Clinical Biochemistry 47 (2014) 327–337

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

Cardiac biomarkers in heart failure

Michael E. Liquori [a,*], Robert H. Christenson [b], Paul O. Collinson [c], Christopher R. deFilippi [d]

[a] University of Maryland School of Medicine, Department of Internal Medicine, 22 S. Greene St, Baltimore, MD 21201, USA
[b] University of Maryland School of Medicine, Department of Pathology, 22 S. Greene St, Baltimore, MD 21201, USA
[c] St. George's Hospital, Clinical Blood Sciences, Blackshaw Rd, London SW17 0QT, UK
[d] University of Maryland School of Medicine, Department of Medicine, 22 S. Greene St, Baltimore, MD 21201, USA

ARTICLE INFO

Article history:
Received 29 September 2013
Received in revised form 25 January 2014
Accepted 27 January 2014
Available online 12 February 2014

Keywords:
Heart failure
Biomarkers
Cardiac
Troponin
Natriuretic peptide

ABSTRACT

Background: Heart failure is a syndrome characterized by the inability of the heart to meet the body's circulatory demands. Heart failure is a growing health issue worldwide and the prevalence of heart failure is expected to rise as populations age. Therapies and interventions for a variety of cardiac conditions continue to advance and biomarkers will play an increasing role in patient management.

Methods: This is a review of the clinical research in blood based biomarkers for diagnosis, prognosis and therapeutic guidance of heart failure. The focus of this review is biomarkers that are currently available for clinical measurement, and their current and potential for applications for managing heart failure patients.

Results: The various biologic pathways and physiologic processes of heart failure biomarkers represent a host of different including inflammation, remodeling, strain, neurohormonal activation, metabolism and cardiac myocyte injury. The clinical characteristics and applications of each heart failure biomarker are discussed.

Conclusion: As populations age and effective treatments and interventions for coronary artery disease improve, heart failure will increase in incidence and prevalence. Blood biomarkers will play an increasing role in the early diagnosis, therapeutic monitoring and management of heart failure patients in the future.

Contents

Introduction . . . 328
Markers of inflammation . . . 328
C-reactive protein . . . 328
Myeloperoxidase . . . 329
Tumor necrosis factor α . . . 330
Markers of fibrosis and extracellular matrix remodeling . . . 330
Procollagen . . . 330
Galectin-3 . . . 330
ST2 . . . 331
Matrix metalloproteinases and tissue inhibitors of metalloproteinases . . . 331
Markers of biochemical strain . . . 331
Natriuretic peptides . . . 331
Growth Differentiation Factor 15 . . . 332
Markers of neurohormonal activation . . . 332
Copeptin . . . 332
Adrenomedullin . . . 333
Markers of cardiomyocyte injury . . . 333
Cardiac troponins . . . 333
Conclusion . . . 334
References . . . 334

* Corresponding author.
E-mail address: mliquori@umm.edu (M.E. Liquori).

http://dx.doi.org/10.1016/j.clinbiochem.2014.01.032
0009-9120/

Introduction

Heart failure (HF) is a syndrome characterized by the inability of the heart to meet the circulatory demands of the body leading to many symptoms including dyspnea and fatigue. HF can arise from a host of conditions involving the myocardium or heart valves. HF occurs in about equal frequency with and without a reduced ventricular ejection fraction (EF). Each of these categories accounts for approximately 50% of all cases [1]. Regardless of category, HF is staged according to the American College of Cardiology/American Heart Association guidelines (Table 1) [2]. Additionally, a patient's functional status can be classified according to the New York Heart Association classification (Table 1) [2]. As can be seen from Table 1, there is overlap between HF stage and NYHA classification of symptoms.

HF is a burgeoning health and healthcare problem. There are an estimated 20 million affected individuals worldwide [3], of which 5.7 million are in the United States [4]. HF accounts for over one million hospitalizations in the United States, over three million physician office visits, and nearly 57,000 deaths annually [4]. In Canada hospitalizations for heart failure were reported as more than 106,000 annually [5]. The prevalence of HF is expected to continue to rise as early detection therapies for myocardial infarction (MI), valvular diseases and arrhythmias improve, thereby allowing patients to survive longer [3].

