Biomarkers in Cardiology – Part 1 – In Heart Failure and Specific Cardiomyopathies

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Abstract

Cardiovascular diseases are the leading causes of mortality and morbidity in Brazil. The primary and secondary preventions of those diseases are a priority for the health system and require multiple approaches to increase their effectiveness. Biomarkers are tools used to more accurately identify high-risk individuals, to speed the diagnosis, and to aid in treatment and prognosis determination. This review aims to highlight the importance of biomarkers in clinical cardiology practice, and to raise relevant points of their use and the promises for the coming years. This document was divided into two parts, and this first one discusses the use of biomarkers in specific cardiomyopathies and heart failure.

Introduction

Although in the broad sense the term 'biomarkers' can consist of findings of imaging or functional tests showing deviations from normality, therefore indicating diseases or risk for their development, from the current medical practice viewpoint, biomarkers are considered when measured in bloodstream or secretions.

Organizing the knowledge on biomarkers and their applicability to medical practice is mandatory. Based on state-of-the-art knowledge, the desirable basic characteristics of a biomarker are easily designed. A biomarker measurement should be easy, rapid, accurate, reproducible, and cost-effective, and the assessing capacity of a novel biomarker should exceed that of clinical processes or already existing biomarkers.

As a corollary of their development, in addition to serving to screen diseases, biomarkers should contribute to increase diagnosis speed and accuracy, or their measurement should be either the target or the marker of therapeutic response. They should also aid in decision-making, considering that some of them play a predictive role.

The present paper is an important contribution to cardiology because its writing gathered experts aimed at delineating evidence for the use of currently available biomarkers in the area.

Keywords

Biological markers; Heart Failure; Cardiomyopathies; Evidence-Based Practice.

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Biomarkers of Heart Failure

Natriuretic peptides

Natriuretic peptides – B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) – are considered standard biomarkers in decompensated heart failure (HF). A BNP value < 100 pg/mL practically excludes HF in patients with acute dyspnea[1], while for a BNP value > 400 pg/mL, that is a likely diagnosis. Other situations (acute ischemic syndrome, renal failure, atrial fibrillation, chronic obstructive pulmonary disease, pulmonary embolism, advanced age) can have BNP within the "gray zone", where its measurement is less accurate. The NT-proBNP cutoff point to exclude the diagnosis of HF is 300 pg/mL, and its cutoff points to diagnose HF for the age groups < 50 years, 50-75 and > 75 years are 450, 900 and 1800 pg/mL, respectively. Natriuretic peptides are influenced by renal function. In patients with clearance <60 mL/min, those cutoff points should be higher. Conversely, obese patients (body mass index > 35) should have lower cutoff points.

Elevated natriuretic peptide levels on admission indicate worse in-hospital outcome[2]. On hospital discharge, BNP measurement ('dry BNP') has a high predictive value for death and new hospitalization.

In chronic HF, natriuretic peptides have a recognized value in situations of diagnostic doubts for both systolic and diastolic HF, and some studies have shown that their measurement in association with clinical examination increases diagnostic accuracy[3]. The cutoff points of BNP and NT-proBNP to exclude HF in the outpatient context are 35 pg/mL and 125 pg/mL, respectively.

In addition, as prognostic markers, their value is recognized. We have observed the following: BNP levels in patients with Chagas disease and HF are high; they are markers of disease severity; and can be used non-invasively to better stratify individuals with Chagas heart disease and HF[4].

The serial measurement of either BNP or NT-proBNP has been tested as a strategy to guide the outpatient treatment of those with chronic HF. A meta-analysis of eight clinical trials involving 1726 patients has shown a 30% reduction in mortality in the group guided by natriuretic peptides as compared with that of conventional management, especially in individuals younger than 75 years[5]. However, there was no reduction in hospitalization rates. A recent study has shown a reduction in major cardiovascular events in patients undergoing NT-proBNP-guided treatment regardless of age[6].

