[69] A meta-analysis showed that elevated troponin concentrations were associated with an increased risk of mortality, both in unselected patients (odds ratio 5.2, 95% CI 3.3–8.4) and in those who were hemodynamically stable at presentation.[70] Elevated cTn on admission may be associated with a worse prognosis in the acute phase of pulmonary embolism; about 60% of pulmonary embolism patients have elevated cTnI and cTnT values when high-sensitivity methods are used.[69] Increased circulating levels of cTns have relatively low specificity and positive predictive value, but high-negative predictive values for early mortality in the setting of acute pulmonary embolism.[69,71] Right ventricular pressure overload due to acute pulmonary embolism is associated with increased myocardial stretch, which leads to the release of CNP.[69] Similarly to cTns, elevated CNPs show specificity and positive predictive value (for early mortality) in normotensive patients with pulmonary embolism, but low levels of CNPs are capable of excluding a hemodynamic compromise in acute pulmonary embolism.[69,72]

Stroke

AMI, ischemic heart diseases, and stroke are serious cardiovascular diseases which may lead to hospitalizations, and require periodical medical monitoring and lifelong drug use, thus having a high impact on public health and Healthcare Service expenditure,[73] also in Italy.[74] Cerebrovascular accidents (stroke) together with AMI constitute the most important causes of death and are the major causes of disability in developed countries.[74] From a pathophysiological point of view the ischemic stroke, caused by thrombosis or embolism (about 80% of cases), should be distinguished from the hemorrhagic type, due to the rupture of an artery in the cerebral circle.[73] Brain imaging technologies [such as computed tomography (CT) and MRI] are currently considered indispensable for the diagnosis of stroke,[75] but they, nevertheless, have limitations that concern above all the fact that they are expensive and time-consuming, requiring a relatively long time for the investigation.[76,77] Considering these limitations of CT and MRI examinations, some authors have advocated the use of cardio-specific biomarkers, not only for cardiovascular risk stratification,[76,77] but also for detection of concomitant presence of cardiovascular complications (such as myocardial dysfunction, myocardial injury, or AMI) in patients with stroke.[78–81] Indeed, alterations of myocardial function (systolic and/or diastolic) are quite frequent in patients with hemorrhagic stroke or ischemic stroke.[78–82] On the

other hand, it is well known that atrial fibrillation is often associated with systemic thrombo-embolism, which in turn can cause cerebral ischemia.[83,84] According to these pathophysiological considerations, it is not surprising that many studies (including two meta-analyses) report that patients with stroke, both ischemic and hemorrhagic, currently show elevated CNPs.[85–92] Furthermore, using high-sensitivity cTn assays, the vast majority of patients with acute ischemic stroke show detectable circulating cTn values[93–99] whereas approximately half of patients show cTn levels elevated above the 99th percentile URL.[99]

Both high values of cardio-specific biomarkers (CNPs and cTn) are associated with a more severe prognosis and mortality risk, even in the short term (within 3 months).[90–97] Due to the close association between stroke and cardiac disease, since 2013 the AHA/ASA guidelines for the early management of patients with acute ischemic stroke recommend assessment of cardiac biomarkers (preferably cTn) in all patients presenting with acute ischemic stroke.[100] Indeed, results of some recent studies suggest that the presence of AMI in patients with stroke may be underestimated.[98,99] In addition, these results indicate that hs-cTn assay may be very useful to detect the presence of AMI in patients with stroke early on.[98,99] According to these results,[98,99] a positive hs-cTn test can allow more rapid access to specific thrombolytic treatment and cardiac coronary intervention, as recommended by international guidelines.[5,100]

Sepsis

Sepsis still remains a significant clinical problem with a very high prevalence of the syndrome called SIRS (systemic inflammation response syndrome), which can affect up to a third of patients admitted to the hospital and up to 50% in patients admitted to the ICUs.[101–104] Septic shock is present in about 2–3% of hospitalized patients, with a greater incidence (10–15%) in patients admitted to the ICU.[101–104] The incidence of sepsis is increasing in European and North American countries, whereas mortality appears to be slightly but continuously decreasing from 1990 to the present (by about 20–30%).[102–104] However, in patients admitted to the ICU mortality is still 40–70% and septic shock still represents the leading cause of death in the ICU.[102–104]

Heart failure is a frequent complication of severe sepsis and septic shock, reaching a 50% incidence in this serious clinical condition.[104–107] Consequently, an early detection of the presence of a ventricular dysfunction is fundamental to establishing an appropriate therapy.[103,104,107] Many studies (including two meta-analyses) have shown that CNPs are elevated in patients with sepsis and are associated with a poor prognosis.[108–119] The results of these studies suggest that the CNPs assay can identify patients early on with sepsis with a ventricular dysfunction, even subclinical, and in this way clinicians can establish an adequate therapy.[108,120,121]

Regarding the measurement of cTns, practically all studies that used high-sensitivity methods,[122–131] including a meta-analysis,[132] reported elevated cTns in patients with severe sepsis, or septic shock. These results indicate that myocardial damage is almost always detectable with hs-cTn methods in patients with severe sepsis and above all septic shock.[122–134] In the last 5 years, the type 2 AMI, secondary to supply-demand oxygen mismatch, has been more frequently observed in patients with sepsis in relation to the progressive increase in the use of hs-cTn methods.[134–137] On the contrary, at this moment, there is no gold standard that discriminates type 2 AMI and nonischemic myocardial injury from each other and from type 1 AMI,[136–139] so clinicians should take care to make an accurate differential diagnosis between type 1 and type 2 AMI according to the recommendations of international guidelines.[4,5,136,137] As expected, the presence of high values of both cardio-specific biomarkers (CNPs and hs-cTn) in patients with sepsis is associated with significantly worse prognosis.[115,131]

Pathophysiological considerations

In this review we discussed some severe clinical conditions that are very frequent in patients admitted to the ED and are characterized by the presence of cardiac dysfunction and myocardial damage. Indeed, the aim of this article was to discuss the hypothesis that the presence of cardiac dysfunction associated with myocardial damage greatly affects the patient's outcome, even when the disease is not strictly primitively cardiological, but recognizes a primitive etiopathology in other organs (cerebral stroke and pulmonary embolism) or is systemic (sepsis).

