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Recent Advances in Biomarker Discovery — from Serum to Imaging-based Biomarkers for a Complex Assessment of Heart Failure Patients

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ABSTRACT

Over the last years, a vast majority of serum biomarkers and imaging techniques have been used alone or combined in the diagnosis, management and prognosis of numerous pathologies. This review provides a brief insight into the novelties from the last 6 years (2010–2016) regarding serum and imaging markers in heart failure (HF). New information about natriuretic peptides (NPs), soluble ST2 (Sst2), growth differentiation factor 15 (GDF-15), myeloperoxidase (MPO), C-reactive protein (CRP), procalcitonin (PCT), troponins (Tns), myoglobin (Mb), galectin-3 (Gal-3), micro ribonucleic acids (microRNAs) and long non-coding ribonucleic acids (lncRNAs), copectin and cardiac magnetic resonance (CMR) measurements were summarized in this review in order to guide the practitioner.

Keywords: heart failure, biomarkers, cardiac imaging

INTRODUCTION

Heart failure (HF) represents one of the most frequent cardiovascular diseases and various serum biomarkers and imaging techniques have been developed for a proper assessment of its evolution. This review provides a brief insight into the novelties from the last 6 years (2010–2016) regarding serum and imaging markers characterising different stages of heart failure.

NATRIURETIC PEPTIDES

According to the BACH trial (Biomarkers in Acute Heart Failure), run in 15 clinical sites, several new natriuretic peptides (NPs) such as midregion pro-atrial NP (MR-proANP) can be a biomarker as valuable as the brain natriuretic peptides (BNP) for diagnosing acute heart failure (AHF) in subjects presenting with dyspnea, and they may also have clinical utility in unclear cases, when elevated

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levels of BNP are difficultly interpreted in the clinical context. Mid-regional pro-adrenomedullin (MR-proADM) represents another biomarker with an accuracy of 73% for predicting 90-day survival in HF patients, higher than the accuracy reported for BNP, which has been demonstrated to be only 62%.[1]

In a prospective study addressing the function of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in guiding the treatment options for cases with impaired left ventricle (LV) systolic function, NT-proBNP-guided therapy was associated with lower event rates, improved living conditions, and superior LVEF (left ventricular ejection fraction) compared to standard therapies, independent on the age of the subjects ($p = 0.03$).[2]

The Atherosclerosis Risk in Communities (ARIC) Study, recruiting 12,230 patients with a body mass index (BMI) of ≥18.5 kg/m^2 and no history of HF at baseline, followed-up their evolution for a median of 20.6 years, and showed that NT-proBNP represents a valuable biomarker that offers significant prognostic information regarding the risk of developing HF.[3]

SOLUBLE ST2

In a study conducted on 107 subjects with EF >50%, evaluating echocardiography-derived imaging biomarkers, serum NT-proBNP and soluble ST2 (sST2) levels in patients with arterial hypertension and HF, the multivariate analysis showed that an sST2 value >13.5 ng/mL was independently connected to a normal ejection fraction, concluding that in addition to NT-proBNP, sST2 could be useful for a more complex risk assessment in heart failure patients with diastolic impairment of the left ventricle.[4]

ST2 proved to be superior to Gal-3, as biomarkers characterizing myocardial fibrosis in CHF. In a head-to-head evaluation of 3 biomarkers (sST2, growth differentiation factor (GDF)-15, and highly-sensitive troponin T – hsTnT) in 151 patients with CHF, the only biomarker that showed predictive power in foreseeing changes in the left ventricular function, was sST2. All these results indicate that sST2 is a useful biomarker in subjects with CHF.[5,6]

GROWTH DIFFERENTIATION FACTOR 15

In a study conducted on 269 subjects with coronary heart disease (CAD), out of which 98 had chronic HF, plasma growth differentiation factor 15 (GDF-15) showed higher levels in individuals with CAD and heart failure, as compared to those with CAD and no HF. Simultaneously, GDF-15 was positively correlated to NT-proBNP levels, and negatively correlated to the ejection fraction. Importantly, GDF-15 showed no association with gender, age, BMI, alcohol consumption, smoking, diabetes, or hypertension.[7]

