Erythropoietin Levels in Cardiac Resynchronization Patients

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Abstract: Cardiac resynchronization therapy (CRT) is indicated in patients with advanced heart failure secondary to severe systolic impairment and refractory symptoms despite optimized medical treatment and evidence of electro-mechanical dyssynchrony with a QRS complex greater than 120 milliseconds (msec). Approximately 20%-30% of patients who receive CRT fail to respond with little improvement in subjective symptoms, functional capacity, and left ventricular indices. To date, there fails to be a serologic marker to adequately assess the degree of ventricular dyssynchrony and electro-mechanical dissociation. Increased levels of erythropoietin (EPO), a hematopoietic cytokine, has been demonstrated in patients with more advanced stages of heart failure and is associated with an increase in mortality and hospital re-admission. A recent study demonstrated a significant response to CRT in patients with higher baseline EPO levels (> 25mU/mL) with improvements in cardiac function and reduced heart failure symptoms. The presence of elevated EPO levels in addition to traditional determinants of cardiac dyssynchrony may effectively predict those that will benefit from CRT.

Keywords: Erythropoietin levels, biventricular, pacing, CRT.

LETTER TO THE EDITOR

Cardiac resynchronization therapy (CRT) is indicated in patients with advanced heart failure secondary to severe systolic impairment and refractory symptoms despite optimized medical treatment and evidence of electro-mechanical dyssynchrony with an ECG QRS complex greater than 120 msec. Simultaneous pacing of both the right and left ventricle (BiV pacing) has been shown to restore electro-mechanical synchrony, improve overall cardiac function, reduce hospitalizations, and confer a mortality benefit [1]. Despite the cardiovascular benefits of BiV pacing demonstrated in recent trials, approximately 20%-30% of patients who receive CRT fail to respond with little improvement in subjective symptoms, functional capacity, and left ventricular functional indices [2]. Absence of electro-mechanical dyssynchrony despite prolonged QRS duration (>120ms), pre-existing right bundle branch block (RBBB), inappropriate lead placement and continued disease progression have been shown as causes for non-response to CRT. To date, there fails to be a serologic marker to adequately assess the degree of ventricular dyssynchrony and electro-mechanical dissociation.

Erythropoietin (EPO), a hematopoietic cytokine, has traditionally been associated with erythropoiesis in response to anemic stress. Several studies have indicated the positive effects of EPO treatment in heart failure patients with concomitant anemia resulting in reductions in hospital re-admission, improved cardiac and renal function, as well as subjective improvement in the overall reported quality of life [3, 4]. Early correction of anemia by administration of EPO may serve to avoid the deleterious cardio-renal-anemia syndrome, which is associated with a high overall mortality. Non-hematopoietic effects of EPO are presently being explored with prior studies demonstrating elevated levels in conditions of tissue hypoxia irrespective of shifts in hemoglobin [5]. Increased levels of EPO appear to confer cellular protection by modulation of cellular integrity in the cerebrovascular and peripheral vascular system, reduction in oxidative stress and inflammation, and the promotion of angiogenesis fueled largely by a decrease in tissue oxygen supply [6]. Despite the above "protective" effects, a prior study demonstrated that EPO levels greater than 23 mU/mL were associated with increased mortality, hospital re-admission, and severity of heart failure. When compared to traditional cardiac markers, the degree of EPO elevation paralleled the increase in C-reactive protein (CRP) and NT-proBNP with the highest levels seen in those patients with advanced heart failure (NYHA functional class III and IV) emphasizing its crucial role in the heart failure mediated neuro-hormonal axis [5].

Lack of response to CRT in those with advanced heart failure remains a clinical challenge. As mentioned previously, the etiology of non-response to CRT has largely been attributed to the degree of measured dyssynchrony by electrocardiographic (ECG) or echocardiography, as well as technical considerations (i.e., left ventricular lead placement, device settings). Presently there fails to be a single best predictor for response to CRT amongst patients with advanced heart failure and dyssynchrony. The ability to preselect responders to CRT is of clinical benefit given the potential hazards of device implantation, arrhythmogenic potential of CRT [7], and the economic implications of poor

