Clinical features and prognosis of patients with acute and chronic myocardial injury admitted to the emergency department

Running head: **Acute and chronic myocardial injury**

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Abbreviations: ED: Emergency Department. Cardiac troponin levels (cTn)

Abstract

BACKGROUND: This study aimed to investigate the clinical features and prognosis of acute and chronic myocardial injury without clinical evidence of myocardial infarction in patients admitted to the emergency department.

METHODS: We analysed the clinical data of all consecutive patients admitted to the emergency department during the years 2012 and 2013 who had at least two determinations of troponin I (TnI Ultra Siemens, Advia Centaur) and without a diagnosis of myocardial infarction. Clinical events were evaluated in a 3-year follow-up.

RESULTS: A total of 1201 patients met the study's inclusion criteria and were included in the analysis (833 with cTnI below the 99th percentile, 261 with acute myocardial injury and 107 with chronic myocardial injury). During a median follow-up equal to a more than 36 months, mortality and rehospitalisation for heart failure were significantly higher in patients with acute or chronic myocardial injury with respect to patients without myocardial injury. No differences were observed in overall mortality between patients with acute and chronic myocardial injury, or in the rate of readmission due to acute coronary syndrome. However, the risk of readmission due to heart failure (adjusted HR 2.17, 95%CI: 1.26-3.75, p=0.005) was higher in patients with chronic myocardial injury.

CONCLUSIONS: Mortality in the long-term follow-up is high and similar in acute and chronic myocardial injury; however, the risk of readmission due to heart failure is higher in patients with chronic myocardial injury compared to patients with acute myocardial injury.

INTRODUCTION

In the Emergency Department (ED), it is usual to detect cardiac troponin levels (cTn) above the 99th percentile of reference in patients who do not have a definitive diagnosis of type 1 myocardial infarction (1). In this clinical context, the fourth universal definition of myocardial infarction emphasises the need to distinguish between myocardial injury and type 2 myocardial infarction, depending on the presence or absence of symptoms or clinical signs of acute myocardial ischaemia. However, the distinction between type 2 myocardial infarction and myocardial injury is sometimes controversial because they can coexist (2). In addition, both type 2 myocardial infarction and myocardial injury are very frequent in clinical practice and both processes are associated with poor prognosis (3,4,5).

Myocardial injury is acute when a new dynamic rise/fall pattern in cTn levels is detected, while myocardial injury is considered chronic when this pattern is absent and there are persistently high levels of the biomarker. It has been described that the prognosis of (acute or chronic) myocardial injury depends on the cardiac or non-cardiac condition that causes it (5) and that the prognosis of chronic myocardial injury is closely related to the elevation level of cTn (6). To date, differences between the processes that cause acute myocardial injury and chronic injury have not yet been studied in depth, and even less, the impact that these processes have on the prognosis. Our hypothesis is that the prognosis of acute myocardial injury could be different from that of chronic myocardial injury because the two processes occur in different clinical scenarios: in acute myocardial injury, the presence of detectable and in some cases reversible physio-pathological events is frequent, while in the chronic injury, the presence of cardiac or structural systemic disease is not modifiable.

The aim of our work is to characterise the population with acute and chronic myocardial injury detected in an emergency department and determine whether there are differences in the long-term prognosis of the two entities.

METHODS

Study population

A retrospective cohort study that includes all patients admitted to the emergency department of a university hospital between 1 January 2012 and 31 December 2013 who underwent serial determination of Troponin I (cTnI) at the discretion of the treating physician. The cTnI determinations were carried out in accordance with the chest pain protocol of the centre, which specifies that an initial cTnI determination must be made at the time of admission and

at least one more determination 6 hours later. The biomarker determination was also requested at the discretion of the attending physician in patients with less typical symptoms or in those with suspected acute coronary syndrome. The patients were identified through the determinations made in the Central Laboratory. The exclusion criteria were: age under 18 years, patients who had recovered from cardiac arrest, patients with myocardial infarction (type 1 or 2), patients with an isolated cTnI determination, patients with a residence outside of our reference area, or those lost to follow-up.

