Identifying patients at risk of progressive left ventricular dysfunction

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Conflicts of interest: None.

Abstract

Left ventricular remodeling* is a strong predictor of cardiovascular events after acute myocardial infarction. Although transient, in only a few months this process will lead to heart failure. Recent improvements in therapeutic strategies have not led to the abolition of left ventricular remodeling, which remains a relatively frequent event after an initial acute myocardial infarction. Investigation of several approaches to the prevention and reversal of cardiac remodeling is needed, to reduce the number of patients progressing from myocardial infarction to endstage heart failure. The clinical setting of left ventricular remodeling after acute myocardial infarction lends itself to the use of global approaches in the search for circulating biomarkers* of this progression, to help to identify patients who are at high risk of heart failure after myocardial infarction.
■ *Heart Metab.* 2009;42:10–14.

Keywords: Heart failure, left ventricle, myocardial infarction, plasma markers, remodeling

Introduction

Left ventricular remodeling after acute myocardial infarction (AMI) is a dynamic and complex process that occurs in response to myocardial damage [1]. It is a transient process that leads, in only a few months, to heart failure [2]. Several mechanisms implicated in left ventricular remodeling have been identified, including hypertrophy, fibrosis, apoptosis, and activation of proteolysis [1,2]. However, the exact molecular determinants of left ventricular dilatation after AMI are not completely understood, and the severity of left ventricular remodeling cannot be fully predicted on the basis of its known determinants such as the extent of AMI [3]. The responses that occur after AMI can be divided into early (within 72 h) and late (after 72 h) remodeling. One of the early changes in left ventricular remodeling is expansion of the infarct, and there is a clear association between infarct expansion and a poor diagnosis [4]. Late remodeling includes changes in the geometry and size of the entire left ventricle [5]. The failure to normalize increased wall stresses results in progressive dilatation, recruitment of border-zone myocardium into the scar, and deterioration of contractile function [6].

Development of a more highly integrated, systematic, and focused research approach is required, to ensure more effective management and improved outcomes for patients with AMI. Left ventricular remodeling after AMI is well described, but there are few data on the incidence of and risk factors for left ventricular remodeling that incorporate widespread use of acute reperfusion strategies and almost systematic use of ''anti-remodeling'' medications, such as angiotensin-converting enzyme inhibitors and β-blockers. A recent prospective study was performed

to analyze left ventricular remodeling in patients with acute AMI, using serial echocardiography at baseline, 3 months and 1 year after AMI [7]. The investigators chose to use echocardiographic indices of left ventricular remodeling because other studies have shown that these are strong predictors of heart failure and death [8]. Their findings demonstrated that left ventricular remodeling remains a frequent event after anterior wall AMI (31% of patients), despite recent improvements in the management of myocardial infarction [7].

Current status of cardiovascular biomarkers

Circulating biomarkers that have been used successfully in cardiology and classified as diagnostic biomarkers of heart failure include troponin I and troponin T (myocardial infarction), and brain natriuretic peptide. However, the concentrations of biomarkers vary widely, and concentrations in individuals with and without disease overlap substantially [9].

Left ventricular remodeling after AMI is a clinical situation that lends itself to the search for circulating biomarkers that control the progression from myocardial infarction to endstage heart failure [2] using a global approach without knowledge of pre-existing conditions. The study performed by Savoye et al [7] enabled patients to be carefully phenotyped and classified into groups exhibiting no (−10.9%), or low (+7.5%) or high (+39.7%) degrees of left ventricular remodeling, for a comparative analysis. Despite having the same baseline end-diastolic volume during their stay in hospital after AMI and undergoing the same therapeutic strategies, the patients could be classified according to the percentage of left ventricular remodeling that they exhibited (*Figure 1*). A greater than 20% increase in end-diastolic volume has previously been taken to indicate severe remodeling [10]; thus it would be very helpful to discover biomarkers that made it possible to identify patients at risk of a high degree of remodeling earlier than 1 year after AMI.

