Basic Science and Experimental Studies

Carvedilol Modulates the Expression of Hypoxia-Inducible Factor-1α and Vascular Endothelial Growth Factor in a Rat Model of Volume-Overload Heart Failure

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ABSTRACT

Background: The use of β-blockers has emerged as a beneficial treatment for congestive heart failure. Hypoxia-inducible factor-1α (HIF-1α) is tightly regulated in the ventricular myocardium. However, the expression of HIF-1α in chronic heart failure resulting from volume overload and after treatment with β-blocker is little known.

Methods and Results: To test the hypothesis that HIF-1α plays a role in the failing myocardium because of volume overload, an aorta-caval shunt was created for 4 weeks in adult Sprague-Dawley rats to induce volume-overload heart failure. Carvedilol at 50 mg/kg body weight per day after surgery was given. The heart weight and body weight ratio increased from 2.6 ± 0.3 in the sham group to 3.9 ± 0.7 (P < .001) in the shunt group. Left ventricular end-diastolic dimension increased from 6.5 ± 0.5 mm to 8.7 ± 0.6 mm (P < .001). Treatment with carvedilol in the shunt group reversed the heart weight and ventricular dimension to the baseline values. Western blot showed that HIF-1α, vascular endothelial growth factor (VEGF), and brain natriuretic peptide (BNP) proteins were upregulated and nerve growth factor-β (NGF-β) downregulated in the shunt group. Real-time polymerase chain reaction showed that mRNA of HIF-1α, VEGF, and BNP increased and mRNA of NGF-β decreased in the shunt group. Treatment with carvedilol reversed both protein and mRNA of HIF-1α, VEGF, BNP, and NGF-β to the baseline values.

Increased immunohistochemical labeling of HIF-1α, VEGF, and BNP in the ventricular myocardium was observed in the shunt group and carvedilol again normalized the labeling.

Conclusion: HIF-1α and VEGF mRNA and protein expression were upregulated in the rat model of volume-overload heart failure. Treatment with carvedilol is associated with a reversal of abnormal regulation of HIF-1α and VEGF in the failing ventricular myocardium.

Key Words: β-blocker, congestive heart failure, gene expression, growth factor.