Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

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

Original article

Association between the baseline peripheral blood monocyte counts, the size of spleen, and the response to cardiac resynchronization therapy

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ARTICLE INFO

Article history:
Received 21 March 2017
Received in revised form 22 July 2017
Accepted 5 September 2017
Available online xxx

Keywords:
Monocyte
Spleen
Heart failure
Cardiac resynchronization therapy
Long-term outcome

ABSTRACT

Background: Spleen reserves monocytes, which deploy to inflammatory sites. Monocytosis is known to be observed in chronic low-grade inflammatory state, including chronic heart failure (CHF). CHF also induces splenomegaly. We tested the hypotheses that the number of peripheral blood monocytes and size of spleen at baseline could be related to the response to cardiac resynchronization therapy (CRT).
Methods: From 2010, a total of 49 consecutive patients implanted with CRT device were evaluated at baseline and 6–8 months later. The size of spleen was evaluated at baseline by computed tomography. Blood monocyte counts (BMCs) were examined by blood test apparatus.
Results: Patients were categorized as responders (13 female, mean age 69.0 ± 7.9 years, $n = 34$) and nonresponders (2 female, mean age 72.0 ± 8.8 years, $n = 15$) according to echocardiographic findings. In non-responders, spleen index was also greater in non-responders than in responders (4504 ± 1338 mm^2 vs. 3240 ± 1115 mm^2; mean ± SE, $p < 0.01$). Median baseline BMCs were significantly smaller in responders than non-responders (537 ± 211/μl vs. 336 ± 107/μl, $p < 0.01$). In addition, BMC is positively correlated with the spleen index ($R^2 = 0.179$, $p = 0.02$). Based on the receiver-operating characteristic curve, low BMC was set at <400/μl. Kaplan–Meier survival analysis demonstrated that the low BMC patients had lower prevalence of new hospitalization due to HF progression (log rank 5.35, $p = 0.02$).
Conclusions: Our results demonstrated that BMC and the size of spleen might be important factors for response to CRT.

Introduction

The primary functions of the spleen are to remove aging erythrocytes, recycle iron, and initiate an immune response [1]. An additional role for the spleen has also been reported. Spleen acts as a reservoir for monocytes, which are deployed to inflammatory sites [2–4]. For example, myocardial infarction induced by left coronary artery ligation in mice increased the egress of monocytes from the spleen, resulting in their accumulation in the infarct area. Splenectomy attenuated the infiltration of monocytes to the infarcted myocardium in mice. Monocytosis (increase in the number of peripheral blood monocytes) is known to be observed in chronic low-grade inflammatory state, including chronic heart failure, which also induces splenomegaly [5]. We previously demonstrated that monocytosis and enlarged spleen are observed in a heart failure (HF) rat model, which is induced by pressure overload [6]. Monocytes are major regulators of cardiac inflammation and fibrosis with complex cell interactions among monocytes/macrophages, cardiomyocytes, and cardiac fibroblasts in myocardium underlying the development of cardiovascular disease and HF [3]. It has been reported that β-blockers prevent monocytosis observed in patients with myocardial infarction due to suppression of monocyte recruitment from spleen [3].

In patients with severe HF, cardiac resynchronization therapy (CRT) is a therapeutic modality for improving symptoms, exercise capacity, cardiac function, and prognosis [7–11]. However, little is known about the relationship between the outcome of CRT-treated

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http://dx.doi.org/10.1016/j.jjcc.2017.09.004
0914-5087/

patients with HF and the baseline peripheral blood monocyte counts (BMCs) or spleen. The purpose of this study was to assess whether the size of spleen and the number of peripheral blood monocytes at baseline can predict the response to CRT. The relationship between spleen size and the number of peripheral blood monocytes was also evaluated.

Methods

Patient selection

The study consisted of 49 HF patients implanted with CRT device for the treatment of advanced HF from 2010. Patients with cardiac sarcoidosis and amyloidosis were excluded due to the characteristics of the diseases. This disease is characterized by systemic inflammation, and it can present monocytosis. In addition, receiving steroid therapy also could affect the results of monocyte count. The inclusion criteria were: New York Heart Association (NYHA) class III-IV, left ventricular ejection fraction (LVEF) $< 35\%$, and QRS duration ≥ 130 ms. Their mean age was 70.6 ± 8.9 years, LVEF was $29.0 \pm 7.9\%$, and QRS duration was 160 ± 22 ms. The study group comprised 15 females and 34 males. Responders to CRT were defined as patients displaying a $\geq 15\%$ reduction in left ventricular end-systolic volume (LVESV) [12] at 6–8 months follow up after CRT implant. Patients who had hospitalization for HF, or died before the 6–8 months follow-up were considered non-responders. The study was approved by the ethics review board of our institution and written informed consent was obtained from all subjects.