Despite its high prevalence, the diagnosis of HF remains difficult as none of the signs and symptoms are specific or particularly sensitive. Due to this, history and physical examination may not be sufficient to reach the diagnosis. Traditional adjuncts to diagnosis include echocardiography, stress testing, and various forms of radionuclide imaging. Each of these has their short-comings and for this reason, diagnostic aids in the form of blood-based biomarkers have been sought. Much research for the past decade has examined numerous possible biomarkers and in general these biomarkers can be broken down into six categories: markers of inflammation; extracellular matrix turnover and remodeling markers; markers of biochemical strain; markers of neurhormonal activation; markers of nutrition and metabolism; and markers of cardiomyocyte injury (Table 2). Given the large number of candidates, a systematic manner of assessing biomarkers and identifying those most likely to be relevant was needed. In 2007 Morrow and de Lemos [6] put forth three criteria for the evaluation of new biomarkers: first, the marker must be able to be measured reliably, quickly, and at reasonable cost; second, the marker must provide additional information that the physician cannot obtain from a historical and physical examination; and third, the marker must influence clinical decision-making.

Few biomarkers have successfully fulfilled each of these criteria. However, there are several promising targets. In this review, we will focus on markers that are either available for utilization by clinicians or have at least been evaluated rigorously in multiple research studies.

Markers of inflammation

Inflammation is now widely accepted as a component of the pathogenesis and progression of HF. This, however, has not always been the case. Initially, attempts were made to explain HF from a purely hemodynamic perspective. This “hemodynamic hypothesis” was unable to adequately explain the progression of HF so alternative explanations were sought. In 1996, Seta et al. put forth the “cytokine hypothesis.”[7] In this, they suggested that the progression of HF is, at least in part, explained by the activation of cytokine cascades following an initial cardiac insult. At first, many of these cytokines may serve adaptive and compensatory purposes. However, with continued and excessive production of these cytokines, they become maladaptive and contribute to the progression of HF. In this section, we will discuss three of the most studied circulating markers of inflammation.

C-reactive protein

C-reactive protein (CRP) is a 23-kDa pentraxin protein which is known to be involved in the immune response. With the introduction of high sensitivity assays in the 1990s it became possible to measure subtle manifestations of systemic inflammation resulting in multiple insights into the role of inflammation in a variety of cardiovascular pathophysiologies. CRP has been demonstrated to be both a mediator of inflammation as well as a marker for the presence of an inflammatory process [8]. There has been great interest in CRP in many disease processes over the years. In the cardiac arena, CRP has been studied for its relation to atherosclerosis, coronary artery disease (CAD), acute coronary syndromes (ACS), and HF. Ultimately these evaluations led to mixed results.

Elevated levels of CRP have been shown to predict future vascular events, even out to 20 years [8]. CRP has been found to be prognostic of poor outcomes in multiple settings. In a large group of patients with stable CAD and preserved ejection fraction, CRP was a strong predictor of new HF, MI, stroke, cardiovascular death and new diabetes [9]. In a group of patients with ACS from the OPUS-TIMI 16 trial, CRP was strongly associated with death or new HF in both the short term and long term [10]. In patients with HF, CRP levels corresponded to New York Heart Association (NYHA) class and poor outcomes [11,12]. An elderly cohort from the Heart & Soul Study who had known CAD were shown to have higher rates of hospitalization for HF, regardless of a prior history of HF, if they had elevated CRP levels [13]. CRP has alternately been associated with diastolic dysfunction alone [13,14] or systolic function alone [15,16]. Michowitz et al. showed that CRP levels were predictive of HF hospitalizations in patients with systolic but not diastolic dysfunction [12]. Numerous studies have demonstrated that the addition of CRP to B-type natriuretic peptide (BNP) provides greater prognostic information than either marker alone [14,16–18].

However, a large population based study showed that whereas CRP levels were elevated in patients with higher levels of subclinical atherosclerosis, this relationship was not independent of other markers of atherosclerosis [19]. Furthermore, CRP has not been shown to be prognostic in all studies [20,21]. Even when CRP has been shown to be a predictor of CAD, its prognostic ability was moderate at best [22]. Additionally, CRP levels are not reduced by treatment with ACE inhibitors [9] or spironolactone [23] but they are reduced with statins [24]. The reduction of CRP levels has been confirmed in multiple studies; unfortunately the reduction in CRP levels in HF patients with the use of statins has not resulted in improved outcomes [25,26].

Despite the fact that measurement of CRP is readily available for clinical use and generally the assays are in harmony across different laboratory platforms, it is not currently part of the guidelines for screening, diagnosing or prognosticating in HF [27].

Table 1
Stages of heart failure and NYHA classification of heart failure as per the American College of Cardiology/American Heart Association. From reference [2].

Stages of heart failure	Classes of heart failure
A – At risk for HF but no structural heart disease or HF symptoms	I – No limitation of physical activity. No HF symptoms with ordinary physical activity
B – Structural heart disease but no symptoms of HF	II – Mild limitation of physical activity. HF symptoms with ordinary physical activity.
C – Structural heart disease with symptoms of HF	III – Marked limitation of physical activity. HF symptoms with less than ordinary physical activity.
D – Advanced HF requiring specialized interventions	IV – Symptoms of HF at rest.