How Can Biomarkers Be Useful in the Management of Acute Heart Failure?

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Introduction

Heart failure (HF) can be a serious disease if not treated properly. One of the markers of severity is precisely hospitalization due to HF, often called acute HF or acutely decompensated (ADHF).[1] ADHF involves patients with new HF or an exacerbation of chronic HF. The most common symptoms and signs in ADHF are dyspnea and edema of the lower limbs. Dyspnea, when it occurs in isolation, with no specific signs of HF, can hinder the diagnosis. In this context, HF guidelines recommend the measurement of biomarkers when there is doubt in the diagnosis of HF.[1] Moreover, the measurement of biomarkers is recommended to improve prognostic accuracy.[1]

In this article, we highlight how to use already established cardiac biomarkers, such as natriuretic peptides (NP) and high sensitivity cardiac troponins (HS-cTn) T and I, in the management of ADHF, and point out possible future systemic biomarkers, which may be useful in this scenario.

Natriuretic Peptides

B-type natriuretic peptide (BNP) and the N-terminal pro-B-type natriuretic peptide (NT-proBNP) – are the gold standards in the diagnosis and prognosis of HF.[1,2] These are produced almost exclusively by the myocardium of the ventricles, in response to excessive pressure and volume in the heart. The major stimulus for the release of these peptides is congestion.[2,3] Therefore, their values are quite high in ADHF.

Although these values are continuous variables, the use of cutoff points facilitates clinical application. We recommend the use of two cutoff points – one to rule out the diagnosis of HF and the other to confirm the diagnosis of HF. Between the two cutoff points there is a "gray zone", where we can find different diagnoses, such as HF itself or others, such as pulmonary embolism, respiratory sepsis, chronic obstructive pulmonary disease), among others. In the gray zone, NPs are of little use, and additional tests are necessary to make the diagnosis.[4,5]

The suggested cutoff points to rule out the diagnosis of HF in the emergency room are BNP<100 pg/mL or NT-proBNP<300 pg/mL.[4,5] To confirm the diagnosis, the BNP cutoff point is 400 pg/mL (or 500 pg/mL, for some authors). For NT-proBNP, Januzzi et al. created stratified cutoff points by age group, which correct for age and renal function. For individuals in the age groups <50 years, 50-75 years, and >75 years of age, the suggested cutoff points are 450, 900, and 1800 pg/mL.[5]

In addition to being useful in diagnoses, NPs are important prognostic markers. Patients with NT-proBNP values >5000 pg/mL upon hospital admission are considered to be high-risk patients.[6] Furthermore, BNP and NT-proBNP values measured at the time of discharge are predictors of readmission and post-discharge mortality.[7] The variation in values between hospital admission and discharge is also a prognostic marker, and a reduction of at least 30% in these values during hospitalization is desired.[8] When this mark is not reached, it may indicate residual congestion. After hospitalization, there is evidence that NT-proBNP may be useful to guide rapid therapeutic optimization (within two weeks), leading to a reduction in events, as demonstrated in the STRONG-HFstudy.[9]

In addition to the limitation of the gray zone, other limitations must also be taken into account when interpreting the results of NP.[10] Some variables influence their levels. Age, reduced renal function (glomerular filtration rate <60 mL/min), and atrial fibrillation increase the concentrations of these biomarkers. On the other hand, the levels of BNP and NT-proBNP are reduced in obese patients as compared to non-obese individuals, despite similar HF severity.

Troponin

The use of HS-cTn in clinical practice has provided significant advances in reducing the length of stay in the emergency department for the triage of patients with chest pain or other symptoms of suspected acute coronary syndrome. However, a characteristic of these biomarkers is that, although they are specific for myocardial ischemia, many other non-ischemic conditions can increase their values by causing damage to the heart muscle, either chronically or acutely, including ADHF and chronic HF.[1] These situations are called, respectively, acute myocardial injury and chronic myocardial injury.

Keywords

Heart Failure; Biomarkers; Diagnosis; Prognosis

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The pathophysiology responsible for the elevation of HS-cTn in the absence of acute myocardial infarction (AMI) is poorly understood, but it is believed to result from a leakage caused by pressure overload and/or a volumetric overload, causing increased stress on the heart wall, as well as neurohumoral activation, leading to increases in circulating cytokines, catecholamine peaks, and oxidative stress.[11]

]Although elevations in HS-cTn in HF do not necessarily indicate AMI, they are associated with a worse prognosis. Even before the era of HS-cTn, there was already evidence of a worse prognosis in patients with ADHF and elevated conventional troponins. In 2008, the ADHERE registry, which included 67,924 patients with acute heart failure (AHF), evaluated this issue. Around 6% of patients had values above the cutoff point and presented a significantly higher risk of death during hospitalization.[12]

With the beginning of the use of HS-cTn, the prognostic importance of high levels of these took on even greater importance. The RELAX-AHF study, which evaluated sequential HS-cTnT measurements in 1,074 patients, revealed that both higher baseline and peak values were associated with a greater risk of cardiovascular death and hospitalization due to HF over a period of 180 days.[13] Another publication from the RELAX-AHF study showed that patients who had HS-cTnT ≤14 ng/L upon hospital admission had an extremely favorable prognosis, with no cardiovascular deaths within a period of up to 180 days after discharge, as compared to 79 deaths in patients with levels above this cutpoint.[14]

New Biomarkers with a possible role in Acute HF

PN and HS-cTn are cardiac biomarkers established in clinical practice. However, HF causes systemic repercussions and, at the same time, is influenced by systemic factors, such as inflammation, infections, oxidative stress, and comorbidities.[15] In this way, systemic biomarkers could contribute to the management of ADHF, in addition to cardiac biomarkers, as demonstrated in Figure 1. Below, we discuss some promising biomarkers.

