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EDITORIAL

Unique Effect of Nebivolol on Coronary Hemodynamics: It's All a Matter of Flow

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The concept of coronary flow reserve (CFR) was introduced in the 1960s by Drs. JD Coffman and DE Gregg who tested the reactive hyperemia characteristics of the coronary circulation [1]. Subsequently, the innovative studies of Dr. L Gould have paved the way to better understand coronary flow physiology. Dr. Gould examined the relationship between the anatomic severity of a coronary stenosis and its flow resistance as well as reserve [2, 3]. Based on these research efforts technology has been developed to define the effect of a coronary stenosis on the distal arterial flow response. CFR measures the capacity of the two-component system of coronary artery and supplied vascular bed to achieve maximal blood flow in response to a given hyperemic stimuli. With specialized angioplasty guidewires and induction of maximal coronary blood flow, CFR is often used in research and clinical settings to determine the physiological significance of various coronary stenoses.

The effect of beta-blockers on CFR has been previously studied with beta-blockers—mainly metoprolol [4]. Administration of metoprolol to patients with coronary artery disease is associated with an increase in coronary flow velocity reserve during adenosine-induced hyperemia or after vessel occlusion (post-ischemic). The increase coronary flow velocity reserve with metoprolol can be explained by a reduction in vascular resistance [4]. Nebivolol is a unique beta-blocker. Apart from being a highly selective beta1-adrenergic receptor blocker, it has nitric oxide modulating properties. Specifically, it increases basal and stimulated endothelial nitric oxide release. Given these vasodilating properties it may have beneficial effects on CFR.

The above hypothesis was tested in the study by Dr. M Togni et al in this week's issue of Cardiovascular Drugs and Therapy [5]. In their well-designed and novel study Togni et al tested two groups: patients with coronary artery disease (n=8) and patients with angiographically normal coronary arteries (controls, n=10). Doppler-flow wire derived coronary flow velocity measurements were obtained at rest and after increasing doses of intra-coronary nebivolol (0.1 mg/min, 0.25 mg/min, 0.5 mg/min). Hyperemia was induced by intra-coronary adenosine administration. Although the groups were relatively small and unmatched in some of their clinical characteristics (such as smoking and use of ACE inhibitors), the findings are important. Intra-coronary nebivolol was associated with a significant increase in CFR in both groups, albeit caused by different mechanisms. In the patients with normal coronary arteries the increased CFR was caused by a reduction in resting but not maximal flow, while in the patients with coronary artery disease the increased CFR was mainly due to a reduction in maximal but not resting coronary flow. These differences may be related to differences in endothelial function between the two groups. As the authors suggest, in patients with normal coronary arteries and normal endothelial function the beta-blocking effect of nebivolol most likely predominated, and thus the reduction in resting coronary flow. However, in patients with coronary artery disease and significant endothelial dysfunction baseline CFR is reduced. Stimulation of the endothelium with nebivolol influences the diseased coronary arteries and causes an increase in maximal flow (during adenosine administration).

The effect of nebivolol on coronary flow and hemodynamics has been studied in other populations apart from

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patients with coronary artery disease. Erdogan et al recently reported that in patients with idiopathic dilated cardiomyopathy one month of oral nebivolol treatment was associated with a significant increase in CFR, as measured by trans-thoracic Doppler echocardiography [6]. Similarly, Galderisi et al have shown that in hypertensive patients free of coronary artery disease, one month of oral nebivolol therapy induces a significant increase in CFR, as assessed by Doppler echocardiography [7].

Taken together these findings indicate that nebivolol through its beta-blocking and/or nitric oxide modulating (vasodilating) effects causes an increase in CFR in patients with and without established coronary artery disease. The hemodynamic and clinical value of CFR has been studied in specific settings. In patients with coronary artery disease, undergoing angioplasty, an increased CFR is associated with improved prognostic indices [8]. In patients with hypertension, without coronary artery disease, increased CFR appears to be independently associated with improved myocardial diastolic dysfunction [9]. Therefore, theoretically, a drug which causes an increase in CFR, such as nebivolol may have clinical benefit in certain settings. However, further studies are required to address the short- and long-term benefits of nebivolol for patients with coronary artery disease, heart failure and hypertension, to compare nebivolol with other beta-adrenergic blockers and to evaluate the clinical relevance of the nitric-oxide mediated vasodilatation and increase in coronary flow reserve achieved by nebivolol.

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