Biomarkers in Adult Congenital Heart Disease Heart Failure

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KEYWORDS

• Adult congenital heart disease • Biomarker • Natriuretic peptide • Heart failure
• Ventricular dysfunction • Mortality

KEY POINTS

- Most adults with congenital heart disease (ACHD) show high levels of natriuretic peptides (NP) when compared with normal controls although the magnitude of elevation is less pronounced in patients with ACHD when compared with non-ACHD cardiac patients.
- Norepinephrine and NP levels were strongly related to outcome in studies that included many symptomatic patients, especially those with unrepaired ACHD, Eisenmenger syndrome, and pulmonary hypertension.
- Limited data are available regarding serial assessment of biomarkers, and such information could provide additional important information to help identify patients at risk, as demonstrated during patient follow-up and pregnancy. We provide an overview over the literature of biomarkers in ACHD, including possible associations with symptoms, ventricular function and outcome.

SPECIFIC PATHOPHYSIOLOGY IN ACHD

Major causes of heart failure (HF) in adults with acquired heart disease are myocardial ischemia, systemic hypertension, valvular disease and cardiomyopathies for left-sided HF, and idiopathic and thromboembolic pulmonary hypertension (PH) for right-sided HF. On the other hand, the cause of HF in adult congenital heart disease (ACHD) is different from that of non-ACHD, and the specific causes include single-ventricle physiology, such as Fontan circulation, non–left ventricular (LV) type morphology of the systemic ventricle, and various residual hemodynamic abnormalities, such as valve stenosis and/or regurgitation. In addition, cyanotic patients without definitive repair and those with Eisenmenger syndrome present with unique pathophysiology.

ASSESSMENT OF PATHOPHYSIOLOGY IN ACHD

The first step in managing ACHD HF patients is to understand their pathophysiology and to select the appropriate modalities for assessment. In addition to cardiac echocardiography, magnetic resonance imaging (MRI), and computed tomography (CT) for assessment of the cardiac structure and function, one should not forget that noncardiac global assessment of HF severity is also important for the prognosis and management strategy in both ACHD and non-ACHD HF patients. The major nonspecific assessment modalities include biomarkers and cardiopulmonary exercise testing, such information having become more relevant and established in daily practice in adult cardiac patients with non-ACHD. However,

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there are limited data regarding these parameters, and the clinical significance of biomarkers remains largely unknown in ACHD.

CRITERIA FOR BIOMARKERS

Biomarkers of HF may be subdivided into 7 categories (**Box 1**),[1] and 3 criteria for biomarkers have been proposed. First, accurate, repeated measurements must be available to the clinician at a reasonable cost and with short turnaround times; second, the biomarker must provide information that is not already available from a careful clinical assessment; and third, knowledge of the measured level should aid in medical decision making.[2]

Box 1
Definitions and categorization of biomarkers in heart failure

Definition

1. Available to clinicians
2. The biomarker adds new information
3. The biomarker helps the clinician to manage patients

Category

1. Inflammation
   C-reactive protein, tumor necrosis factor-α, interleukin-6, etc
2. Oxidative stress
   Oxidized low-density lipoproteins, myeloperoxidase, etc
3. Extracellular-matrix remodeling
   Matrix metalloproteinases, plasma procollagen type III, etc
4. Neurohormones
   Norepinephrine, renin, aldosterone, endothelin-1, etc
5. Myocyte injury
   Troponins I and T, creatinine kinase MB fraction, etc
6. Myocyte stress
   Atrial and brain natriuretic peptides, NT-proBNP, etc
7. New biomarkers
   Adiponectin, asymmetric demethylarginine, etc

Data from Braunwald E. Biomarkers in heart failure. N Engl J Med 2008;358:2149, with permission; and Morrow DA, de Lemos JA. Benchmarks for the assessment of novel cardiovascular biomarkers. Circulation 2007;115:950.

EVIDENCE OF BIOMARKERS IN ACHD

There has been large number of studies on circulating biomarkers in adult HF patients without ACHD. However, this evidence may not be always applicable to unique ACHD HF pathophysiology. This article subdivides documented studies into 6 categories, as follows: (1) studies of heterogeneous ACHD cohorts with various kinds of systemic ventricle (SV) (mixed group); (2) studies of ACHD patients with biventricular physiology with a morphologic right ventricle (RV) as a pulmonary ventricle (PV) (PRV group); (3) studies of ACHD with an RV as an SV (SRV group); (4) studies of adult patients with Fontan physiology (Fontan group); (5) studies of hypoxic ACHD without definitive repair, including Eisenmenger syndrome (Unrepaired group); and (6) studies of female ACHD patients during pregnancy and delivery (Pregnancy group) (**Table 1**).

Correlations between biomarkers and clinical variables and predictive and/or prognostic values of biomarkers in ACHD are summarized in **Tables 2** and **3**, respectively.

Mixed Group

Patients' characteristics

Heterogeneous ACHD patients with and without definitive repair were included in this category.[3–10] These studies consisted of 7 to 94 clinically stable patients with a mean age of 26.6 to 39.4 years, and a relatively large percentage of symptomatic ACHD patients, that is, New York Heart Association (NYHA) functional class II or higher (although those with NYHA class IV were rare). Ventricular function was assessed by echocardiography in all studies except 1,[3] and subjective visual assessment of SV function was used because of the difficulty in the measurement of SV volume. Several exclusion criteria were also applied variably, such as acute HF,[4,7] liver and/or renal dysfunction,[3,4,8] infection,[4] NYHA class IV,[10] and LV dysfunction.[3]

Biomarkers

All studies measured brain natriuretic peptide(s) (BNP), including one study of N-terminal pro-BNP (NT-proBNP),[10] and 3 studies measured atrial natriuretic peptide (ANP).[3,4,9] Catecholamines, hormones of the renin-angiotensin-aldosterone system (RAS) and asymmetric dimethylarginine were measured in 1 study each.[4,10] ACHD patients showed significantly higher levels of natriuretic peptides (NPs) compared with controls, and the