Another objective of this review was to highlight how in some critical clinical conditions the impairment of cardiac function (detected by high CNPs) is often associated with myocardial damage (detected by high hs-cTn). It must still be emphasized that it is possible to demonstrate this association between dysfunction and cardiac damage only when sensitive immunometric methods with adequate reference values are used for the measurement of the two cardio-specific markers.[6,8,11,12,15,26,136] Furthermore, the presence of cardiac dysfunction and myocardial tissue damage may still be subclinical in the early stages of these clinical conditions, and so it cannot be detected solely with the help of clinical examination and the most advanced cardiac imaging techniques. The use of cardio-specific markers allows the early detection of cardiac dysfunction and myocardial damage and therefore clinicians can quickly establish an adequate therapy, to reduce mortality and morbidity, especially in critically ill patients.[6,8,11,12,15,26,136]

Another important observation is that the associated measurement in the same patient of CNPs and hs-cTn is never redundant, but instead complementary. Indeed, high values of both biomarkers always increase the risk of

Table 3 Comparison of circulating levels of brain natriuretic peptide/N-terminal pro-brain natriuretic peptide and cardiac troponins I/cardiac troponins T in patients admitted to emergence department with some common cardiac or extra-cardiac diseases

Clinical conditions	BNP/NT-proBNP	cTnI/cTnT*
(A) Cardiovascular diseases		
Acute heart failure	Greatly increased	Increased
Type 1 and 2 AMI	Increased	Greatly increased
Hypertensive cardiomyopathy	Increased	Normal or increased
Supraventricular tachyarrhythmias	Greatly increased	Normal
Myocarditis	Increased	Increased or greatly increased
Cardiac amyloidosis and sarcoidosis	Increased	Increased
Aortic dissection	Increased	Normal or increased
Takotsubo syndrome	Increased	Increased
(B) Pulmonary diseases		
Pulmonary embolism	Greatly increased	Normal or increased
Chronic obstructive pulmonary disease	Increased	Normal or increased
(C) Acute or chronic renal failure	Greatly increased	Normal or increased
(D) Ischemic or hemorrhagic stroke	Increased	Normal or increased
(E) Syncope	Increased	Normal or increased
(F) Sepsis and septic shock	Greatly increased	Increased

* Measured with high-sensitivity assay methods. AMI, acute myocardial infarction; BNP, brain natriuretic peptide; cTnI, cardiac troponins I; cTnT, cardiac troponins T; NT-proBNP, N-terminal pro-brain natriuretic peptide.

mortality and severely debilitating outcomes in patients admitted to the ED in critical conditions.[115,131]

Although in severe acute pathologies the two biomarkers are currently both abnormal, one biomarker is more increased above the critical threshold than the other. In Table 3 some clinical conditions with the respective circulating levels of CNPs and hs-cTn are reported. The relationship between the circulating levels of the two biomarkers in these different clinical conditions covers a wide range of values and can, therefore, be used as additional information to be used for a differential diagnosis (Table 3). For example, we can consider on the one hand the AMI type 1, which presents very high circulating levels of the hs-cTnI and hs-cTnT (more than three times the 99th percentile URL),[4,5] whereas CNPs in patients with AMI are generally only moderately elevated no more than two or three times the decision value,[27] unless severe ventricular dysfunction is also present, which may suggest the presence of (or the high risk of developing) a cardiogenic shock.[120,140,141] On the other hand, we can consider an acute episode of heart failure, in which CNPs values are generally very high by more than five times the threshold value (distinct for age and sex),[2,3,7,27] while often hs-cTn values are not generally so increased, unless AMI type 1 or 2[4,142,143] is also present. Moreover, in atrial arrhythmias (fibrillation and flutter) the CNPs are generally elevated, whereas hs-cTn can be, especially in younger patients, below the 99th percentile URL, suggesting that the acute arrhythmic episode did not cause significant cardiac damage.[4,27,62–64]

Conclusion

In patients admitted to ED in critical conditions, the combined use of the two cardio-specific markers turns out to be of help in the differential diagnosis and in the stratification of the risk, but above all it is able to detect a dysfunction and cardiac damage early on. This evidence of myocardial damage allows the clinicians to establish a more adequate and more effective therapy for the patient early on, especially in some critical conditions, in which the primitive pathophysiological mechanism of the acute event is not of a cardiac nature (stroke, pulmonary embolism, sepsis). Although the guidelines have not yet fully take into consideration the clinical importance of the combined measurement of the two cardio-specific biomarkers, the available evidence in the literature suggests that the combined measurement of CNPs and hs-cTn is always appropriate when a cardiac or extra-cardiac disease can cause myocardial dysfunction and/or injury.

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Conflicts of interest

There are no conflicts of interest.

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