Another study showed that sST2, galectin-3 and GDF-15 were not correlated with other noncardiac diseases in patients with HF (such as pneumonia, chronic obstructive pulmonary disease [COPD], renal disease, sepsis). However, GDF-15 levels were strongly correlated with galectin-3.[8]

In a study that included 916 consecutive patients, the prognostic role of plasma GDF-15 vs. NT-proBNP in HF with preserved EF vs. reduced EF was evaluated. From the study population, 488 were retested after 6 months. The results showed similar levels of elevated GDF-15 regardless of the LVEF, while NT-proBNP was more elevated in subjects with HF. At the same time, the prognostic role of a >20% increase in GDF-15 was a stronger predictor compared with a similar increase in the NT-proBNP levels.[9]

MYELOPEROXIDASE

In the Ludwigshafen Risk and Cardiovascular Health study, plasma levels of myeloperoxidase (MPO) and of eight MPO polymorphisms were measured in 3,036 subjects, and their evolution was followed-up for 7.75 years. The results of this study indicated that MPO does not hold any role in the progression of cardiovascular conditions but, it indicated a good correlation between MPO concentrations, and cardiovascular and all-cause death rates.[10]

In another prospective study, a significant association was demonstrated between MPO levels, heart-type fatty acid-binding protein (H-FABP) and troponin T (TnT) levels as markers of myocardial damage in HF patients. The results showed that MPO could have a say in the development and progression of myocardial injury in cases with CHF, even if MPO levels were not associated with TnT levels.[11]

C-REACTIVE PROTEIN

The role of C-reactive protein (CRP) in acute coronary syndromes, added to the GRACE risk score, was studied in a large study performed on 1,501 patients. In this study, an elevated CRP level was a moderate, but independent factor in predicting the 30-day mortality in acute coronary syndromes, even after correction for associated diseases, hemodynamic conditions, and therapeutical management, demonstrating that a joint approach based on addition of CRP test to the GRACE risk score can improve the accu-

racy of risk assessment in subjects with heart failure and ACSs.[12]

A very large trial including 10,160 participants aimed to find the correlation between high-sensitivity CRP (hs-CRP) and the risks of diabetes, cardiovascular disease or mortality at 6 years of follow-up. In this study, a significant increase or sustained elevation of serum hs-CRP during the 6-years, was directly linked to a higher risk for diabetes, ischemic heart disease, ischemic stroke, HF, and death.[13]

CRP was also linked to a higher possibility of thromboembolic events and mortality secondary to vascular events in atrial fibrillation (AF) patients.[14]

It has been demonstrated that for individuals with CAD and chronic HF with systolic dysfunction, the degree of the systemic inflammatory status quantified through serum CRP levels is directly correlated with the cardiopulmonary exercise performance. These results indicate the need for initiation of anti-inflammatory treatments in HF.[15] Also, an older study from 2010 showed that hs-CRP can offer additional prognostic value for the risk stratification of CHF.[16]

Another study of 966 patients with CHF showed that severe central sleep apnea (CSA) was associated with high levels of CRP, explaining thus the negative prognostic effect of sleep apnea.[17]

PROCALCITONIN

Procalcitonin (PCT) represents an inflammatory marker characteristic for early atherosclerosis. A study on 77 patients with ACS showed that an increased PCT in the first 48 h from admission in the hospital may be correlated to higher early and 6-month death rates.[18] In acute myocardial infarction (AMI) survivors, PCT was also related with the rate of major adverse cardiac events (MACE), LV dysfunction and the remodeling process.[19] In another study on 2,131 patients with CAD, PCT was related with a higher cardiovascular mortality, but without being superior to the CRP predictive value.[20]

A large prospective study on 3,713 patients without any previous history of cardiovascular disease, demonstrated a significant relationship between PCT levels and the rate of coronary events and cardiovascular mortality. At the same time, PCT was associated with other cardiovascular risk indicators such as CRP, arterial hypertension, diabetus mellitus, renal function, and showed to be inversely correlated with HDL levels and smoking.[21]