Troponin

Troponins are regulatory proteins of the cardiac and skeletal muscle contraction. Cardiac troponin has three subunits:

cTnI, cTnC and cTnT. The subunit cTnI is not expressed in skeletal muscle injury, being specific to myocardial injury. Their measurement should be performed to rule acute myocardial infarction (AMI) out as a cause of cardiac decompensation. Mild elevations, in the absence of AMI, can occur, indicating poor prognosis. In the Acute Decompensated Heart Failure National Registry (ADHERE)[7], 5.6% of the 42,636 episodes of decompensated HF had a positive troponin T or I test. Troponin adds value to BNP. Patients with BNP >840 pg/mL and positive for troponin have an in-hospital mortality of 10.2% as compared with only 2.2% of those with BNP <840 pg/mL and normal troponin. Serial measurements seem to increase the prognostic power. Patients with normal troponin on admission and who, on the seventh day of hospitalization, become positive for troponin, have a worse outcome than those negative for troponin, and that long-term outcome is similar to that of patients with an altered troponin test on admission[8].

High-sensitivity troponins

Currently there are troponin kits capable of detecting troponin T values as low as 0.003 ng/mL (or 3 pg/mL). There might be some confusion in clinical practice regarding the interpretation of such low troponin levels. To differentiate whether the elevation is due to AMI or minimum cellular damage, such as in acute HF, serial measurements are required. A study on patients with final diagnosis of AMI has reported a variation greater than 117% between the first and second troponin measurements at a 3-hour interval[9]. Thus, if troponin levels are not increased on the second measurement, the troponin elevation should be considered as resulting from acute HF. Nevertheless, it is worth noting that a detectable troponin level is a sign of poor prognosis, even in the absence of AMI.

Troponin T is raised in approximately 50% of patients with acutely decompensated HF, and seems to indicate higher severity and increased risk for mortality[10]. In the ADHERE registry, involving 84,872 patients, those with high cardiac troponin (4,240 patients, 6.2%) had higher in-hospital mortality as compared with those with normal troponin (8% *versus* 2.7%, p < 0.001) regardless of other predictive factors[7]. It is worth noting that 40% of patients with elevated troponin had an ejection fraction (EF) higher than 40%.

In the chronic HF setting, the importance of troponin detection has increased, mainly in myocardial injury assessment, prognostic stratification and in the search for a more optimized clinical treatment. The development of high-sensitivity troponin has increased the accuracy of the detecting method as compared with that of conventional troponin.

A study assessing 5,284 patients of the Val-HeFT and GISSI-HF trials has shown that, despite low circulating concentrations, changes in serum high-sensitivity troponin are strong predictors of future cardiovascular events in patients with chronic HF, contributing to worsen the prognosis[11]. In another study assessing 876 treated patients with a mean 34% EF, the combination of biomarkers, such as high-sensitivity troponin and NT-proBNP, has been used to establish mortality along with other risk factors. It has concluded that adding the measurement of high-sensitivity troponin and NT-proBNP to a model including known risk factors can improve the prognostic stratification of mortality[12].

High troponin levels (> 99th percentile) are frequently found in stable patients with HF followed up at outpatient clinics, particularly when high-sensitivity assays are used, and they are associated with high likelihood of future adverse events. In that scenario, its predictive capacity does not depend on the measurement of natriuretic peptides. However, there are no studies assessing specific interventions for patients with chronic HF and high troponin levels.

A study with 1,089 patients with no history of HF, valvular disease or left ventricular (LV) hypertrophy has shown that high levels of cTnI were associated with the risk of developing HF. The cTnI has predicted HF in individuals with no ischemic etiology. The cutoff point of 0.04 ug/L best identified patients at risk for developing HF[13].

The usefulness of the routine assessment of troponin levels in patients with HF with preserved EF (HFPEF), as well as the therapeutic approach and correct diagnosis for raised troponin levels in patients with non-acute coronary syndrome, requires further assessment.

C-reactive protein and micronutrients

C-reactive protein (CRP) is an easily measured biomarker of acute and chronic inflammation, whose prognostic value has been widely demonstrated in HF.

