

# This Week's Citation Classic®

Dietz J R. Release of natriuretic factor from a rat heart-lung preparation by atrial distension. *Amer. J. Physiol.* 247:R1093-6, 1984. [Department of Physiology and Biophysics. College of Medicine. University of South Florida, Tampa, FL]

This study used an isolated perfused rat heart-lung circuit to demonstrate the release of atrial natriuretic factor (ANF) from the heart by large increases in venous return. The study provided the first evidence that atrial distension was an important regulator of ANF secretion. [The *SCF*® indicates that this paper has been cited in more than 395 publications.]

## Release of Atrial Natriuretic Factor (ANF) by Atrial Distension

John R. Dietz  
Department of Physiology  
and Biophysics  
College of Medicine  
University of South Florida  
Tampa, FL 33612-4799

In 1975 I began working in the Department of Physiology at the University of Nebraska as a technician under Irving H. Zucker and Joseph P. Gilmore, who were studying atrial receptors and their role in the control of renal excretion. I was given an opportunity to attend graduate school with Zucker as my mentor at a time when the department had a major emphasis on neural and humoral control of kidney function. Among the other outstanding investigators in the department were Tom Peterson, now at Texas A & M University and Peter Bie, a visiting professor from Copenhagen. As a consequence, I became acquainted with much of the literature on natriuretic hormones and the numerous unconfirmed reports in this area.

Upon graduation, I joined James O. Davis and Ronald H. Freeman as a postdoctoral fellow in the Department of Physiology at the University of Missouri, studying renin secretion and renal hypertension. Some of our results were presented at the fall 1980 meeting of the American Physiological Society in Toronto, and I was fortunate to hear Harold Sonnenberg present a paper showing that rat atrial extracts produced a striking natriuretic response when injected into anesthetized rats.<sup>1</sup> Afterward, I heard a great deal of skeptical banter in the meeting hallways, but a few of us left this meeting convinced that the Toronto

group had finally found the elusive natriuretic hormone. I mentioned the atrial natriuretic factor (ANF) experiments to another post-doctoral fellow, Daniel Villarreal. Dan, a cardiologist, was interested in sodium balance in heart failure, and he immediately saw the potential importance of an atrial factor regulating sodium excretion and its implications in the pathophysiology of heart failure. In our discussions, Dan, Ron, and I hypothesized that ANF was probably secreted in response to atrial stretch, but we had no way at that time to test the hypothesis.

I joined the Department of Physiology at the University of South Florida in Tampa in 1982 and began studying ANF secretion as a sideline using a small seed grant from the College of Medicine. The first study used a perfused rat heart-lung circuit to show that large increases in venous return produced marked atrial distension and the release of a natriuretic substance measured by a crude bioassay. The results were rapidly confirmed by several laboratories, including our own,<sup>2</sup> using radioimmunoassays. ANF grew from being a sideline in my research to the major thrust. Dan and Ron also remained interested in ANF and published several papers concerning its role in experimental heart failure.<sup>3</sup> I have continued to study ANF but more recently have focused on the physiological role of N-terminal proANF peptides,<sup>4</sup> collaborating with Stanley Nazian, an endocrinologist in our department who helped develop the radioimmunoassays, and David Vesely, who arrived at the university in 1989.

This paper has been highly cited because it was the first report to suggest that ANF is released by a physiological stimulus, atrial distension. Since that time, several factors have been shown to modulate ANF secretion, but atrial stretch still appears to be the primary factor regulating its release. Just prior to the publication of this paper, A.T. Veress and Sonnenberg<sup>5</sup> demonstrated that removing the right atrial appendage markedly attenuated the natriuretic response to volume expansion. This was a very important paper in its own right but it also increased the significance of my paper on ANF secretion.

1. Sonnenberg H, Veress A T, Borenstein H B & DeBold A J. Rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Physiologist* 23:13, 1980.
2. Dietz J R. Control of atrial natriuretic factor release from a rat heart-lung preparation. *Amer. J. Physiol.* 252:R498-502, 1987.
3. Villarreal D, Freeman R H & Johnson R A. Captopril enhances renal responsiveness to ANF in dogs with compensated high-output heart failure. *Amer. J. Physiol.* 262:R509-16, 1992.
4. Dietz J R, Vesely DL & Nazian S J. Effect of changes in sodium intake on atrial natriuretic factor (ANF) and peptides derived from the N terminus of the ANF prohormone in the rat. *Proc. Soc. Exp. Biol. Med.* 200:44-8, 1992.
5. Veress A T & Sonnenberg H. Right atrial appendectomy reduces the renal response to acute hypervolemia in the rat. *Amer. J. Physiol.* 247:R610-3, 1984. (Cited 110 times.)

Received August 3, 1993