Global approaches

Emerging technologies are making possible the systematic, unbiased characterization of variations in genes, RNA, proteins, and metabolites that are associated with disease conditions (*Figure 2*). From among the growing flow of new data and approaches, the selection that follows has been chosen to give a better illustration of the potential of such a global approach in the search for new biomarkers to explain the mechanisms of cardiovascular disease. Several approaches will be considered in relation to genetics, transcriptomics, and proteomics, with additional
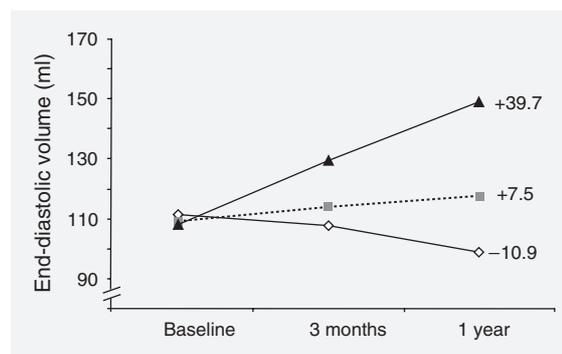

Figure 1. Distribution curves of end-diastolic volume (EDV) at baseline, 3 months and 1 year in patients from the Remodelage Ventriculaire study [7] having a first acute myocardial infarction with echocardiographic follow-up. The percentage of left ventricular remodeling was calculated by the formula $(EDV_{1\,year} - EDV_{baseline}) / EDV_{baseline}$. Patients were divided into three groups: no remodeling (−10.9%; ◇), low remodeling (+7.5%; ■), and high remodeling (+39.7%; ▲). A greater than 20% increase in EDV has been taken to indicate severe remodeling [10].

reference to the models used in comparing them: well phenotyped patients, and appropriate experimental models. The samples to be analyzed – mainly plasma, serum, or both, in the case of cardiovascular diseases – will also be mentioned. Independent of the global analysis chosen, the research strategy utilized will have been the same (*Figure 3*): comparison of ''control'' and ''case'' samples using the best technique for genetic, transcriptomic, proteomic, or metabolomic analysis. A further requirement in our choice was that the discovery of a potential biomarker was
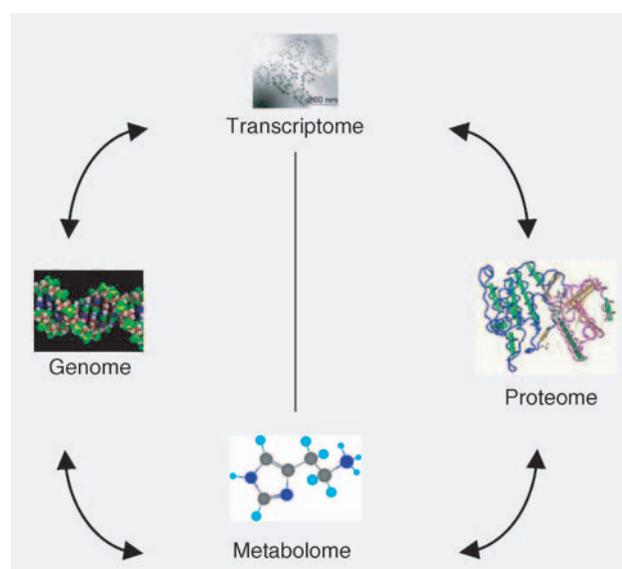