Mueller et al. have reported that patients in the highest CRP tertile have higher in-hospital mortality than those in the first tertile (15% vs 2%). The accumulated mortality rates in up to 24 months for the first, second and third CRP tertiles were 33.5%, 42.4% and 53.6%, respectively[14]. In a Brazilian study, patients with CRP > 3.0 mg/dL on admission (excluding those with manifest infection) had higher mortality in a mean 12.4-month follow-up as compared with those with CRP below that value[15]. Thus, CRP acts as a marker of mortality during hospitalization and after discharge of patients with decompensated acute HF. Similarly, high CRP also predicts the risk of cardiovascular events in individuals with chronic HF in the outpatient context. A large study on the impact of CRP on morbidity and mortality in chronic HF has been published by the CORONA trial researchers. Of 4,000 patients with HF, those with high CRP levels had characteristics of severe syndrome, such as low EF, high prevalence of New York Heart Association (NYHA) functional class III/IV, poor quality of life and worse neurohormonal profile[16]. Although there are numerous studies supporting the role of CRP in prognostic stratification, its routine measurement is not recommended in any HF clinical scenario, because high levels of that marker determine no specific therapy. However, it is worth noting that CRP elevation is particularly common in acute HF and can help the diagnosis of infections, which often cause clinical decompensation or coexist with it.

Micronutrients, such as coenzyme Q10, L-carnitine, thiamine, amino acids, vitamins (A, D and E), zinc and selenium, are defined as essential cofactors for energy transfer, biochemical maintenance and cardiac function. Several studies have suggested that those micronutrients can contribute to the HF pathophysiology, influencing pathological ventricular remodeling[17]. Severe selenium and thiamine deficiencies are reversible causes of HF. Although the levels

of micronutrients, such as thiamine, coenzyme Q-10 and L-carnitine, can be reduced in patients with acute HF, there is no large randomized study demonstrating the benefits of their replacement. In addition, recent observational studies have suggested that vitamin D deficiency is an independent marker of worse prognosis in HF in the outpatient context, and that its supplementation has a clinical benefit[18]. Considering that most studies on micronutrients are observational and have a small case series, their measurement is not routinely recommended in HF.

Galectin

Heart failure remains one of the most prevalent and challenging clinical conditions in cardiology, with high mortality in both its acute and chronic forms, mainly in individuals older than 65 years. As the early identification of the increased risk of HF patients can affect their outcomes, biomarkers begin to be recognized for diagnostic and prognostic purposes[19].

Experimental and clinical studies have associated galectin-3 with myocardial hypertrophy, reporting its stimulating effect on cell migration, fibroblast proliferation and fibrosis development.

A study assessing galectin-3 in patients with acute dyspnea at the emergency room has reported higher galectin-3 levels in patients with acute dyspnea due to HF than in those with dyspnea due to other causes. In addition, it was the best independent predictor of 60-day mortality or of the combined outcome of death and relapse, even after correction for age, sex, BNP, renal function and diabetes mellitus[20].

The DEAL-HF study, following up 232 patients with HF and NYHA functional class II-IV for 6.5 years, has concluded that galectin-3 is an important predictor of mortality risk when adjusted for sex, age, HF severity, and renal dysfunction, being, thus, a prognostic marker[21].

In addition, high galectin-3 levels have been reported to associate with echocardiographic ventricular remodeling characteristics and to predict mortality in patients with severe chronic HF[22].

The predictive value of galectin-3 seems to be stronger in patients with HFPEF than in those with HF and reduced EF. Galectin-3 measurement in chronic HF in the outpatient setting is considered experimental.

Biomarkers in viral and non-viral myocarditis

The biomarkers of myocardial damage can be increased in a small group of patients with acute myocarditis, but they can help the diagnosis. Troponin I is a biomarker that reflects the existence of myocardial necrosis in the course of an inflammatory process, and can be increased in at least 50% of the biopsy-confirmed viral myocarditis cases. Troponin I has 89% specificity and 34% sensitivity in adults with acute myocarditis, but, in the pediatric population, troponin T has 83% specificity and 71% sensitivity. Troponin is more often present than CK-MB, which is elevated in only 5.7% of patients with biopsy-confirmed viral myocarditis[23].