Categorization of the studied population

To exclude patients with myocardial infarction, the diagnosis of type 1 infarction was established by the consensus of 2 cardiologists when patients with cTnI levels higher than the 99th percentile had clinical and/or electrocardiographic alterations compatible with myocardial ischaemia in which the pathophysiological mechanism was suspected to be due to rupture of an atheromatous plaque resulting in an intracoronary thrombus (7). Patients were diagnosed with type 2 myocardial infarction when there was evidence of myocardial injury and clinical data compatible with myocardial ischaemia due to an imbalance between the myocardial supply and the consumption of oxygen following the criteria of Saaby (8).
The final study population consisted of patients with cTnI levels below the 99th percentile (cTnI negative - reference population) and patients with at least one cTnI determination above the 99th percentile, and who met the diagnostic criteria for acute or chronic myocardial injury as set out in the fourth universal definition of myocardial infarction. Patients with evidence of a dynamic rise/fall pattern (changes above 20% in cTnI levels) are classified as Acute Myocardial Injury. When this pattern is absent, the elevated cTnI level is considered to be stable or without dynamic changes and patients are classified as Chronic Myocardial Injury. Thus, the cohort was divided into 3 groups: patients with negative cTnI, patients with Acute Myocardial Injury and patients with Chronic Myocardial Injury.
The local ethics committee approved carrying out the study and declared it exempt from the request for informed consent.

The evaluated clinical variables

The following variables were collected from the electronic medical record: baseline characteristics (cardiovascular risk factors and all the background included in the Charlson index (9)), reason for consultation (chest pain, dyspnoea, syncope), clinical constants of the acute episode (blood pressure, heart rate), electrocardiogram data (rhythm, interventricular

conduction disorder), analytical data (glycaemia, haemoglobin count, glomerular filtration determined with the formula MDRD-4 (Modification of Diet in Renal Disease)), clinical assessment by the on-call cardiologist, hospital admission decision and main diagnoses upon discharge.

Troponin I

All determinations of cTnI were performed with the same immunoassay technique (Tn I-Ultra from Siemens, Advia Centaur) in the same laboratory. The reference limit for TnI positivity was >0.039 ng/mL, which corresponds to the 99th percentile of a reference control group, with an analytical imprecision expressed by a coefficient of variation less than 10%. The analytical performance of this assay has been previously validated (10).

Events

The main variable of the study was the combined event of death and rehospitalisation for heart failure. As a secondary variable, each component of the combined event was analysed separately as was re-admission for acute coronary syndrome. The information of events was obtained for the follow-up by reviewing the electronic medical record and the mortality records.

Statistical analysis

Categorical variables are presented as a number and percentage. Continuous variables are reported as a median and interquartile range. The baseline characteristics of patients were compared using the Kruskal-Wallis test for continuous variables and Pearson´s c^2 test for categorical variables. The Wilcoxon rank sum test was used for continuous variables when patients with acute and chronic myocardial injury were compared. We performed survival analyses using univariable and multivariable Cox regression models to assess the relationship of acute and chronic myocardial injury with all-cause death and the composite of all-cause death and HF. The proportional hazards assumption was tested by assessing the constancy of the parallel plotted lines in the log-log graph. The Gray method, including all-cause death as a competing risk, was adopted for analyses of HF and MI readmission. The following variables were included in the multivariable model as covariates: age, sex, history of myocardial infarction, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, arterial hypertension, diabetes mellitus, glomerular filtration rate and maximum cTn level. Adjusted survival and cumulative incidence curves were plotted. The statistical analysis was

performed using STATA V.13.0 (College Station, Texas, USA). A p value of <0.05 was considered significant.

RESULTS

Baseline characteristics

A total of 1201 patients met the study inclusion criteria and were included in the analysis (Figure 1). Patients with myocardial injury were older and had more cardiovascular history, higher comorbidity, as expressed by the Charlson index, and a lower prevalence of chest pain with respect to patients with cTnI levels below the 99th percentile of reference (Table 1). Patients with myocardial injury also showed signs of greater haemodynamic affectation (increased tachycardia, less O_2 saturation), greater deterioration of renal function, lower haemoglobin levels and a higher frequency of atrial fibrillation at the time of emergency care. Admission to hospital and hospital mortality were also higher among patients with myocardial injury.

Clinical profile of patients with acute or chronic myocardial injury

Compared to patients with acute myocardial injury, patients with chronic myocardial injury were older, had a similar comorbidity index, chest pain as an index symptom was less prevalent, and the maximum cTnI level was lower. Patients with acute myocardial injury were admitted more frequently than those with chronic myocardial injury, but hospital mortality was similar.

Table 2 shows the main diagnoses among patients with acute and chronic myocardial injury. Heart failure, tachyarrhythmias, sepsis and anaemia were the most prevalent among patients with acute myocardial injury compared to patients with chronic myocardial injury. Syncope was more prevalent in patients with chronic myocardial injury.

