

The broad goals of the present proposal are to delineate the mechanisms by which ET-1 regulates right ventricular hypertrophy in response to afterload stress. The guiding hypothesis is ET-1 is important in right ventricular remodeling in a pressure overload model, that ET-1 acts locally within the right ventricle to effect change, and that signaling cascades driving right ventricular remodeling are different from those in the left ventricle in this model. A key novel feature of our experimental system is that the mechanism for inhibiting hypertrophy is applied in the adult animal and does not entail an embryologic gene-targeted defect. Furthermore, in studies involving ET-1 antagonism, we will be inhibiting a native protein rather than modifying expression by constitutive activation or inhibition. Physiologic effects of ET-1 in this instance bespeak of a fundamental significance of native protein activity. The Specific Aims will determine the functional and histologic evidence for sustained benefits and determine the primary down-stream effectors of ET-1 in the right ventricle.