Promising biomarkers

Exhaled acetone in heart failure

Recently, a Brazilian study has confirmed that exhaled acetone is increased in patients with HF as compared with healthy individuals, and that is even higher in decompensated patients admitted to the clinical emergency than in compensated patients. That study has also reported that the new biomarker correlates positively with BNP in both compensated and decompensated HF patients, and that it increases progressively with the NYHA functional class. Therefore, exhaled acetone is a new and promising non-invasive biomarker of HF diagnosis[24].

Specific Cardiomyopathies

Genetic Biomarkers in Cardiology

Inherited cardiovascular diseases, cardiomyopathies and channelopathies have familial presentation, being caused by gene mutations. Those diseases have highly variable clinical characteristics, with phenotype overlapping in several cases, the genetic diagnosis being, thus, useful to individualize the diagnosis, predict disease progression and guide therapy.

As a rule, genetic tests should not be ordered without signing the written informed consent, and should be accompanied by genetic counselling before and after testing.

Genetic tests in cardiovascular diseases

Inherited cardiovascular diseases are usually monogenic (one single genetic variant is responsible for the disease, usually with a Mendelian inheritance), even when a substantial proportion of affected patients has more than one pathogenic variant. That group includes cardiomyopathies (hypertrophic, dilated, restrictive, arrhythmogenic, and non-compacted), channelopathies (long and short QT syndromes, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, inherited conduction disorders), and the inherited diseases that affect the aorta (Marfan, Loeys-Dietz, familial aneurysms of the thoracic aorta).

Those conditions share the percent increased risk for sudden death of young and athletic individuals and of older patients, and can be asymptomatic. Although clinicians should be aware of the genetic testing limitations, considering that not all mutations have been identified, current tests already assess the most prevalent gene mutations.

The frequency of detection of mutations by use of genetic testing is different for each type of disease, being as follows: 75% for channelopathies; 60% for hypertrophic cardiomyopathies; and 5%-20% for dilated cardiomyopathy.

Recently the European and North American Societies of Cardiac Arrhythmia have developed guidelines for the adequate use of genetic tests in cardiomyopathies and channelopathies (Tables 1 and 2)[25]. Regarding channelopathies, the guidelines recommend changes in the therapeutic management when certain genetic changes are detected, determining progressive incorporation of genetic tests into clinical practice.

Table 1 – Recommendations for genetic testing in cardiomyopathies (*Adapted from Ackerman et al.*[25])

Hypertrophic Cardiomyopathy (HCM)
Panel targeted to HCM (beta-myosin heavy chain gene, myosin binding protein C gene and troponin T gene) – The patient clinically diagnosed with HCM based on clinical and family history, as well as on the electrocardiographic/echocardiographic phenotype; – In family members, after confirming the specific mutation in the index case.
Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy (ARVD/CM)
Panel targeted to ARVD/CM (Mutations in PKP2, DSC2, DSG2, DSP, JUP and TMEM43 genes) – Any patient clinically suspected of having ARVD/D based on clinical and family history, as well as on the electrocardiographic/echocardiographic phenotype; – In family members after identifying an ARVD/D-associated mutation in an index case.
Dilated Cardiomyopathy (DCM)
Comprehensive panel or targeted to DCM (LMNA and SCN5A genes and others) – Patients with DCM and significant cardiac conduction defect (such as first-, second- and third-degree heart block) and/or family history of early sudden death; – Genetic testing with investigation of specific mutations in family members after identifying a DCM-associated mutation in an index case.
Progressive Cardiac Conduction Defect (CCD)
Panel targeted to CCD (specific mutations in SCN5A or Lamin A/C genes) – As part of the diagnostic algorithm in patients with isolated CCD or CCD with congenital heart disease, in the presence of documented family history of CCD. – In family members after identifying a CCD-associated mutation in an index case.