Regarding the role of PCT as a biomarker for heart failure patients, a retrospective smaller case-control study showed that serum PCT levels can differentiate between HF patients and healthy controls with a sensitivity of 88.9% [95% confidence interval 75.9–96.2%] and a specificity of 100% [82.2–100.0%]), thus demonstrating the role of PCT as a potential biomarker that can influence the evolution of HF.[22]

PCT has also proved to have an important value for the prediction of all-cause mortality or hospitalization at 3 months in individuals with acute decompensated HF (ADHF) without clinical indicators of infection upon admission.[23] As regards to patients with signs of bacterial infection at presentation, a study on 4,698 cases from China concluded that PCT expression should be carefully examined in elderly patients with an infection complicating CHF, indicating a high positive predictive value of PCT decrease in assessing the evolution of HF.[24]

The importance of PCT values was also demonstrated by two other studies, one that emphasized the essential role of PCT in diagnosing pneumonia in the emergency department (ED) for patients with dyspnea, and another one that used a PCT-based algorithm in choosing the right treatment for patients with respiratory diseases, indicating that antibiotic treatment cannot replace diuretics and HF medication in symptomatic HF patients without a confirmed pulmonary infection.[25,26]

TROPONINS

High-sensitive troponin T (hsTnT), a biomarker for myocardial necrosis, was evaluated in a prospective reasearch, conducted on 107 subjects with ADHF. In this study, hsTnT, NT-proBNP and sST2 offered complementary prognostic information in patients with ADHF, concluding that a panel containing these 3 biomarkers can provide superior risk stratification compared to the isolated use of each one.[27]

Another prospective study on 202 patients with ADHF demonstrated that hsTnT assay offered an overall comparable prognostic information to conventional troponin T(cTnT). However, in unclear cases where cTnT was less precise or negative, increased levels of hsTnT were able to provide the requested prognostic information.[28]

This has been also demonstrated in another study on 504 patients followed during a 5-year follow-up period, which showed higher detection rates in CHF, and independent and better prognostic value for mortality when using hsTnT assay as compared to standard assay.[29]

Regarding the isoforms of troponin, another prospective global multicenter study demonstrated that high-sensitivity cardiac troponin T (hs-cTnT) was more reliable for predicting long-term mortality than high-sensitive cardiac troponin I (hs-cTnI).[30]

MYOGLOBIN

Myoglobin (Mb) is a cardiac enzyme released by the injured myocardium. In its oxygenated state it protects the heart from excessive nitric oxide (NO) levels via scavenging NO, however, in hypoxic conditions it becomes deoxygenated Mb, which has the opposite role, producing NO and protecting the myocardial cells from the lesions associated with myocardial ischemia/reperfusion injury.[31]

Mb is one of the first biomarkers released after an ACS, and an Mb concentration can be discovered in the peripheral blood immediately after an acute myocardial infarction. New point-of-care devices have been proposed for the detection of Mb, used as a simple and reliable tool for the early diagnosis of AMI.[32,33] Regarding the association between survival and serum concentrations of various biomarkers, a cohort study conducted on 310 patients with idiopathic dilated cardiomyopathy (IDC) showed that from a panel of 3 biomarkers (cardiac troponin I, creatine kinase, and Mb) only cTnI proved to independently predict the all-cause death rates in IDC subjects.[34]

GALECTIN-3

Galectin-3 (Gal-3) is also a valuable biomarker in heart failure patients. In a small study that included 44 subjects with HF and 38 healthy controls, Gal-3 serum levels were correlated with other biomarkers characterizing ventricular function, such as serum NT-proBNP, hs-CRP levels and echocardiography-derived biomarkers.[35]

Gal-3 proved to have limited intraindividual biological variability as a biomarker in HF subjects.[36]

It was demonstrated that protein kinase C (PKC-α) increases Gal-3 levels, promoting cardiac fibrosis and HF, and the effect of angiotensin II (Ang II) could be partly mediated by the activation of the PKC–Gal-3 pathway.[37]

Serum levels of Gal-3 have been shown to be increased in both CHD and HF patients, and to independently predict the all-cause death and re-hospitalization rates caused by new episodes of decompensated HF. Gal-3 levels also had a better prognostic role in HFpEF patients than in HFrEF patients.[38]

