Integrated Biomarkers in Cardiomyopathies

Cardiovascular Magnetic Resonance Imaging Combined with Molecular and Immunologic Markers – a Stepwise Approach for Diagnosis and Treatment

Jeanette Schulz-Menger¹, Bernhard Maisch², Hassan Abdel-Aty¹, Sabine Pankuweit²

Abstract
In an integrated approach, the authors examine the most efficient combination of noninvasive and invasive biochemical, immunologic, functional, molecular, imaging and biopsy-derived biomarkers for their applicability in the diagnosis of cardiomyopathies in general and dilated cardiomyopathy (DCM) in particular. A careful selection out of the cascade of available biomarkers will allow, in individual patients, to diagnose certain conditions of cardiomyopathies without endomyocardial biopsy, e.g., borreliosis, rickettsiosis, HIV cardiomyopathy. Viral persistence in DCM associated with inflammation will need both noninvasive (echocardiography, cardiovascular magnetic resonance) and invasive biomarkers (polymerase chain reaction for viral persistence or their exclusion in case of autoreactive myocarditis and quantitative immunohistology, both from endomyocardial biopsy).

Zusammenfassung

Key Words:
Biomarkers · Cardiac MRI · Immunoserology · Cardiac enzymes · Immunohistology · Viral PCR

Schlüsselwörter:
Biomarker · Kardio-MRT · Immunoserologie · Herzenzyme · Immunhistologie · Virus-PCR

Integrated Biomarkers
According to the definition of the NIH Working Group in 2001, biomarkers for cardiovascular diseases can be biochemical, immunologic, histologic, molecular and serologic markers as well as cardiovascular imaging, which has been defined as a biomarker for its capability to visualize pathologic processes [10]. Biomarkers can be acquired by noninvasive and invasive measures, the latter also including the information by heart catheterization and endomyocardial biopsies (EMB).

With respect to dilated cardiomyopathies (DCMs), a stepwise approach appears preferable in chronic cases, by which noninvasive biomarkers will precede invasive measures to reach a definite diagnosis. This algorithm has been alluded to as integrated biomarkers. So parts of the spectrum of markers will be available to the general practitioner or the internist such as family history, predisposition, clinical symptomatology, which are part of a detailed patient’s work-up anyhow. Several of the biochemical markers of heart failure (e.g., brain natriuretic peptide [BNP]), inflammation (e.g., C-reactive protein [CRP]), myocyte destruction (e.g., troponins, myocardial component of creatine kinase [CK-MB]), viral or bacterial etiology (viral or bacterial serology such as human immunodeficiency virus [HIV] or borreliosis), and anticardiac autoantibodies are also easily accessible. Here, the decision-making process is to select not all but the ones leading to the correct diagnosis. Echocardiography and electrocardiography (ECG) can be carried out in each cardiology practice,
specialized cardiology units also perform cardiovascular magnetic resonance (CMR), which is the ideal situation for the combination of this new imaging modality with profound cardiologic competence.

CMR as an imaging test offers the unique possibility to differentiate myocardial injury in relation to functional changes free from radiation.

Noninvasive differentiation of myocardial injury is an ongoing diagnostic challenge in cardiology. Echocardiography is a basic tool to assess wall motion abnormalities, but it cannot differentiate between underlying pathophysiological processes of these functional abnormalities, e.g., inflammation or ischemia. Meanwhile, the indications of CMR in various cardiovascular disorders are steadily growing. Besides the assessment of ischemia and viability in coronary artery disease (CAD), a main advantage is the use in cardiomyopathies and the differentiation of heart failure origins. Recently, the criteria of appropriateness in CMR were published with a special focus on the use of CMR in this setting [22]. The position paper of the German Society of Cardiology published in 2007 followed on the track of the aforementioned report stressing the value of CMR in cardiomyopathies and heart failure.

Besides the characterization of tissue changes, CMR has the potential to prospectively differentiate between reversible and irreversible myocardial injuries. The changes can be monitored during follow-up. CMR in DCM can differentiate some of the underlying causes, e.g., inflammatory myocardial disease (IMD). In hypertrophic cardiomyopathy (HCM), it is helpful in identifying different causes of “left ventricular hypertrophy” (LVH).

Despite its possibilities to sort out special forms of cardiomyopathies, e.g., hemochromatosis, CMR cannot identify the etiology of inflammatory cardiomyopathy. Nor has the issue been resolved how sensitive and how specific it really is in the detection of lower grades of inflammation with and without necrosis when compared to the present standard of EMB, which allows to identify the infiltrating cell population, the degree of fibrosis, the presence of necrosis or apoptosis, and the viral or microbial pathogen by polymerase chain reaction (PCR). EMB in turn faces the problem to identify these features in tiny and hopefully representative tissue specimens from the left or right ventricle in an often spotty disease such as viral myocarditis.

Many biomarkers are available in the setting of a specialized secondary or tertiary referral center, in which EMB may be needed for a comprehensive and final analysis.

In a stepwise approach from noninvasive biomarkers including CMR to invasive heart catheterization, we also attempt to identify useful biochemical and immunologic biomarkers to define the extent of inflammation, necrosis and fibrosis by peripheral blood analysis in order to reach a final etiologically based diagnosis for the optimal treatment of a patient beyond conventional heart failure therapy.

It is obvious that the stepwise approach may be helpful in many cases, but this is not necessarily so, particularly in patients, in whom immediate therapeutic consequences are mandatory. Here, a “detour” by using various chemical biomarkers may confirm the critical clinical situation of a fulminant inflammatory process, but only EMB will lead to a definite etiologic diagnosis and to specific treatment [40–43].

**Dilated Cardiomyopathies**

DCMs are an important part of the heart failure spectrum. The most frequent causes of heart failure are CAD and hypertension. Like heart failure, cardiomyopathies, which are third in prevalence and clinical importance, are not a homogeneous disease. The most frequent phenotype of cardiomyopathies according to the WHO/ISFC (World Health Organization/International Society and Federation of Cardiology) 1995 classification, which distinguishes dilated from hypertrophic, restrictive, right ventricular and nonclassifiable forms, are the DCMs. Primary cardiomyopathies were classified as any of the above with unknown etiology [59]. Specific cardiomyopathies or secondary forms may occur under the same functional or pathologic phenotype but have known etiologies.

Since 1996 and 2007, several major changes in the scientific appreciation of the cardiomyopathic entities have occurred. The most important are listed in the following:

1. At least 25–30% of DCMs belong to familial forms, many of which are monogenetic. We know the family trees and the mutations [20, 52] and we have tools to define the algorithms for their classification [48]. Predisposition for viral infection or autoimmunity can also be inherited and play an increasingly better understood role [41].

2. The nonfamilial forms are, in most cases, not idiopathic. Either a viral, bacterial, autoimmune, metabolic or toxic etiology plays a decisive role [40, 53]. Alterations in receptor morphology or in ion channels may but do not necessarily lead to changes in myocardial function. Channelopathies [46] as such are therefore not necessarily cardiomyopathies in “sensu strictu” but rather cardiopathies [40], as the position statement of the ESC (European Society of Cardiology) Working Group correctly points out, when defining the European point of view [14] in comparison to the...