Table 2 – Recommendations for genetic testing in hereditary channelopathies (*Adapted from Ackerman et al.*[25])

Long QT Syndrome (LQTS)
Panel targeted to LQT1-3 (mutations in KCNQ1, KCNH2 and SCN5A genes) – Any patient to whom a cardiologist has established a strong diagnostic suspicion of LQTS based on clinical and family history, as well as on the electrocardiographic phenotype (12-lead ECG at rest and/or exercise test or dobutamine stress test); any asymptomatic patient with QT prolongation in the absence of other clinical condition that can prolong that interval (such as electrolyte abnormalities, hypertrophy, block, considered idiopathic) based on ECG with 12 serial leads defined as QTc >480 ms (pre-puberty) or >500 ms (adults); – In family members after identifying a LQTS-associated mutation in an index case.
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)
Panel targeted to CPVT1 or 2 (mutations in RYR2 and CASQ2 genes) – Any patient clinically suspected of having CPVT based on clinical and family history, as well as on the electrocardiographic phenotype (bicycle or treadmill exercise test or dobutamine stress test); – In family members after identifying a CPVT-associated mutation in an index case.
Brugada Syndrome (BrS)
Panel targeted to BrS (Specific mutation in the SCN5A gene) – Comprehensive panel for BrS (SCN5A gene mutations): recommended for any patient clinically suspected of having BrS based on clinical and family history, as well as on the electrocardiographic phenotype (12-lead ECG at rest and/or dobutamine stress test). Genetic testing is NOT indicated in the context of an isolated type 2 or type 3 Brugada ECG pattern. – In family members after identifying a BrS-associated mutation in an index case.
Short QT Syndromes (SQTS)
Panel targeted to SQTS (Specific mutations in KCNQ1, KCNJ2 and KCNH2 genes) – Any patient to whom a cardiologist has established a strong diagnostic suspicion of SQTS based on clinical and family history, as well as on the electrocardiographic phenotype. – In family members after identifying an SQTS-associated mutation in an index case.

Restrictive Cardiomyopathies

Amyloidosis

Of the restrictive cardiomyopathies, amyloidosis has the highest correlation with biomarkers in literature. It is characterized by heterogeneous disorders caused by extracellular deposition of fibrillar proteins, with two major cardiac forms.

Light-chain or primary systemic amyloidosis

Light-chain amyloidosis is acquired, related to bone marrow changes, two thirds of the affected patients are of the male sex, and most of them are older than 50 years. Treatment outcome and prognosis are highly dependent on cardiac involvement and severity. The treatment outcomes of patients with similar clinical presentations vary greatly, which is partially related to the subjectivity of the heart

involvement assessment. Thus, developing risk classification systems became essential, especially associating the use of cardiac troponins and BNP.

a) Troponins: Several studies on troponin I or T of patients with systemic amyloidosis have shown that those proteins are often detectable in cardiac disease and associate with survival. A recent study has shown that plasma high-sensitivity troponin levels of patients with light-chain amyloidosis are invariably associated with the cardiac involvement severity, even in patients with insignificant troponin release, and are likely to improve early diagnosis[26]. Its association with NT-proBNP has proved to be useful for therapeutic follow-up and prognosis.

b) Natriuretic peptides: Several studies have demonstrated the efficacy of natriuretic peptides in predicting cardiac involvement in amyloidosis even before the presence of ventricular dysfunction on echocardiography, suggesting that their variation is due not only to the elevation of ventricular filling pressures, but also correlates with myocyte damage resulting from the extracellular amyloid deposition[27]. BNP and NT-proBNP seem to be sensitive biomarkers of myocardial dysfunction and prognosis. A recent analysis of renal failure has shown the need to use higher NT-proBNP and BNP cutoff points to detect cardiac involvement and to assess prognosis in that group. Both natriuretic peptides are independent prognostic markers, but only BNP has maintained its acuity in end-stage renal disease patients[28].