MICRO RIBONUCLEIC ACIDS AND LONG NON-CODING RIBONUCLEIC ACIDS

MicroRNA (miRNA) have been proposed to serve as circulating biomarkers in the early stages of CHF, and can also represent therapeutic targets in these patients. A recent study indicated that selected micro ribonucleic acids (microRNA) involved in apoptosis, hypertrophy and fibrosis are up-regulated in the myocardium of patients with a history of HF episodes, in contrast to those without HF.[39]

A study on a small number of patients showed that a panel of miRNAs may have a prognostic role in predicting heart failure following an AMI, identifying patients at risk for LV remodeling.[40]

The role of mitochondrial long non-coding ribonucleic acid (mitocondrial IncRNA) uc022bqs.1 (LIPCAR) has been analysed in a prospective research, carried out in multiple centers, which demonstrated that LIPCAR was up-regulated in patients with CHF, and that higher levels of LIPCAR were linked to a higher cardiovascular mortality.[41]

COPEPTIN

Copeptin has been proposed as a new biomarker associated with HF, after a study on 145 patients undergoing successful primary percutaneous transluminal coronary angioplasty (PTCA), who exhibited a distinct release pattern for this biomarker, with a peak in the first hour after the debut of an acute coronary event.[42]

The association of hs-cTnT with copeptin in a common biomarker panel slightly increased the rate of ACS detection at admission.[43]

A more recent study of copeptin on 195 patients with a 5-year follow-up demonstrated that copectin is an independent long-term prognostic indicator in HfrEF patients.[44]

RECENT IMAGING-BASED BIOMARKERS

Right ventricular (RV) function is currently evaluated using standard and pulsed Doppler tissue cardiac ultrasonography and magnetic resonance imaging (MRI). Tricuspid annular plane systolic excursion, systolic longitudinal velocity, tissue strain, and 2-dimensional (2D) strain) proved to be valuable imaging biomarkers for the assessment of RV function, showing a good correlation with the MRI - calculated RV EF (RVEF).[45]

LA emptying function (LAEF) was also identified as a relevant biomarker associated with left and right ventricular function, patients with low LAEF exhibiting lower LV and RV EF, greater LV and RV mass, and increased serum NT-proBNP levels. This biomarker has been proved to represent a powerful predictor of adverse outcomes, independent of other biomarkers characterizing cardiac dysfunction.[46]

The diagnostic value of cardiac MRI (CMR) with late gadolinium enhancement (LGE) for the evaluation for HF with ischemic versus nonischemic etiology has also been

studied in several trials. An ischemic pattern on both LGE and cine sequences diagnosed ischemic cardiomyopathy with a specificity of 87%, showing a great potential in differentiating the ischemic form of LV cardiomyopathy from its nonischemic form.[47]

Several studies suggested new imaging-based biomarkers to assess the ventricular functions, such as late heart-to-mediastinum ratio (HMR) during cardiac metaiodobenzylguanidine (MIBG) imaging in the ADRECARD study, or (123)I-metaiodobenzylguanidine ((123)I-MIBG) imaging in the ADMIRE-HF study (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure).[48,49]

The potential role of CMR-derived T1 mapping in evaluating myocardial fibrosis was demonstrated by several studies, which showed that this new biomarker can independently predict invasively measured LV stiffness.[50]

CONCLUSION

Serum biomarkers such as natriuretic peptides, soluble ST2, growth differentiation factor 15, myeloperoxidase, C-reactive protein, procalcitonin, troponins, myoglobin, galectin-3, micro ribonucleic acids and long non-coding ribonucleic acids are useful in the diagnosis, management and prognosis of heart failure patients. Besides them, imaging biomarkers derived from echocardiography, cardiac magnetic resonance, with late gadolinium enhancement, cardiac metaiodobenzylguanidine imaging using dual isotope (123)I and (99m)Tc, or CMR-derived T1 mapping can add relevant value to biomarker panels characterizing this devastating disease. Further studies are necessary to identify the most relevant imaging and serum biomarkers in a common panel that is easy to use, cost-effective and easily accessible for the patients.

CONFLICT OF INTEREST

Nothing to declare.

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