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Editorial

Beta Blockers in Heart Failure: More Evidence for an Old Friend

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▸ See the article "Impact of Heart Rate Reduction with Maximal Tolerable Dose of Bisoprolol on Left Ventricular Reverse Remodeling" in volume 33, e171.

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High resting heart rate (≥ 70 bpm) was common in heart failure with reduced ejection fraction (HFrEF; ejection fraction ≤ 35%) patients and is associated with adverse outcomes in a real-world analysis. For heart failure (HF) hospitalization, hazard appeared to be more closely associated with heart rate rather than β-blocker dose.[1]

Chronic β1-adrenergic receptor overactivation is well known to be an important component of pathologic ventricular remodeling, and evidence-based β-blockers are a clinically effective treatment of HFrEF owing in part to their reverse-remodeling effect. Current HF guidelines recommend the use of β-blockers based on many randomized controlled trials showing a reduced mortality rate > 35%. Although the beneficial effect of β-blocker seems undisputed, whether the target heart rate or target dose is more important in β-blocker therapy is the subject of debate. Meta-analysis showed that heart rate should be considered more important than the actual dose when tailoring β-blocker therapy. In particular, the target resting heart rate might be < 70 beats/min in HF patients. The reason why heart rate reduction is more important than β-blocker dose might be related to the large pharmacogenomic heterogeneity of β-blockers.[2]

In the current issue, Choi et al.[3] concluded that high baseline HR (≥ 75 bpm) showed an association with left ventricular reverse remodeling (LVRR) and improvement of NT-proBNP and global assessment score in patients with HFrEF < 40% at baseline and 6-months (n = 157). LVRR was identified in 49 patients (32%) and patients with ischemic etiology of HF were 19%. They suggest that this effect seems to be due to a large HR reduction after treatments with bisoprolol.

There are current challenges in the management of HF with β-blockers. Could we predict who would be the responder or non-responder of evidence-based β-blockers in HFrEF? Could we also predict who would be reverse-remodeling responders or not with β-blockers in HFrEF? Those are a couple of important questions in HF clinical practice.

The ST2-R2 score was recently developed to predict relevant LVRR in patients with HF. The ST2-R2 score includes the biomarker ST2 (< 48 ng/mL), and five conventional risk parameters (non-ischemic etiology, absence of left bundle branch block, HF duration [< 12 months], baseline LVEF [< 24%], and β-blocker treatment). However, more solid clinical outcome evidence would be necessary for generalizing the usage of the ST2-R2 score in HF clinic.[4]

The phamarcogenomic clinical study using bisoprolol in Korean HF patients showed the ADRB1 Gly389X genotype showed a greater response to bisoprolol than the Arg389Arg genotype. However, there were no significant differences in LVEF changes or remodeling between Arg389Arg genotype group and Gly389X (Gly389Arg + Gly389Gly) group because of the small sample size. However, this result suggested the potential of individually tailoring β-blocker therapy according to genotype.[5]

Although the exact mechanism of LVRR is still unknown, Sucharov et al.[6] reported a difference in gene expression including β-myosin heavy chain (MYH7) and atrial natriuretic peptide (NPPA) between those with LVRR (+) and LVRR (−). Reverse-remodeling is accompanied by normalization of certain pathological changes in ventricular myocardial gene expression, the origins of which are incompletely understood. Such gene expressions regulate calcium-handling, sarcomeric/adrenergic signaling and consequently associate with LVRR. The expression of microRNAs is also altered in dilated cardiomyopathy. The myocardial microRNAs might predict the time-dependent reverse-remodeling response to β-blocker treatment, in dilated cardiomyopathy. More studies are necessary to confirm the specific reverse-remodeling-associated microRNAs as described.

In conclusion, it is clinically important to predict β-blocker responders and reverse-remodeling responders with β-blocker in HFrEF. The precision medicine using microRNA strategy would allow us to better understand the therapeutic response of β-blocker in HFrEF in the future.

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