Transthyretin amyloidosis

Transthyretin amyloidosis is related to a molecule produced by the liver, transthyretin. There are two types: a genetic/inherited form, and a non-inherited form, resulting from the breakdown of normal transthyretin molecules. The latter is called senile systemic amyloidosis and affects mainly men from the seventh decade of life on. Apparently, it is less harmful to myocytes than the systemic form, which is justified by the mild change in troponins T and I, as well as the unchanged echocardiographic pattern. In that context, BNP seems to be a sensitive marker of HF and could be useful for the purpose of follow-up[29].

Differential diagnosis between pericarditis and restrictive cardiomyopathy

The clinical distinction between restrictive cardiomyopathy and constrictive pericarditis is difficult, representing a diagnostic challenge. A small recent series has shown that BNP levels are markedly high in patients with restrictive cardiomyopathy and NYHA functional class III or IV, while, in patients with similar clinical findings and constrictive pericarditis, BNP levels are much lower[30]. However, BNP levels vary with the different etiologies of restrictive cardiomyopathy and constrictive pericarditis[31], requiring new studies to assess whether the BNP/proBNP ratio plays a potential role in that scenario and in variations, such as associated renal disease.

Endomyocardial fibrosis

The measurement of NT-proBNP as a biomarker has been assessed in some studies, which have shown its increased serum levels in endomyocardial fibrosis as compared with a normal control group[32].

Although scarce, studies have shown that measuring natriuretic peptides can be useful for the diagnosis, follow-up and prognosis of restrictive cardiomyopathy, especially amyloidosis (in association with troponins or not), endomyocardial fibrosis and pericardial diseases.

Prognostic Biomarkers in Hypertrophic Cardiomyopathy

B-type natriuretic peptide

In hypertrophic cardiomyopathy, the mechanism leading to an increase in BNP levels is myocyte stretching related to myocyte hypertrophy and disarrangement, in addition to hemodynamic changes related to LV outflow tract obstruction, increased LV filling pressure and myocardial ischemia.

Studies on BNP in hypertrophic cardiomyopathy have shown that high BNP levels correlate with the intensity of symptoms (dyspnea) and NYHA functional class, presence and degree of LV diastolic dysfunction, LV systolic dysfunction, LV hypertrophy degree and LV outflow tract gradient. High BNP levels can also associate with the presence of myocardial late enhancement imaging (fibrosis) in patients with symptomatic sustained ventricular tachycardia.

Studies on prognosis are scarce. Kitaoka et al[33], assessing the outcomes of cardiac death and hospitalization in 130 patients (mean age, 60 years; mean follow-up, 3.7 years), have observed that BNP was not a predictor, its use for prognostic assessment being, thus, limited. Pieroni et al[34], following 40 patients (mean age, 42 years) up for six years, have reported that 10 patients who progressed to the dilated form had a significant increase in plasma and myocardial BNP levels as compared with previous values. That fact correlated significantly with the elevation in LV end-diastolic pressure.

N-terminal pro B-type natriuretic peptide

Comparative studies have shown that both methods (BNP and NT-proBNP measurements) are similar regarding systolic and diastolic heart function assessment. The study using NT-proBNP as a diagnostic marker in family members with hypertrophic heart disease confirmed on echocardiography and genetic testing has shown high sensitivity and specificity as compared with electrocardiography[35]. The prospective multicenter study by D'Amato et al[36], assessing the prognostic value of NT-proBNP in 128 patients (mean age, 50 years; mean follow-up, 4 years), has reported that NT-proBNP predicted events related to HF and not to cardiac mortality.

The genetic study of mutations in beta-myosin heavy chain gene, myosin binding protein C gene and troponin T gene, which account for two thirds of mutations, is currently performed at Brazilian research centers and tertiary referral hospitals. It is recommended for the index case and relatives after providing written informed consent. It helps the diagnosis in cases of doubt and mainly in descendants to define those with the mutation, considering that they might not develop the disease.

Diagnostic and Prognostic Biomarkers in Chagas Disease

In Chagas disease, predicting the factors that correlate with disease progression, morbidity and mortality to aid in decision-making, follow-up and treatment of that complex disease is a challenge. A simple, quantitative and inexpensive risk biomarker, which adds value to conventional methods, is required to help in the diagnosis and prognosis of patients with chagasic HF[37].

