Journal of Critical Care (2012) **27**, 415.e13–415.e18

ELSEVIER

Journal of Critical Care

Usefulness of heart-type fatty acid–binding protein in patients with severe sepsis

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Keywords:
Cardiac markers;
Sepsis;
Prognosis;
Myocardial dysfunction;
Heart fatty acid–binding protein (hFABP)

Abstract

Purpose: The purpose of the study was to evaluate the value of heart-type fatty acid–binding protein (hFABP) as a novel clinical biomarker in patients with severe sepsis.

Methods: Serum concentrations of hFABP and traditional cardiac biomarkers including cardiac troponin I, creatine kinase–MB, and B-type natriuretic peptides levels were measured within 6 hours after admission in 93 severe septic patients. The value of hFABP for the diagnosis of sepsis-related myocardial dysfunction (SRMD) and for the prediction of 28-day mortality was evaluated by receiver operating characteristics curve analysis. The prognostic value of elevated hFABP was subsequently confirmed by multivariate Cox proportional hazards analysis and Kaplan-Meier survival analysis.

Results: Heart-type fatty acid–binding protein was elevated (≥4.5 ng/mL) in 58 (62.4%) patients; patients with elevated hFABP appeared more likely to have SRMD (84.5% vs 31.4%, $P < .001$) and have higher prevalence of 28-day death (37.9% vs 8.6%, $P = .002$). Heart-type fatty acid–binding protein offered superior value over conventional biomarkers in both diagnosis of SRMD (area under the curve, 0.767; $P < .001$) and prediction of 28-day death (area under the curve, 0.805; $P < .001$).

Conclusions: Serum hFABP is frequently elevated among patients with severe sepsis and appears to be associated with SRMD. Elevated hFABP independently predicts 28-day mortality in severe sepsis.

1. Background

It is reported that up to 50% of septic patients may have a complication of cardiac dysfunction that contributes to an elevated mortality rate compared with those without cardiovascular impairment [1]. In this regard, a number of cardiac biomarkers such as cardiac troponins (cTns), MB isoenzyme of creatine kinase (CK-MB), and B-type natriuretic peptides (BNP) are now commonly used in the intensive care unit (ICU) [2-4]. However, although interpretation of these biomarkers may be confounded by several conditions, including severity of the disease, coexisting organ dysfunction, multiorgan involvement, or altered

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doi:10.1016/j.jcrc.2012.01.004

synthesis/clearance [5,6], it is still necessary to find additional novel biomarkers for clinical use.

Heart-type fatty acid–binding protein (hFABP), an emerging cardiac biomarker, is a small cytosolic protein abundant in cardiomyocyte that binds long-chain fatty acids and functions in uptake and transport of long-chain fatty acids. It is rapidly released from cardiomyocytes into the circulation shortly after the onset of cell damage. Heart-type fatty acid–binding protein has been reported to be a promising biomarker of myocardial damage and clinical outcome in acute coronary syndrome [7,8] and to be useful in the prediction of cardiac dysfunction and adverse outcomes in congestive heart failure, pulmonary embolism, and cardiac surgery with cardiopulmonary bypass [9-11]. Heart-type fatty acid–binding protein offers better sensitivity than cTnT for detecting ongoing myocardial damage in congestive heart failure [12] and better discriminatory ability for pulmonary embolism–related complications than cTnT and N-terminal-proBNP [10]. Few studies, however, have investigated the utility of hFABP in critically ill patients; whether hFABP offers similar and even superior power to conventional cardiac biomarkers in critically ill septic patients is to be elucidated.

In the present study, we aim to investigate the relationship between concentration of hFABP and prevalence of *sepsis-related myocardial dysfunction* (SRMD), defined as the transient depression in left ventricular function in patients with sepsis, and evaluate the prognostic values of hFABP for adverse outcomes in septic patients without prior cardiovascular impairment.

2. Methods

2.1. Study population

Ninety-three patients, aged 35 to 94 years (male, 54; female, 39), hospitalized in a 27-bed medical ICU of Zhejiang Hospital during April 2008 through December 2010 were enrolled when they first met the criteria of severe sepsis and/or septic shock defined by the American College of Chest Physicians and the Society of Critical Care Medicine consensus conference [13]. Patients with preexisting reduction of left ventricular function, dilated cardiomyopathy, acute or chronic valvular disease, acute and chronic renal failure, acute coronary ischemia, or cardiogenic or hemorrhagic shock were excluded from the study.

All patients were evaluated by complete history taking, physical examination, serum biochemistry panel, and arterial blood gas analysis and treated with the evidence-based 6-hour resuscitation and 24-hour management bundles according to the Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock [14]. The efficacy of therapy is based on 28-day survival from study enrollment [13]. The severity of illness was assessed according to the Acute Physiological and Chronic Health Evolution (APACHE) II score within 24 hours after admission [15]. Heart-type fatty acid–binding protein, conventional cardiac markers (CK-MB, cTnI, and BNP), and inflammatory biomarker (procalcitonin [PCT]) were drawn within 6 hours after admission. Both the need for and the timing of inotrope support defined as continuous infusion of milrinone, dobutamine, dopamine (>5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), epinephrine, norepinephrine, or vasopressin based on the professional guidelines [14] were recorded. All clinical events and outcomes were followed throughout the hospitalization. The follow-up was limited to the period of hospitalization.

This study was approved by the hospital's ethics committee. Written informed consent was obtained from all patients, their relatives, or legal guardians before enrollment.

2.2. Blood sample collection

The blood samples from central venous line were drawn for complete blood count, biochemical assay, cardiac biomarkers (cTnI, CK-MB, BNP, and hFABP), and PCT detection. For detection of cTnI, hFABP, and PCT, serum samples were collected after 15-minute centrifuge at 3000*g* and stored in sterile tubes at −40°C until assayed. For BNP measurement, 4-mL blood samples were taken after 20 minutes of supine rest, then withdrawn into chilled tubes containing EDTA and aprotinin (50 IU/mL) (Bayer AG, Leverkusen, Germany) and centrifuged at 3000*g* for 10 minutes at 4°C; the separated plasma was stored at −40°C before assay. In addition, 0.5 mL of arterial blood was also obtained for an instant blood gas analysis plus lactate detection by using an automated Easystat Analyzer and matched reagent (Medica Co, Bedford, MA, USA).

2.3. Biochemical assays

Complete blood count test was carried out using the Coulter LH 700 automated system (Beckman Coulter, Inc, Brea, CA, USA). The conventional biochemical panel including liver function, renal function, and electrolytes as well as CK-MB (reference range, <10 U/L) was measured by using an Olympus AU 2700 Chemistry Analyzer (Diamond Diagnostics, Holliston, MA, USA) with commercially available reagent (AusBio Laboratories, Yantai, China). The detection limit of CK-MB is 1.0 U/L with an upper limit of 200 U/L and a total imprecision of 3.8% to 6.5%.

Serum cTnI levels were measured via the 2-site immunoassay with direct chemiluminometric technology (ADVIA Centaur; Bayer Diagnostics, Tarrytown, NY, USA). Negative controls were included in each run. The 99th percentile was used as a cutoff value for troponin assays, above which any value is considered abnormal. For the ADVIA Centaur assay, a value 0.1 ng/mL or greater is considered an elevated level representing myocardial injury. The lower limit of detection for this assay was 0.02 ng/mL. The coefficient of variation was 5%.