Study design

In all studied patients, transthoracic echocardiography was assessed by the Vivid 7 (GE Vingmed, Horten, Norway) and the size of spleen was evaluated at baseline by computed tomography, and quantitated by measuring maximum diameter and spleen index (Fig. 1). BMC was examined by blood test apparatus. The examination was repeated twice to confirm the reproducibility of the count. The initial data of BMC were used for this study. Blood samples were taken at 6–8 days before the CRT implantation. We obtained cut-off values of baseline BMC by creating receiver-operating characteristic (ROC) curve (Fig. 2). The best BMC with the highest sensitivity and specificity was 400/μl to predict the responders. Therefore, we defined low BMC patients as the value ≤400/μl. From 2010, accurate follow-up information for 323 ± 100 days was obtained in 30 low BMC patients (11 females and 19 males, mean age 71.0 ± 6.3 years) and 19 high BMC patients (4 females and 15 males, mean age 70.0 ± 11.0 years).

Assessment of echocardiography

Complete M-mode, 2-D, and Doppler evaluations were performed using a 1.5- to 4.0-MHz transducer at an appropriate depth in the parasternal and apical views. Left ventricular end-

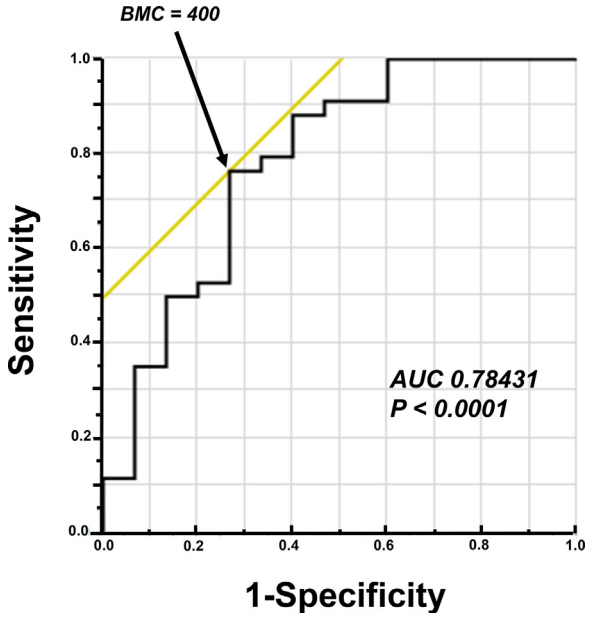

Fig. 2. The best BMC value with the highest sensitivity and specificity was 400/μl to predict the responders, determined by creating receiver-operating characteristic curve. AUC, area under the curve; BMC, blood monocyte count.

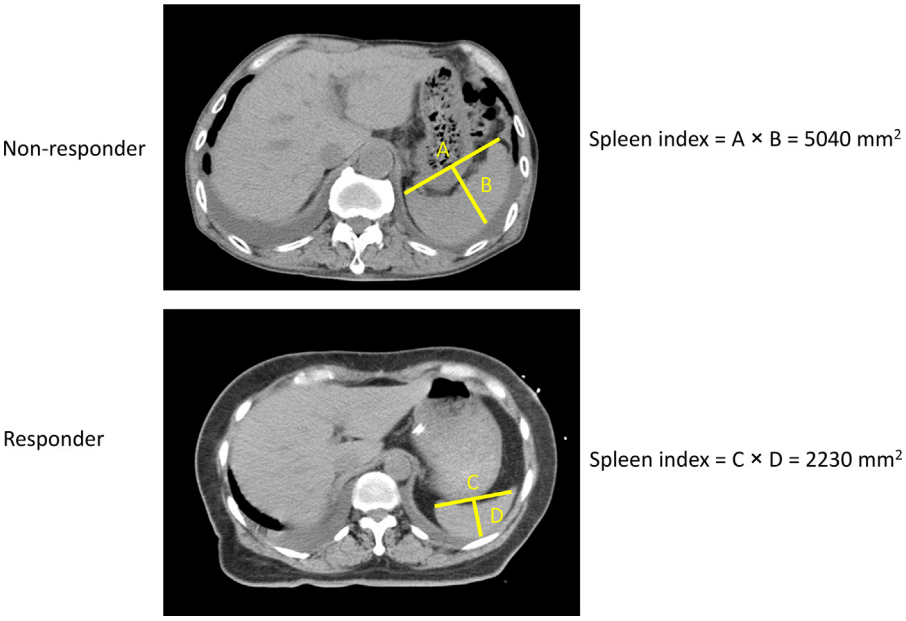

Fig. 1. Representative computed tomography images of spleen of each group (responder and nonresponder) are shown. The size of spleen was quantitated by measuring maximum diameter (A and C) and spleen index (A × B and C × D).

Please cite this article in press as: Fujinami M, et al. Association between the baseline peripheral blood monocyte counts, the size of spleen, and the response to cardiac resynchronization therapy. J Cardiol (2017), http://dx.doi.org/10.1016/j.jjcc.2017.09.004