The natriuretic peptide family and cardiac troponins are currently the most promising tools. Thus, the identification and risk stratification of patients with *T. cruzi* infection, with or without apparent heart disease, is paramount to decision-making and treatment.

There are no clinical randomized studies assessing the role of biomarkers in patients with Chagas disease. Consequently, their measurement is not routinely indicated to assess that disease. However, there are specific clinical circumstances under which those markers can estimate prognosis and help the diagnosis and early treatment.

Some studies have assessed natriuretic peptides (ANP and BNP) and shown that those biomarkers have diagnostic and prognostic power in patients with several forms of Chagas disease, with and without HF, and even in asymptomatic individuals. A cohort of 110 patients with Chagas disease, with and without heart disease, has been clinically assessed and the natriuretic peptides (ANP and BNP) were analyzed[37]. Patients were followed up for as long as three years, when the outcomes 'death' and 'need for cardiac transplantation' were assessed. Mild elevations in ANP (> 47.6 pg/mL) and BNP (> 62.6 pg/ml) levels could predict those outcomes. In addition, the levels of those peptides were higher in patients with chagasic HF than in those with dilated cardiomyopathy of other etiologies for the same functional class of HF. The ANP and BNP levels were also high in asymptomatic patients with Chagas disease and no evidence of ventricular dysfunction, and had a high predictive value for the outcomes analyzed[38].

Pericardial Diseases

Etiological diagnosis and activity of acute pericarditis

Therapeutic response monitoring and clinical outcome

Pericarditis is an inflammatory disease, thus the use of biomarkers that identify pericardial injury is fundamental to the diagnosis and clinical follow-up of patients.

Most patients with pericardial impairment have an increase in CRP levels. Those, who initially have normal CRP levels, eventually develop an elevation. False negative results are present in patients on anti-inflammatory drugs and in those with myocarditis. Measuring and monitoring CRP until normalization are required for the removal of the drugs used in acute pericarditis[39].

Imazzio et al, prospectively assessing 200 patients with viral and idiopathic acute pericarditis, have measured their CRP levels on presentation and every week until normalization. CRP was increased in 156 patients (78%) and negative in 44, the possible causes being: initial early measurement, in 15 patients

(34%); and previous use of anti-inflammatory drugs, in 22 (50%). The CRP levels normalized as follows: 60% of patients in the first week; 85% in the second week; 95% in the third week; and 100% in the fourth week. Persistent CRP elevation after one week was considered a risk factor for recurrence[40].

The implication of that information, according to those authors, is that the treatment with anti-inflammatory drugs from one to two weeks is empirical, and approximately 40% of patients after the first week still have high CRP levels and would benefit from a more prolonged attack dose.

Another sensitive and highly specific marker for cardiac injury is troponin I. A retrospective single-center study has shown increased troponin I levels in 49% of 69 patients with acute pericarditis, values over the threshold for myocardial infarction being observed in 22%. Troponin I elevation was almost exclusively present in patients with ST-segment elevation, and those with higher values were young and had recent infection. Troponin elevation in those patients suggests myocardial lesion associated with acute pericardial inflammation[41].

Another study has reported troponin I elevation in 32.2% of 118 consecutive patients, associated with early age (32 years), male sex, ST-segment elevation (97.4%), and pericardial effusion on presentation (86.8%). In that study, troponin was measured on admission, every 6 hours in the first 24 hours from symptom onset, and, then, daily. An increase over the threshold for myocardial infarction was observed in 7.2%. Two patterns of troponin I elevation were observed: mild troponin I elevation (0.4 ng/mL) without CKMB elevation for 3 days; and greater troponin I elevation (1.5 ng/mL), similar to the threshold for myocardial infarction, associated with CKMB elevation and segmentary echocardiographic abnormalities. All patients had normal coronary arteries on coronary angiography, the change resulting from myopericarditis. The authors have attributed the longer duration of troponin I elevation to more severe myocardial impairment. Despite the different time patterns of troponin progression, the complications were similar between both groups[42].

