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Bristow M R, Ginsburg R, Minobe W, Cubicciotti R S, Sageman W S, Lurie K, Billingham M E, Harrison D C & Stinson E B. Decreased catecholamine sensitivity and beta adrenergic receptor density in failing human hearts. *N. Engl. J. Med.* 307:205-11, 1982. [Stanford University Hospital, Stanford, CA]

Using recently developed methods for radiolabeling receptors, this study reported evidence for 3 receptor pathway subsensitivity, explained by down-regulation of 13 adrenergic receptors. [The SCI® indicates that this paper has been cited in more than 805 publications.]

13 Receptor Down-Regulation in the Failing Human Heart

Michael R. Bristow
Division of Cardiology
University of Colorado Health
Sciences Center
Denver, CO 80262

Unlike other critical organs, the heart can dramatically increase its functional capacity almost instantly. The adrenergic nervous system is responsible for this impressive modulation of activity, effectively controlling the contractile state of the heart on a beat-to-beat basis.

In the late 1970s, I became interested in the cardiotoxic effects of cardiac norepinephrine (NE) and histamine release. My colleagues Robert Ginsburg and Wayne Minobe and I decided to examine in detail the 13 adrenergic receptor pathway(s) in the failing heart, testing the hypothesis that in the failing heart the previously described depletion of cardiac neuronal stores would produce receptor pathway supersensitivity.¹ We reasoned that such a regulatory response might make elevated circulating NE² cardiotoxic. We chose the human "model" because we had an unlimited supply of failing human heart from Stanford University's pioneering transplant program and also because we appreciated the formidable difficulties inherent in animal models of heart muscle disease. The study was made possible by new biochemical and pharmacologic tools for directly examining components of 13 adrenergic receptor pathways.

Surprisingly, we did not find 3 receptor pathway supersensitivity in the failing heart, but rather consistent evidence for a profound subsensitivity that appeared to be explained by down-regulation of 13 adrenergic receptors. Using the receptor pathway as an index of adrenergic activity, the interpretation was that despite depletion of neuronal stores of NE the failing human heart experiences a high level of cardiac adrenergic drive, which then results in receptor pathway desensitization. We subsequently demonstrated that although both (3, and R₂ receptors are present in the human heart, the receptor which down-regulates is the 3, receptor. Although we and others also demonstrated numerous additional abnormalities of this pathway, the most consistent abnormality present across all forms of dilated cardiomyopathy is down-regulation of B₁ receptors.³ Finally, the explanation for this form of agonist-induced receptor down-regulation appears to be altered gene expression leading to a decrease in 13₁ receptor mRNA abundance.⁴

Evidence that the failing human heart is exposed to and senses a high level of adrenergic activity provided part of the pathophysiologic rationale⁵ for the treatment of human heart failure with antiadrenergic agents. It also led to the development of short-term strategies designed to restore 13 adrenergic pathway function in situations where higher levels of inotropic action are desirable.³ I believe this paper is frequently cited because it was the first reproducible work that demonstrated a molecular or nonstructural abnormality in a contractility-regulating mechanism in the failing human heart. It was also the first study to extensively use human ventricular myocardium as an experimental model, and it probably demonstrated to many investigators the feasibility and utility of the "human approach" to the problem of heart failure.

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2. Thomas M A & Marks B H. Plasma norepinephrine in congestive heart failure. *Amer. J. Cardiol* 41:233-43, 1978.

3. Bristow M R, Hershberger R E, Port J D, Gilbert E M, Sandoval A B, Rasmussen R, Cales A E & Feldman A M.

S-adrenergic pathways in nonfailing and failing human ventricular myocardium. *Circulation* 82(suppl.1):M2-1-25, 1990.

4. Bristow M R, Minobe W, Reynolds M V, Port J D, Rasmussen R, Ray P E & Feldman A M. Reduced S₁ receptor mRNA levels in the failing human heart. *J. Clin. Invest.* (In press.)

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