Impact of Anemia on Left Ventricular Reverse Remodeling in Response to Carvedilol

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Anemia is frequently observed in patients with heart failure (HF) and is associated with high mortality rates (Figure). Although the mechanisms by which anemia worsens the prognosis of HF patients are yet unclear, it has been recently reported that anemia correlates with high cardiac index and low systemic vascular resistance index in congestive HF patients. The association of anemia with both cardiac and renal dysfunction is widely recognized as cardio-renal-anemia syndrome. Recent guideline-recommended therapies, including β-blockers, have lowered the mortality rate of HF patients with reduced left ventricular ejection fraction (HFrEF). Beta-blockers decrease sympathetic nervous activity, renin secretion, calcium overload, myocardial oxygen demand, vasoconstriction, fluid retention and oxidative stress, with resultant left ventricular (LV) reverse remodeling, and improvement in the prognosis of HFrEF patients. The effect of β-blockers on an improved prognosis may vary according to the patient’s clinical background, such as age, baseline heart rate, etiology of HF, presence of atrial fibrillation, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and peripheral artery disease, among others (Table). The differences in the effect of β-blockers on the prognosis of HF patients with and without anemia still remain unclear. It has been recently reported that recovered and/or improved LV ejection fraction (LVEF) is associated with better prognosis, so LV reverse remodeling seems an appropriate surrogate marker of prognosis for HFrEF patients.

In this issue of the Journal, Nagatomo et al report their clinical study from the Japanese chronic HF (J-CHF) Study showing that the presence of anemia (based on WHO criteria) at baseline, but not chronic kidney disease, was associated with blunted LV reverse remodeling. Improvement in LVEF and B-type natriuretic peptide levels, 56 weeks post-administration of carvedilol, differed between the groups with and without anemia. The authors assumed that anemia induces a hyper-hemodynamic state and increases work load through increased heart rate and stroke volume, leading to higher sympathetic nervous activity, which can contribute to the attenuation of reverse remodeling. This study suggests that a blunted response...
reverse remodeling, a simple predictor of poor responders to carvedilol in LV unclear. Not only anemia, but also iron deficiency anemia, chronic inflammation, as well as other causes, was
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7. Florea VG, Rector TS, Anand IS, Cohn JN. Heart failure with improved ejection fraction: Clinical characteristics, correlates of recovery, and survival: Results from the Valsartan Heart Failure Trial. Circ Heart Fail 2016; 9: e003123.

Table. Possible Factors Associated With the Effects of β-Blockers on Improvement of HF Prognosis

<table>
<thead>
<tr>
<th>β-blocker therapy</th>
<th>Patient's clinical background</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>• β-blocker type (carvedilol, bisoprolol, nebivolol etc.)</td>
<td>• Age</td>
<td>• Atrial fibrillation</td>
</tr>
<tr>
<td>• β-blocker dose</td>
<td>• Heart rate</td>
<td>• Diabetes</td>
</tr>
<tr>
<td>• Combination medicines (renin-angiotensin system inhibitors etc.)</td>
<td>• Body mass index</td>
<td>• Chronic kidney disease</td>
</tr>
<tr>
<td></td>
<td>• Etiology of HF (ischemic or non-ischemic)</td>
<td>• Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>• Baseline LVEF</td>
<td>• Peripheral artery disease</td>
</tr>
<tr>
<td></td>
<td>• Degree of sympathetic nervous activity</td>
<td>• Anemia?</td>
</tr>
<tr>
<td></td>
<td>• Degree of myocardial fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• β1 adrenergic receptor polymorphism</td>
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</tbody>
</table>

HF, heart failure; LVEF, left ventricular ejection fraction.

to carvedilol in LV reverse remodeling may be one of the causes of adverse prognosis in HF+EF patients with anemia (Figure). It has been reported that iodine-123 meta-iodobenzylguanidine imaging and β1 adrenergic receptor polymorphism are useful for predicting LV reverse remodeling. Although the present study adds novel insights regarding anemia as a simple predictor of poor responders to carvedilol in LV reverse remodeling, there are some limitations to this study. First, the etiology of anemia, such as iron deficiency, renal anemia, chronic inflammation, as well as other causes, was unclear. Not only anemia, but also iron deficiency and renal dysfunction are associated with adverse prognosis in HF patients. Second, it has been reported that carvedilol administration affects hemoglobin levels, erythropoietin levels, inflammation and renal function (Figure). Thus, detailed time-course data on the serum levels of iron, ferritin, unsaturated iron binding capacity, erythropoietin, renal function and inflammatory markers after administration of carvedilol may strengthen their results. Hence, further study may reveal the detailed mechanism of how anemia affects LV reverse remodeling in response to carvedilol with consideration of the type(s) of anemia associated with HF.

References