Etiological diagnosis and activity of chronic and constrictive pericarditis

Pericarditis, with or without chronic pericardial effusion, can progress slowly and even lead to tamponade. Constrictive pericarditis results from chronic inflammation of the pericardium, which becomes thick and calcified, leading to restriction of diastolic ventricular filling, decreased systolic volume and low cardiac output. Viral infection, tuberculosis, connective tissue diseases, neoplasms, previous heart surgery, metabolic diseases and radiotherapy are frequent causes of the disease, which can manifest differently according to the location, extension and severity of pericardial thickening or effusion.

Because the prognosis varies depending on the cause of pericarditis, etiological assessment is important. In that scenario, etiological biomarkers can be used:

a) Tuberculosis: in pericardial fluid, and, thus, only in cases of pericardial effusion, adenosine deaminase (ADA) activity ≥ 40 U/L has 89% sensitivity and 72% specificity, being thus a good etiological marker. Other markers in pericardial

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fluid: lysoenzyme > 6.5 μg/dL has 100% sensitivity and 91% specificity; and interferon γ > 200 pg/mL has sensitivity and specificity of up to 100%[43].

b) Connective tissue diseases: those most often leading to chronic pericardial effusion are: systemic lupus erythematosus, Sjogren syndrome, rheumatoid arthritis, systemic scleroderma, Behcet syndrome, Mediterranean familial fever and systemic vasculitis. Markers of acute inflammation, such as erythrocyte sedimentation rate (ESR), CRP and alpha1-glycoprotein acid, can aid the diagnosis of inflammation, mainly when persistently increased. Antinuclear antibody (ANA) titles ≥ 1/640 can suggest connective tissue diseases associated with the rheumatoid factor (RF), whose sensitivity and specificity depend on the underlying disease[44]. Other tests can be used, depending on the rheumatological disease in question.

c) Neoplasms: when measured in pericardial fluid, carcinoembryonic antigen (CEA) levels > 5 ng/mL have maximum sensitivity and specificity of 75% and 100%, respectively, for the diagnosis of malignant effusion[45]. Other markers, such as alpha-fetoprotein, CA19-9, CA125, CA72 and CA 15-3, should be measured in the pericardial fluid when malignant effusion is suspected.

Measuring BNP or NT-proBNP can be useful for differential diagnosis and follow-up. The increase of those markers in patients with constrictive pericarditis, as well as their correlation with echocardiographic rates that assess diastolic function, has been well defined[46]. In the post-pericardiectomy follow-up of patients with constrictive pericarditis, BNP can be used to assess the results and diastolic function improvement. NT-proBNP has proved to correlate with the severity of clinical decompensation, and values > 436 ng/L are associated with tamponade[47]. In the differential diagnosis between constrictive pericarditis and restrictive myocardial syndromes, BNP can be useful, with much higher levels in the latter. However, data derive from studies with small populations and are controversial in constrictive pericarditis, while in pericardial effusion they seem much more consistent, although a cutoff point has not been well established. A single study has defined the NT-proBNP level of 800 pg/mL as cutoff to differentiate between restrictive cardiomyopathy and constrictive pericarditis, the former having higher levels[48].

Currently, there are few methods to predict reversibility with treatment based on anti-inflammatory drugs. A pilot study with 29 patients has shown that those with higher serum levels of CRP and ESR usually progress to reversibility with anti-inflammatory therapy. However, those data still need to be confirmed in cohorts with larger samples[49].

In addition, CRP has been suggested for the differential diagnosis between constrictive pericarditis and restrictive cardiomyopathies, and a cutoff of 0.57 mg/dL has been proposed, with higher levels in pericardial disease[50].

Anti-heart antibodies (AHA) and anti-intercalated disk antibodies (AIDA) can be used to assess the risk for recurrent pericarditis, and have been observed in as much as 70% of patients with that clinical condition. A higher risk for recurrence is suggested by AHA titles ≥ 1/80[51].

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