The Thyroid Hormone Analog, 3,5 Diiodothyropropionic Acid (DITPA) Restores Diminished Vascular Beta-Adrenergic and Endothelial Mediated Vasorelaxation in Heart Failure

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This study was designed to determine if the mycroc hormone analogs, 3,5 diiodothyropropionic acid (DITPA), which is being developed to treat heart failure, affects vascular function. This is important because vascular reactivity is altered in heart failure due to decreased endothelial vasorelaxation and decreased sensitivity to beta adrenergic receptor (β-AR) stimulation, both systems in which thyroid hormone has been shown to have an effect. Myocardial infarction (MI) was created in adult Sprague Dawley rats by ligating the left coronary artery. Three weeks after ligation, rats were randomly assigned to DITPA or no treatment or sham or MI in a 2x2 factorial design. DITPA (75 mg/kg) was given subcutaneously daily for 3 weeks. At the end of the study, hemodynamics were measured and thoracic aortic rings were harvested for vasorelaxation studies. Cultured bovine pulmonary endothelial cells were exposed to DITPA for 24 hours and assayed for endothelial nitric oxide synthase (eNOS) levels. In isolated arterial segments from heart failure rats, DITPA enhanced the vasorelaxation response to acetylcholine (45% at 10⁻⁶ M acetylecholine, P=0.003) and to indomethacin (20% at 10⁻⁶ M indomethacin, P=0.05). DITPA at 1 μM, 10 μM and 20 μM increased (P=0.007) eNOS protein expression in cultured endothelial cells from a baseline value of 22.0±4.7, to 29.8±6.8, 52.7±16.8 and 49.0±15.2 (ml/mg protein, respectively). Thus, after myocardial infarction, DITPA enhances vasorelaxation through two mechanisms: 1) Increased responsiveness of β-AR stimulation and 2) Increased eNOS expression. The possible vascular action of DITPA is mediated through β-AR stimulation, which in turn increases nitric oxide release in the endothelium.