GDF-15

GDF-15 is released in response to cellular stress and inflammation, and its levels can increase in patients with various medical conditions, including cardiovascular diseases.[15] In patients with ADHF, high levels of GDF-15 have been associated with a worse prognosis and an increased risk of adverse events, such as death and hospital readmission.[16] It can also be considered an additional marker, adding information to cardiac biomarkers. However, its performance still needs to be validated in prospective studies.

Exhaled acetone

In 1995, it was demonstrated that patients with HF and systemic congestion, assessed by the presence of jugular distension >5 cm, had higher levels of a biomarker called exhaled breath acetone.[17] It is postulated that patients with HF and major venous congestion have a greater predisposition to ketosis, which can hypothetically be explained by metabolic pathways that generate greater availability of ketone bodies, including acetone, which is more volatile and can be detected early through exhaled air.[17]

Marcondes-Braga et al. demonstrated that exhaled acetone was elevated in patients with chronic HF when compared to controls and was a prognostic marker in this

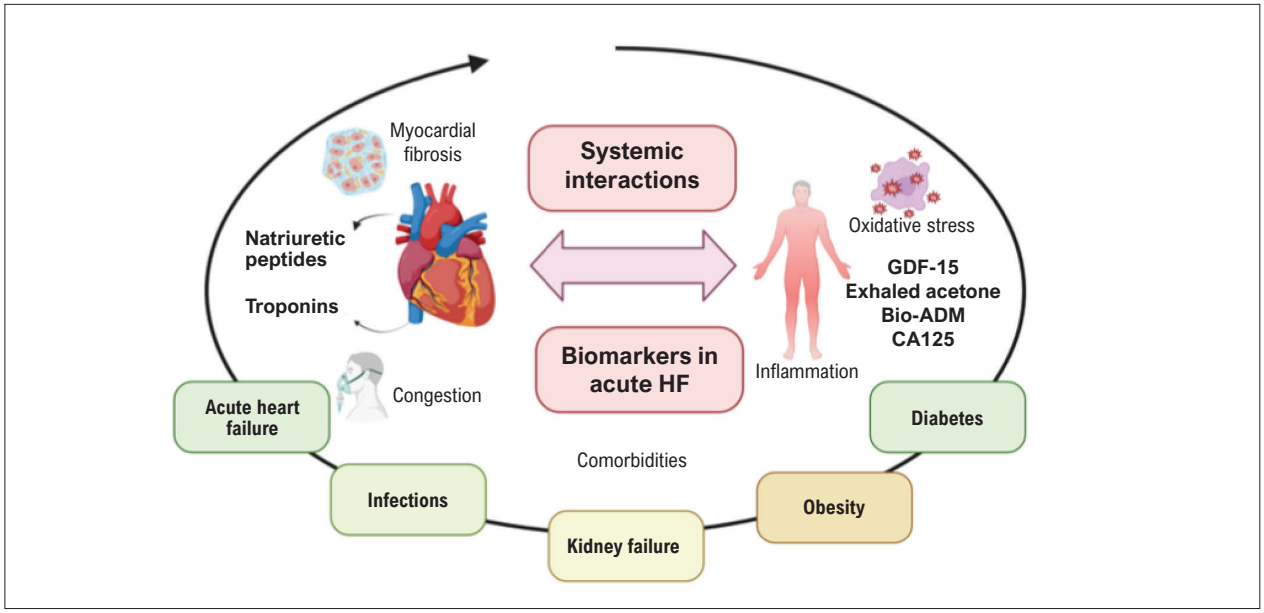

Figure 1 – *Established cardiac biomarkers (natriuretic peptides and troponin), systemic biomarkers with a possible role in the management of acutely decompensated heart failure and mechanisms involved in their release.*

scenario.[18,19] Due to the characteristics of this biomarker, it is possible that it is useful in ADHF as a prognostic marker and to evaluate response to treatment. An ongoing study is evaluating this biomarker in ADHF.[20]

Congestion biomarkers

Plasma bioactive adrenomedullin (bio-ADM) is a peptide hormone of vascular origin associated with congestion in patients with ADHF and is a predictor of mortality in HF.[21] Carbohydrate antigen 125 (CA125) is a glycoprotein synthesized by mesothelial cells, a marker of venous congestion in HF, as well as a prognostic marker.[22] Both markers show promise in managing ADHF.

Conclusions

In conclusion, biomarkers are useful in managing ADHF. NPs are recommended when there is doubt in the diagnosis of ADHF and as prognostic markers. HS-cTn may be high in ADHF, even in the absence of ischemia, and can indicate a worse prognosis. New non-cardiac biomarkers are promising and may add information to traditional biomarkers.

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Conception and design of the research; Acquisition of data; Analysis and interpretation of the data and Writing of the manuscript: Ávila DX, Lira MTSS, Motta D, Villacorta H; Critical revision of the manuscript for important intellectual content: Ávila DX, Motta D, Villacorta H.

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