Figure 2. Functional diversity of eukaryote regulation. Human genome sequencing, completed in 2001, showed the presence of 25 000 genes, encoding more than 1 million proteins and representing 3000 species of small-molecular metabolites. Emerging technologies enable global molecular profiling at the level of the genome, transcriptome, proteome, and metabolome.
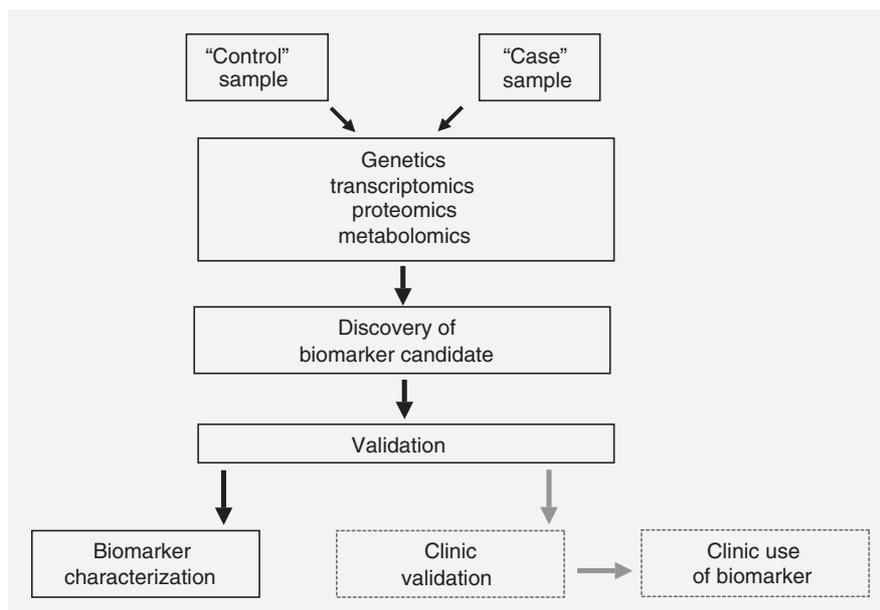
Figure 3. Schematic representation of the strategies behind research into biomarkers using comparative analysis of ''case'' and ''control'' samples. The techniques used for genetic, transcriptomic, proteomic, and metabolomic analyses are chosen according to the nature and number of the samples to be analyzed.

validated using another population and other techniques. After clinic validation and comparison with traditional markers used in the clinic setting, the discovered biomarker could then be used as a clinic biomarker.

Genetics

Genetic studies will identify variants that could be biomarkers themselves or will point to circulating biomarkers for further exploration. However, interindividual variability exists, with some patients experiencing significant left ventricular dilatation despite the absence of evident risk factors. Conversely, other patients, classified as high risk on initial evaluation, do not exhibit left ventricular remodeling.

Several studies with conflicting results have focused on the possible effects of gene polymorphisms in left ventricular remodeling after myocardial infarction. Three studies in which the impact of the angiotensin I-converting enzyme I/D polymorphism on left ventricular remodeling was analyzed yielded divergent findings: two were positive [11,12] with presence of D (deletion) allele associated with ventricule dysfunction and one was negative [13]. Another study analyzed the -1607 1G/2G polymorphism in the promoter of matrix metalloproteinase-1 and found an association with left ventricular remodeling for patients with 2GG alleles compared with homozygotes for the G allele [14].

A recent prospective study was designed to assess the impact of gene polymorphisms on left ventricular remodeling after a first anterior myocardial infarction. On the basis of the pathophysiology of left ventricular remodeling after myocardial infarction, three systems were chosen: the renin–angiotensin–aldosterone, adrenergic, and matrix metalloproteinase systems. The investigators found that left ventricular remodeling after myocardial infarction was not associated with common polymorphisms of these three systems [15].

Genome-wide association studies could be the next step in the identification of genes operative in susceptibility to disease [16]. This technological approach will require large groups of investigators to obtain a substantial cohort of patients. In the case of left ventricular remodeling studies, the largest cohort obtained to date was that of Savoye et al [7], with 266 patients enrolled. One third of that population would form the ''control'' population and one-third the ''case'' population, providing fewer than 90 patients per group. However, in order to perform a reliable genome-wide association study, at least 3000 case and 3000 control patients are required.

Transcriptomics

Gene expression profiling may provide a finer molecular classification of patients with cardiovascular diseases and indicate new markers useful for prognostic and therapeutic strategies [17]. Another obstacle to the discovery of biomarkers of heart disease is that the biomarkers identified might reflect pathological mechanisms that are associated, not with events that trigger disease, but instead with the downstream consequences of the resultant pathology. A comparative study performed by Gao et al [18], who used the canine tachypacing model, transgenic

mouse, and human heart failure, revealed that human disease involved a downregulation of genes in a broad range of biological processes.

The application of transcriptional approaches to the identification of new cardiac biomarkers in humans is clearly limited by the availability of the most relevant tissue, the heart. Some investigators have used cultures of cardiomyocytes for transcriptional screening before testing in the serum of patients [19].

