BRIEF ARTICLE

Prevalence of the Different Causes of Troponin Elevation in a Multicenter Registry in Bariloche. Link Between the Magnitude of Troponin Elevation and its Etiology

Prevalencia de las diferentes causas de elevación de troponinas en un registro multicéntrico de Bariloche. Vinculación entre la magnitud de la elevación y la etiología

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ABSTRACT

Objectives: To determine the prevalence of acute myocardial infarction (AMI) and other etiologies in patients with elevated troponin, to associate troponin values with the etiology, and to define the optimal cut-off point to differentiate AMI from other causes.
Methods: All patients with elevated troponin who were hospitalized within 1 year and registered in the REGIBAR study were included. Magnitude was analyzed with the highest dose value/baseline value. The ROC curve and the Youden index were used to determine the optimal cut-off point.
Results: A total of 150 cases were included (age: 66.3 ± 13.8 years, 71% male); 109 AMI (age: 71.1 years, 63.5% male), 18 (12%) with other cardiac causes, 15 (10%) with non-cardiac causes, and 8 (5.3%) with no evident etiology. The optimal cut-off point for troponin dose/baseline value to discriminate AMI was > 3.15. Conclusions: A 73% of inpatients with elevated troponin were AMI cases (> 3.15 times the cut-off point). Heart failure was the second most common cause of elevated troponin.
Key Words: Troponin - Acute myocardial infarction - Heart failure

RESUMEN

Objetivos: Establecer la prevalencia de infarto agudo de miocardio (IAM) y otras etiologías en pacientes con troponina elevada, relacionar su valor con la etiología y definir el mejor punto de corte para diferenciar un IAM de otras causas.
Material y métodos: Se incluyeron todos los pacientes con troponina elevada internados en un año e incorporados al registro REGIBAR. Para analizar la magnitud utilizamos el valor dosado más elevado/valor de referencia. Para establecer el mejor punto de corte se realizó curva ROC y el índice Youden.
Resultados: Ingresaron 150 casos (edad: 66,3 ± 13,8 años, 71% hombres); 109 IAM (edad: 71,1 años, 63,5% masculinos), 18 (12%) otras causas cardiacas, 15 (10%) causas no cardíacas y en 8 (5,3%) no se obtuvo etiología. El mejor punto de corte troponina dosada/valor de referencia para discriminar IAM fue >3,15. Conclusiones: En pacientes hospitalizados con troponina elevada el 73% de los casos fue IAM (>3,15veces el punto de corte). La segunda causa más frecuente de elevación fue la insuficiencia cardíaca.
Palabras clave: Troponina. Infarto agudo de miocardio. Insuficiencia cardíaca

INTRODUCTION

The functional structure of the cardiac muscle includes different isoforms of tropomyosin and troponin (TnI, TnC, TnT). These proteins are released into the blood, as myocytes are damaged both by ischemia and by direct noxa. The development of even more sensitive assays for measuring TnI and TnT has turned troponins into biomarkers of increasing interest, to the point that the ESC/ACCF/AHA Third Universal Definition of Acute Myocardial Infarction (AMI) (1) prefers troponin over creatine phosphokinase (CPK). Development of highly sensitive troponin assays with internal variation value < 10% enabled the detection of high values (exceeding 99th percentile), which would aid in the detection of myocardial damage that was not detected with previous assays.

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(2) Over the years, it was observed that elevated troponins are also found in non-cardiac diseases. (3) In daily practice, physicians are often faced with a diagnostic challenge when a patient presents with possibly coronary symptoms and troponin elevation. (3) This is partly due to the increase in sensitivity as a result of new high-sensitivity troponin reagents, very useful in these clinical scenarios, which also involves a decrease in specificity that leads to overdiagnosis of AMI and unnecessary hospitalizations. For this reason, an epidemiological study on other cardiac conditions that may increase troponins, and to what magnitude, could contribute to optimizing the interpretation of outcomes. Some registries described case series to identify those other conditions, but in general, they are studies of a reference center. To date, we are unaware of any population-based study on all the cases with elevated troponins in Argentina that could provide those data.

The present study aims at identifying the causes of elevated troponins measured over a year in Bariloche, and whether those causes are due to AMI or other cardiac causes, or have a non-cardiac origin. Similarly, by associating the etiology to the magnitude of elevation, we aimed at determining the optimal cut-off point to discriminate AMI from other causes of troponin elevation.