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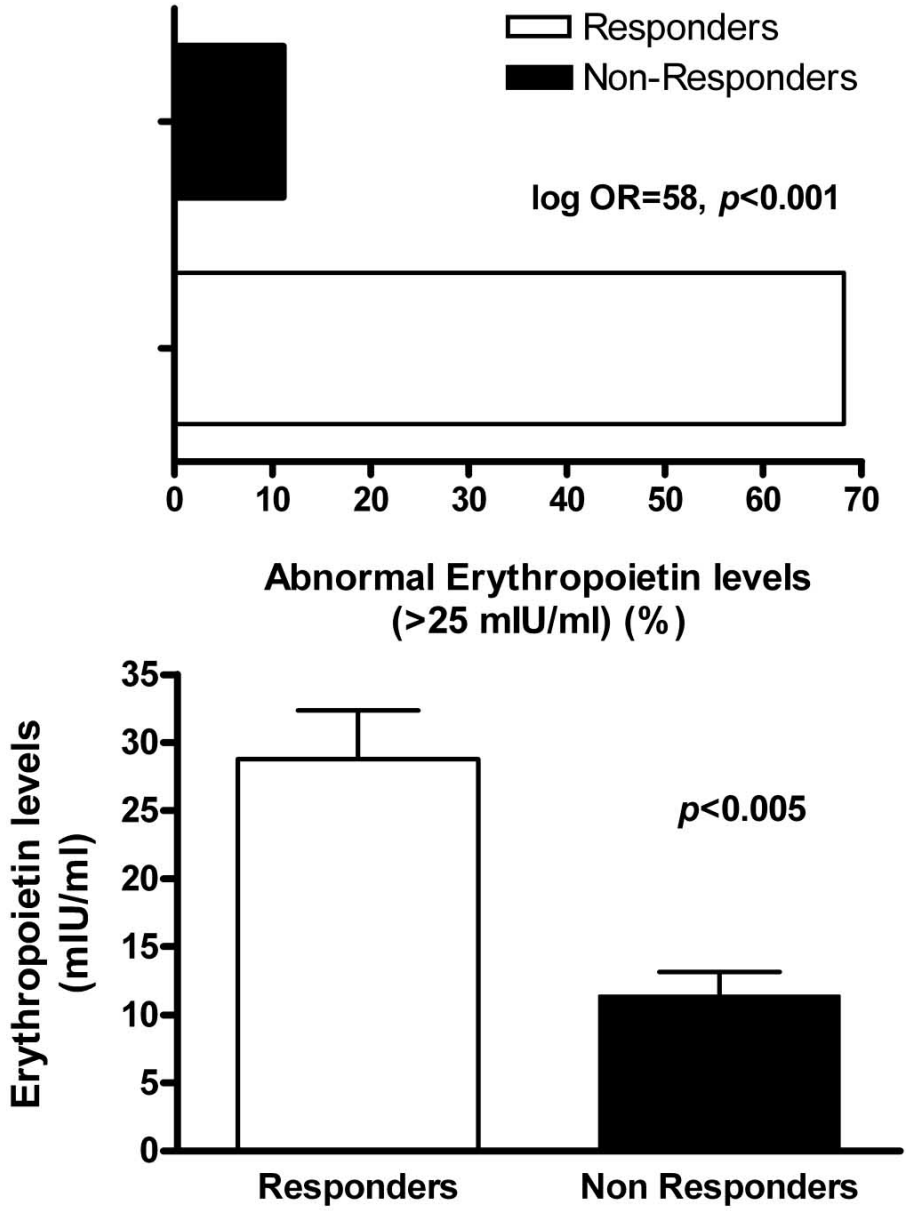

Fig. (1). Erythropoietin levels pre-procedure according clinical response in patients undergoing Cardiac Resynchronization Therapy.

patient selection. The availability of a serum assay to predict response to CRT is desirable and may offer a better means of patient selection. Prior studies have demonstrated EPO as marker of heart failure severity and overall mortality [8]. When evaluated, the degree of EPO elevation was able to predict response to CRT in a small subset of patients at our institution with NYHA class III-IV heart failure, severe left ventricular dysfunction, and QRS duration exceeding 120 ms. Those with chronic kidney disease stages III, IV and V (GFR < 60 ml/min) and/or anemia (Hemoglobin levels < 10 g/dl) were excluded from the study. Response to CRT was defined as an improvement of at least one NYHA class.

Responders to CRT were found to have significantly higher baseline EPO levels (> 25mU/mL) when compared to non-responders, p<0.01 (log OR = 58) (Fig. **1**). This study illustrates the marked elevation in EPO levels in the absence of hematopoietic and renal alteration among a group of patients with severe left ventricular dysfunction. The cause of elevated levels is likely related to poor cardiac output and varying levels of tissue hypoxia among the patients. The use of CRT in this subset of patients with elevated EPO levels led to an improvement in heart failure symptoms, which is likely mediated by improved cardiac function and effective oxygen delivery reducing the degree of tissue hypoxia. Since this was a pilot study our data will need to be confirmed in larger trials and a proof of concept concerning poor cardiac output mediating elevated EPO levels is required. However, no previous study has assessed the potential role of EPO levels as a predictor for CRT response.

Erythropoietin levels in patients with heart failure offers a unique mode of assessing effective oxygen delivery in the absence of underlying renal insufficiency or anemia. The presence of elevated EPO levels in addition to traditional determinants of cardiac dyssynchrony may effectively predict those that will benefit from CRT.

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