Events

During a median follow-up equal to more than 36 months in the three groups analysed, mortality, rehospitalisation for heart failure and the combined mortality and rehospitalisation for heart failure events were significantly higher in patients with acute or chronic myocardial injury with respect to patients without myocardial injury (Figure 2 and Table 3). However, a proportion close to 5% of the 3 groups was re-admitted for acute coronary syndrome, without statistically significant differences between them. When a direct comparison was made

between patients with acute and chronic myocardial injury, no differences were observed in overall mortality (adjusted HR 1.02, 95% CI:0.74-1.40, p=0.914), or in the rate of readmission due to acute coronary syndrome (adjusted HR 1.00, 95% CI:0.37-2.68, p=0.995); however, the risk of readmission due to heart failure (adjusted HR 2.17, 95% CI:1.26-3.75, p=0.005) was clearly higher in patients with chronic myocardial injury (Figure 3).

DISCUSSION

Our study demonstrates that in ED clinical practice, among patients with myocardial injury who do not meet diagnostic criteria for myocardial infarction, approximately two thirds have a dynamic pattern compatible with acute myocardial injury, while one third have a pattern compatible with chronic myocardial injury. Mortality in the long-term follow-up is high and similar in both groups; however, the risk of readmission due to heart failure is clearly higher in patients with chronic myocardial injury compared to patients with acute myocardial injury. Thus, both entities, and especially chronic myocardial injury, probably reflect an underlying structural heart disease, often undiagnosed and unsuspected, which predisposes the patient to the development of heart failure and increases the risk of mortality.

In previous studies we have shown that the prognosis of patients with troponin elevations (with stable levels or dynamic changes) is worse than that of patients with type 1 infarction (1), and that the prognosis of patients with myocardial injury or type 2 infarction is similar (3). The present study adds important information because it uses a study population of patients with acute and chronic myocardial injury, evaluating the appearance of adverse cardiovascular events in a long-term follow-up. Therefore, we can affirm that within the group of patients with elevated troponin levels in the emergency department and without myocardial infarction criteria, those with stable levels have a worse prognosis, especially due to the higher risk of heart failure and mortality.

Myocardial injury in non-hospitalized patients

In the population studies, associations have been consistently found between cTn concentrations and the risk of future cardiovascular events (11,12,13). The temporary increases in the cTn concentrations in mainly healthy individuals of different ages are also associated with an increased risk of incident cardiovascular disease and death. In most studies, it seems that the association between elevated cTn concentrations and cardiovascular disease is stronger with respect to structural heart disease than coronary artery disease (13)(14). Increased cTn concentrations have been associated with an increase in the mass and thickness of the left ventricle wall and a reduction in the left ventricular systolic function in elderly men

(15). Likewise, the increase in cTn concentrations has also been associated with myocardial fibrosis detected through cardiac magnetic resonance, an early sign of subclinical myocardial damage (16). However, the exact mechanism that motivates the release of troponin from cardiomyocytes is unknown. It has been suggested that it could be due to necrosis, apoptosis, normal myocyte turnover or the release of troponin degradation products (17).

Myocardial injury in patients treated in Emergency Departments

There have been few studies on non-ischaemic myocardial injury in patients with an acute pathology treated in an Emergency Department. In the cohorts of patients with chest pain without a diagnosis of myocardial infarction, a gradual increase in the risk of cardiovascular disease and death has been found in relation to increasing concentrations of cTn (18,19). It has been reported that in patients who do not have type 1 myocardial infarction, any elevation in the cTn levels (1), even at levels detectable below the 99th percentile of reference (19), has prognostic implications for total death and/or development of heart failure in the follow-up.

In the Roos series, after excluding patients with myocardial infarction, 19% of the population had elevated levels of Troponin T (cTnT) above the 99th percentile (6). In a total of 4052 patients with elevated cTnT without myocardial infarction, they detected a stable elevation pattern in 1327 patients (33%), which was similar to that of patients with chronic myocardial injury observed in our study. The risk of adjusted mortality doubled for concentrations from 5-9 ng/L compared with concentrations <5 ng/L, and subsequently increased gradually until reaching a risk 10 times higher for concentrations of cTnT ≥50 ng/L. The annual mortality rate in patients with cTn T concentrations between 15 and 29 ng L_1 was 12%. This demonstrates that the risk of adverse events during follow-up is closely related to the magnitude of troponin elevation detected, similarly to patients who survive a myocardial infarction (20). A new study recently published by Roos et al. assesses the risk of adverse events in patients with chronic myocardial injury compared to patients with myocardial infarction without ST-segment elevation, and found an increased risk of death from any cause for patients with chronic myocardial injury (21). Although our results are consistent with those observed by Roos et al., this study differs from ours in several aspects. Firstly, they used the ultrasensitive cTnT as the analytical method, whereas we used cTnI analysed by a contemporary method. Secondly, and perhaps more relevant, the population of the Roos study is clearly selected, and only includes subjects with chest pain, it is a significantly younger sample and with less comorbidity. Our study was carried out in a non-selected population of patients who came to an ED with diverse symptoms, and thus represents a real scenario of usual clinical practice.