METHODS

Troponin data were extracted as part of the REGIBAR study. (4) REGIBAR was a 365-day prospective registry of all patients (P) with first —fatal and non-fatal— AMI, carried out in the city of Bariloche between mid-2014 and mid-2015. To avoid underreporting, all elevated troponins in the city were obtained during the study period. This method allowed us to prospectively include all the elevated troponins requested for suspected ischemic heart disease. All consecutive patients > 18 years of age with elevated troponin, in the 4 hospitalization centers in Bariloche over the year of the registry, were included in this study. The reagent for qualitative troponin was used in only one center (31 patients), and quantitative troponin was used in the remaining 3 (119 patients); troponin I was measured in 2 centers, and troponin T in one center. The magnitude of the increase was analyzed using the ratio of the highest dose value and the maximum normal baseline value for each laboratory. AMI was defined according to the ESC/ACCF/AHA Universal Classification of Myocardial Infarction. In patients with non-AMI-related troponin increase, the study investigator responsible for each center had to record the pertinent alternative diagnosis in a pre-designed chart. An Events Committee made up of two independent cardiologists (D.A. and J.G.) from each center blindly and independently determined the diagnosis in doubtful cases using data from the medical records. The ROC curve and the Youden index were used to determine the optimal cut-off point for troponin with diagnostic precision to discriminate AMI from non-AMI causes.

RESULTS

During the year when patients were included in the REGIBAR, 150 cases with elevated troponins were included (mean age: 66.3 ± 13.8 years, 71% men); 109 (72.7%) were diagnosed AMI (mean age: 71.1 years, 63.5% male), 18 (12%) with other cardiac causes, 15 (10%) with non-cardiac causes, and 8 (5.3%) with no evident etiology (Table 1). The main cardiac cause other than AMI was congestive heart failure (CHF) (13 cases); chronic kidney disease (CKD) (6 cases) was the main cause within the non-cardiac group.

In the 119 cases with quantitative measurements, the level of troponin increase was assessed in terms of the condition causing it: a median of 10.1 was found in the AMI group, 2.7 for other cardiac causes, and 1.4 ($p < 0.001$) for non-cardiac causes (Figure 1).

The optimal cut-off point for the maximum dose troponin ratio/baseline value to discriminate AMI from non-AMI causes in this population was > 3.15, with 74% and 71% sensitivity and specificity, respectively. The area under the ROC curve was 0.769.

DISCUSSION

In this study, which assessed all elevated troponins over one year in the city of Bariloche, we managed to find the probable diagnosis in a large number of cases. In this regard, we found that 72.7% of the cases were attributed to AMI, 12% to other cardiac causes, 10% to non-cardiac causes, and 5.3% to elevated troponins which could not be diagnosed. Similarly, Blich M. et al. (5) in a retrospective analysis of hospitalized patients at Rambam Medical Center, Haifa, Israel, found that 572 (65%) out of the 883 patients with increased troponin levels were diagnosed as having AMI. The study also found that the main non-IAM causes of increased troponin included 89 (28%) sepsis, 49 (16%) congestive heart failure (CHF), 21 (7%) cerebrovascular event, and 11 (4%) myocarditis. As we can see, AMI was the main cause of troponin elevation, followed by non-ischemic cardiac causes. After analyzing the magnitude of troponin elevation, the etiologies causing the increase —following AMI— were myocarditis

Table 1. Causes of positive troponin values during the REGIBAR

Etiology	n	%
AMI	109	72.67
HF	13	8.67
Unknown	8	5.33
CKD	6	4.00
Stroke	2	1.33
Cancer	3	2.00
HBP	2	1.33
Myocarditis	2	1.33
ARDS	2	1.33
Pulmonary fibrosis	1	0.67
Takotsubo	1	0.67
PTE	1	0.67

AMI: Acute myocardial infarction. HF: Heart failure. CKD: Chronic kidney disease. HBP: High blood pressure. ARDS: Acute respiratory distress syndrome. PTE: Pulmonary thromboembolism.

