Scenarios in precision medicine: proteomics in heart failure

Piero Gentile, Matteo Palazzini, Andrea Garascia, and Fabrizio Oliva*

De Gasperis Cardio Center, Niguarda Hospital, Milan

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Proteomics in heart failure (HF) is aimed to study and identify proteins involved in the pathophysiology of this clinical syndrome. Proteins have a role as diagnostic, prognostic and therapeutic markers. This review will unravel the developments and impact of proteomics in HF, focusing on its role in the diagnosis, prognosis and definition of new HF therapies. Proteomics promises to change our approach to HF in the near future, accepting the need for precision medicine, tailored on the characteristics of the single patient.

Introduction

Heart failure (HF) is a clinical syndrome characterized by cardinal symptoms (e.g. breathlessness) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) linked to a structural and/or functional abnormality of the heart, thereby resulting in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise.1

In recent years, the growing incidence of HF matched the important developments in drug therapy: sacubitril/valsartan and the new SGLT2 inhibitors have significantly reduced the mortality and morbidity of HF.1 Despite the benefits of these new molecules, there are still many patients with advanced HF, unable to perform a dosage titration or with contraindication to target therapies.1

Hence, we need to develop a new diagnostic, therapeutic and prognostic patient tailored approach.

In a scenario of precision medicine, proteomics represents one of the major opportunities.

Proteome and proteomics

The term ’proteome’, coined in 1994 by Marc Wilkins, indicates the set of all the proteins present in a cell or in an organism at a precise moment, including both proteins translated directly from the genetic material and those modified following processes of post-translational modification.

The development of analytical technologies and their application in the medical field, starting from the sequencing of the human genetic heritage, have turned the spotlight of the international scientific community on the study of the possible roles of single proteins in different clinical settings, thereby making it necessary to create a new ontology: proteomics.

Proteomics is essentially based on two different consecutive analytical steps: the separation of the proteins that make up the proteome and their subsequent individual identification. The techniques used by proteomics are very versatile and can be applied to different biological samples: biopsies of tissues, plasma, serum, circulating cells, cerebrospinal fluid, urine and finally cells in culture.2

Role of proteomics in heart failure

Proteins are the main regulators of molecular pathways, being also involved in the onset and expression of diseases. As biomarkers, proteins can predict the development of a disease and represent a specific therapeutic target (Figure 1).

Diagnostic role of proteomics

In the field of HF, the incremental diagnostic role of proteins is expressed by natriuretic peptides: since 2015, Echouffo-Tcheugui and colleagues documented the usefulness of BNP or NT-proBNP in recognizing HF patients.
However, the patient characterization cannot be based exclusively on a single parameter, as HF occurs along the entire continuum of the EF. Furthermore, a number of patients with HF and reduced EF at diagnosis can significantly improve with medical therapy, reaching the so-called ‘recovery’ and thus crossing the entire spectrum of HF phenotypes based on the single EF data. The trajectory of a patient in the course of HF history is, therefore, personal and unique and, to date, we have no parameters that allow us to define it accurately a priori.

In this setting, proteomics is trying to offer a more in-depth characterization of the patient, implementing the concept of the disease phenotype based only on the EF parameter. Adamo et al., analyzing the proteome of HF patients with reduced EF (EF <40%), mildly reduced (EF 40-50%) or preserved (EF > 50%), documented the presence of a unique biological pattern for patients with reduced EF, different from patients with slightly reduced or preserved EF. These last two categories presented a partially overlapping proteome. Finally, the patients who registered a recovery in terms of left ventricle function showed peculiar characteristics, identifying a further subgroup of patients. This characterization managed to define different expression profiles within HF, with a different prognostic profile and response to medical therapy. The use of proteomics in the identification and evaluation of HF patients over time could, therefore, change our approach to the disease.

**Prognostic role of proteomics**

To date, the prognostic characterization of HF patients is linked to a multiparametric evaluation, which includes clinical, instrumental and biohumoral analysis. No single variable alone is able to define the prognosis of the patient. Therefore, specific multiparametric scores have been developed, in order to overcome the yield of a single variable. Prognostic stratification is a milestone in the management of HF; particularly in advanced HF, where the use of scores should be linked with functional data to guide the outpatient towards advanced therapies. However, the scores have important limitations: they are built on single populations and therefore the subsequent generalization on the ‘real world’ population can be inaccurate; they adequately predict global mortality but not cardiovascular mortality and hospitalizations; they often use risk markers and not risk factors, therefore their correction does not translate in prognostic benefits.

In this regard, the integration of proteomic parameters within the risk scores could provide a greater accuracy. Troponin T, for example, has been shown to be an independent marker of total and cardiovascular mortality as well as cardiovascular hospitalization.

NGAL, a protein of the inflammatory cascade, correlates with the NYHA class and with the trend of renal function, predicting mortality and events better than BNP and eGFR. Moreover, it is associated with outcomes in peculiar populations, such as that of LVAD carriers.

Biomarkers and ejection fraction

Traditionally, HF has been divided into distinct phenotypes in relation to left ventricular ejection fraction (EF) values. 

*Figure 1* Scenarios of the possible application of proteomics in patients with HF.
Galectin 3 appears as a powerful predictor of adverse events in the context of the patient with acute HF, regardless the NtProBNP values. 12 Some of the new biomarkers combined, such as, for example, sST2, (GDF)-15 and troponin T, are able to add prognostic values to natriuretic peptides alone. In addition, as in the case of sST2, are able to predict changes in EF. 13

In the future, the creation of a proteomic profile of the single patient could therefore add a prognostic value to the common scores described in the literature.

Identification of new therapeutic targets

The medical therapy of HF with reduced EF is based on four pharmacological pillars, acting on the adrenergic system, the renin-angiotensin-aldosterone axis and the inhibition of nephrilysin. 1 To date, the cardioprotective effects of SGLT2 inhibitors are not yet fully understood. The experience provided by these last molecules, however, suggests that there are still unexplored pathogenic pathways on which pharmacotherapies can act by improving the prognosis and quality of life of HF patients.

The role of proteomics may prove to be central in the identification of new therapeutic pathways. Using Mendelian randomization, Henry et al. 14 studied the causal association between circulating proteins and HF, identifying eight proteins that may be therapeutic targets. Of these eight molecules, two are part of specific clinical studies.

The molecular inhibition of galectin-3, tested on a small population, did not significantly affect the level of collagen biomarkers, the echocardiographic parameters of diastolic dysfunction or the arterial stiffness. 15

The experience on adrenomedullin, a peptide involved in volume overload to maintain the endothelial barrier, seems more promising. Adrenomedullin is significantly elevated in patients with acute HF and a specific study with the adrenomedullin binding drug adrecizumab is being prepared in the acute HF setting. 16

Conclusions

The proteome, or the set of proteins expressed by a genome, changes according to the physiological and pathological conditions of the individual. It is the result of numerous processes of gene transcription, translation, and post-translational modifications that can be influenced by endogeneous or exogeneous factors.

The alterations in protein expression that underlie the onset of cardiovascular diseases such as HF are not yet fully known. Proteomics studies represent a useful investigation tool both to acquire new information on cell and tissue biology and to identify proteins that can act as diagnostic, prognostic and therapeutic markers.

Proteomics promises to significantly change the approach to HF by allowing to define the biohumoral profile of a patient in the diagnostic phase, to integrate existing prognostic scores and, finally, to provide specific therapeutic targets. The integration of proteomics with current knowledge in the field of HF will allow a better characterization of the patient, making a precision medicine built on the single individual feasible.

Conflict of interest: None declared.

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