Sarkisian classified patients with myocardial injury without myocardial infarction into 5 clinical conditions: cardiac causes secondary to ischaemia (e.g. arrhythmias, heart failure), cardiac causes not secondary to ischaemia (e.g. cardiac surgery, myocarditis, endocarditis), non-cardiac causes (e.g. infections, renal failure), multifactorial causes and indeterminate causes (5). The 4-year prognosis was different depending on the clinical condition that caused the troponin elevation, and patients with non-cardiac conditions or a multifactorial condition had the highest risk of mortality. However, the Salkisian series does not distinguish transient cTn elevations from stable elevations and therefore is not comparable to our data.

Unlike patients with myocardial infarction, who are investigated, treated and followed-up meticulously, patients with transient or persistently elevated levels of hs-cTn are rarely investigated or even hospitalised (22,23). When they are investigated, some of them have a heart disease that was previously unknown (24). In the Roos series, only 33% of these patients were studied using echocardiography. However, 14% of the patients studied with echocardiography had an ejection fraction lower than 40%, which indicates that some of these patients had a baseline cardiopathy that was not previously detected (24). In addition, there is no consensus on the relative absolute value of change (delta) that allows to differentiate with certainty an acute myocardial injury from a chronic myocardial injury. Several studies have evaluated the diagnostic performance of the delta pattern to establish the differential diagnosis between type 1 and type 2 infarction (25,26). In general, the delta pattern does not provide the diagnostic performance of other clinical variables and in any case it has been shown that patients with a delta pattern and type 2 infarction have an excess of mortality with respect to patients with type 1 infarction, although this is not always confirmed in the adjusted statistical analysis (27). In the case of non-ischaemic myocardial injury, having uniform criteria would simplify and facilitate the study design as well as interpreting the findings. Although the association between high hs-cTn concentrations and the risk of cardiovascular disease and death is strong and begins at normal levels, our data do not confirm an increase in the risk of myocardial infarction. In fact, the rate of myocardial infarction was similar to that of patients with negative cTn. Therefore, assessing these patients to detect a possible baseline coronary disease would probably not lead to a decrease in the infarction rate, but it could lead to a lower rate of heart failure or mortality in the follow-up.

Limitations

Our study has several limitations. First, the times of the onset of symptoms and arrival in the emergency department was not recorded. Second, blood samples were requested upon arrival

at the emergency department and 6 hours later, at the discretion of the attending physician, as occurs in usual clinical practice. The current definition of myocardial infarction requires that a rise/fall pattern is detected in troponin levels. However, in clinical practice, it is not mandatory to detect dynamic changes in troponin levels for the diagnosis of myocardium. In the Bjurman series, a total of 1178 patients had a final diagnosis of myocardial infarction; however, in 26% of these patients, the relative changes in troponin levels were less than 20% (28). Surprisingly, patients with changes in troponin levels below 20% had higher mortality in the adjusted analysis. These limitations in the magnitude of the rise/fall pattern of the cTn levels in myocardial infarction can also occur in patients without myocardial infarction. That is, the distinction between acute and chronic myocardial injury based on the delta pattern also probably has some limitations.

Conclusions

In the absence of clear indications in clinical practice guidelines, we believe that patients with elevated cTn levels without myocardial infarction and without previously diagnosed heart disease should be carefully evaluated, regardless of whether they have acute or chronic myocardial injury (20). Future studies should research the performance of cardiological diagnostic tests in this group of patients to try to determine the cause of cTn elevation and evaluate whether it is possible to modify the adverse prognosis in this population group.

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Figure legends

Figure 1. Flow diagram of patients. The distribution of patients in the three groups of the study is depicted. TnI: Troponin I.

Figure 2. Adjusted survival and cumulative incidence in patients with cTnI <99th percentile and with acute and chronic myocardial injury. A) All-cause death. B) Heart failure. C) MACE.

Figure 3. Forest plot showing adjusted hazard ratios for all-cause death, heart failure readmission and major adverse cardiovascular events for patients with chronic myocardial injury.