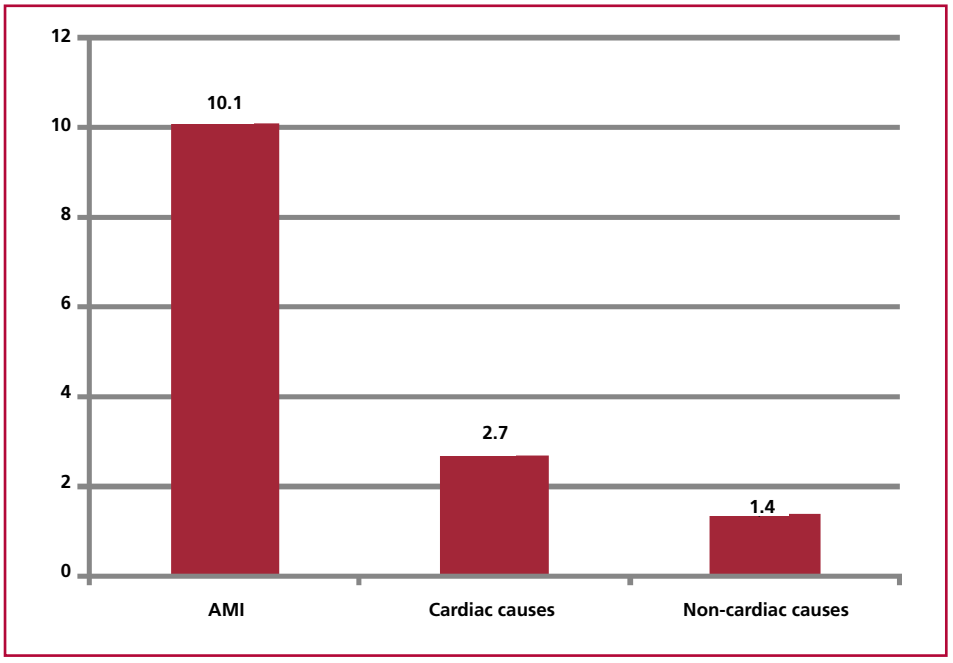

Fig. 1. Number of troponin elevations over the baseline value according to etiology.

AMI: Acute myocardial infarction

and pulmonary embolism.

In the REGIBAR, heart failure was the main non-ischemic cardiac cause, accounting for 8.6% of the cases (13 patients). A major registry like the ADHERE Registry (6), with a significantly larger sample of patients (n = 67924), found that 6.2% of individuals had troponin elevation. This group showed higher in-hospital mortality (OR 2.55), independent of other predictive variables. In this regard, Melki D. et al. (7), in a subanalysis of the SWEDEHEART Registry including all the patients consulting Swedish healthcare facilities because of symptoms suggestive of an acute coronary syndrome, demonstrated that the maximum troponin value discriminated between patients with and without AMI on the one hand, and patients with significant coronary stenosis, left ventricular systolic dysfunction and death during 1-year follow-up on the other.

In our series of patients, the entity that most commonly increased troponin above its cut-off point was AMI (10.1 times), other cardiac causes to a lesser extent, and non-cardiac causes to an even lesser extent. We were unable to find any analysis in the literature on the number of times troponin is elevated above the 99th percentile in the different patient groups. However, when elevation was non-cardiac, or was cardiac but unrelated to acute coronary syndromes, the increased biomarker was slightly above the cut-off point, and for a shorter time. (8)

In our registry, we found that a 3.15-fold increase in the cut-off point has a sensitivity of 74% and a specificity of 71% for the diagnosis of AMI, with lower values in cardiac non-AMI-related causes, and even lower in non-cardiac causes. These attractive data should be taken into account, since in daily practice, physicians sometimes encounter cases of doubtful clinical manifestations and troponin elevation. In this regard, the present study suggests that both dosed troponin values and the magnitude of elevation above the cut-off point could be used to consider different diagnoses, knowing that a cause other than coronary disease is unlikely with a 3-fold increase in the normal value, whereas lower values may open the possibility of other causes.

Limitations

This study has many limitations. While this is a population-based study of consecutive cases and prospective collection, troponin assay is requested at the physician's discretion, which does not allow for homogenization of the study population. Similarly, the cut-off point for troponin elevation to discriminate coronary artery disease from other etiologies should be prospectively validated before taken as definitive. This limitation, however, represents an interesting hypothesis-generating finding. Since this was a multicenter study, reagents for troponin assays were different, including a qualitative equipment in the public hospital, which should be excluded from the evaluation of the range of increase based on the causes.

CONCLUSIONS

In this population-based study, the main cause of troponin elevation in hospitalized patients was acute myocardial infarction, followed by congestive heart failure. Regarding the magnitude of the increase, the etiology causing the highest troponin value was acute myocardial infarction, which confirms that a 3.15-fold increase vs. the baseline value is an adequate cut-off point to discriminate AMI from other etiologies.

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