As left ventricular remodeling is an evolutive disease that succeeds AMI, with little alteration in the early phase, transcriptomic changes in heart tissue could be masked. From an ethical point of view, left ventricular mRNA profiling would be difficult to do. Hope can be derived from the fact that profiling of genes can be performed from circulating platelets, which lack nuclear DNA. Transcriptional profiling of platelets can thus provide biomarkers [20]. Study of the platelet transcriptome from patients who have suffered AMI may lead to the identification of a biomarker than can predict the risk of left ventricular remodeling.

Proteomics and metabolomics

Proteomics and metabolomics offer complementary insights to the full complexity of the disease phenotype, because transcript analysis does not always reflect the corresponding protein/metabolite profiling. Furthermore, proteins and metabolites can change rapidly in response to a changed environment.

The proteome represents, at a given time, the complement of proteins itself or the posttranslational modifications of those proteins, or both. Proteomic biomarkers differ from traditional biochemical markers, in that several interacting protein species are evaluated simultaneously to reflect the response of a cell or an organism to disease [21].

Recently, using samples from the prospective cohort of Savoye et al [7], we performed a systematic comparative proteomic analysis to select circulating biomarkers that may be associated with left ventricular remodeling. We used surface-enhanced laser desorption ionization–time-of-flight mass spectrometry to compare blood from patients with no left ventricular remodeling against that from those with a high degree of remodeling, and found four peaks differentially expressed between the two groups. Mass spectrometry led to the identification of more abundant posttranslational variants of the α1-chain of haptoglobin in the group with a high degree of left ventricular remodeling, and of more abundant hemoglobin in the group with no left ventricular remodeling [22].

The metabolome represents the analysis of biochemical substances such as lipids, sugars, nucleotides, and amino acids and related amines of less than 3 kDa. This collection of metabolites reflects the state of a cell or a group of cells at a given time, giving an integrated picture of the biology over a period of time. Recent publications report estimates of the human metabolome as comprising 3000 small molecules and apparently being easier to detect than the human proteome [23]. A recent serum metabolomic analysis has revealed pseudouridine and 2-oxoglutarate as novel metabolic markers of heart failure [24].

Searching for biomarkers in blood

Because so many cellular types contribute to the plasma proteome and metabolome, ideal technological approaches to the identification of biomarkers will utilize both proteomic and metabolomic analyses.

In the case of the plasma proteome, the 22 most abundant proteins constitute 99% of the total proteome mass [25]. Tens of thousand proteins have been estimated to be unique in the plasma. Indeed, it has been suggested that the entire set of polypeptides resulting from alternative splicing and posttranslational modifications (300 000 species) is represented in the human plasma proteome [25]. However, many of the biologically interesting molecules relevant to human disease are proteins that are low in abundance; for example, cardiac biomarkers such as troponin are found in the nanomolar range, insulin in the picomolar range, and tumor necrosis factor-α in the femtomolar range. This has been addressed in a recent technique of ''equalization'' of serum/plasma that was established in order to study minor proteins of the plasma and serum by dilution of high-abundance proteins and concentration of low-abundance proteins [26].

Future directions

The application of proteomics or metabolomics to common cardiovascular diseases has potential obstacles. For acute events, such as myocardial infarction, the unpredictability of when the event occurs often precludes blood sampling. In some cases, experimental animal models can help for the first screening as myocardial infarction is programmed. A recent paper has demonstrated the usefulness of a rat experimental model of heart failure for the study of protein profiling in the early and late phases of left ventricular remodeling [27].

With the aim of discovering biomarkers of left ventricular remodeling after AMI, it will be important to be able to follow the change in abundance of plasma biomarkers that accompanies the development of left ventricular remodeling.

The interindividual variability of the human proteome and metabolome may prove to be a problem, but this should be overcome by using for comparison

cohorts of about 30 patients per group, carefully phenotyped with a view to discovering biomarkers that can subsequently be validated in large, more heterogeneous populations.

The identification of biomarkers of cardiovascular diseases will depend on the complementary powers of genetics, transcriptome profiling, proteomics, and metabolomics. The newly discovered biomarkers, when combined with existing clinical risk factors, will improve the prediction of risk in an individual and contribute to the development of individualized medication.

*See glossary for definition of these terms. ■

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