Plasma Catecholamines and Chronic Congestive Heart Failure

To the Editor:

We read with great interest the paper by Swedberg et al.1 With respect to it, we will supply additional information that might aid in the understanding of the failure of imidazoline’s agonists to improve chronic congestive heart failure (CCHF) in patients.

We have assessed all plasma neurotransmitters in some 30,000 normal and diseased subjects. Included were noradrenaline (NA), adrenaline (Ad), dopamine (DA), platelet serotonin, free serotonin in the plasma, and tryptophan. These parameters were measured during supine-resting, 1-minute orthostasis, 5 minutes of moderate exercise,2 and after the administration of clonidine.3 We found that the normal NA/Ad ratio >4.5. This ratio is greatly reduced in stressed mammals and severely diseased humans (<1).2 With respect to the above, neural sympathetic activity (sympathetic nerves) is constituted by NA (80%) and DA (20%), whereas adrenomedullary sympathetic secretion is constituted by Ad (80%) and NA+DA (20%). Neural sympathetic activity depends on the firing rate of the locus coeruleus (LC)-NA pontine nucleus, whereas adrenomedullary sympathetic activity depends on the C1 medullary nuclei (located at the rostral ventrolateral medulla).4 Although both central sympathetic nuclei display associated and/or alternating activities during normal situations, dissociation of activities occurs during uncooping stress experimental situations and human diseases.4 Exhaustion of the LC-NA nucleus activity is the rule during these circumstances, which is reflected in deep reductions of the NA/Ad plasma ratio.4

All α2 and imidazoline I1 agonists act on the rostroventrolateral medullary area (C1) nuclei preferentially.5 For this reason, clonidine provokes deep reduction of plasma catecholamines and blood pressure during the first challenges; however, these effects tend to lessen after repeated administration of the drug in normals. This phenomenon should be attributed to down-regulation (sub sensitivity) of the α2 and/or imidazoline I1 receptors located at this area. However, considering that the C1-adrenomedullary nuclei send direct inhibitory axons to the LC-NA pontine nucleus,3 we would expect that the latter might result in disinhibition from the C1 bridle, and thus LC-NA would reassume its central sympathetic regulatory role, during and after α2 and/or imidazoline I1 agonists administration. This does not occur because the LC-NA nucleus is also endowed with these types of inhibitory receptors.

In summary, both imidazoline I1 and α2 agonists, like those used in the experimental trial by Swedberg et al.,1 provoked not central but peripheral (adrenal glands) sympathetic inhibition. In short, CCHF patients present with peripheral but not central sympathetic hyperactivity. The latter, which is dependent upon the LC-NA neurons, is always abolished in these patients. Although they showed increased NA plasma levels, the NA/Ad ratio is <2. This low LC-NA sympathetic activity was further reduced by drugs administered, which resulted in worsening and death, because of absolute parasympathetic vs sympathetic predominance.

Fuaa Lechin, MD, PhD
Depayamento de Ciencias Fisioterapicas
Instituto de Medicina Experimental
Universidad Central de Venezuela
Caracas, Venezuela

Marcel Lechin, MD
Texas A & M University
College Station, Tex

Bertha van der Dijs, MD
Secion de Neuroquimica y Neurofarmacologia
Instituto de Medicina Experimental
Universidad Central de Venezuela
Caracas, Venezuela


Response

We appreciate the further discussion of the regulation/dysregulation of sympathetic activity provided by Dr Lechin et al. Regardless of whether moxonidine is acting centrally or peripherally to reduce sympathetic activity, the drug substantially lowers plasma norepinephrine in chronic heart failure. Thus, it is a suitable tool to test the hypothesis that this pharmacological effect would produce favorable clinical outcomes similar to that shown with β-blocking agents. The lowering of cardiac norepinephrine output has been reported by Waagstein and co-workers to parallel total body spill-over.1 This observation would contradict the observations of Lechin et al. As far as we understand, their observations were not made in patients with chronic heart failure, a situation very different from other forms of increased sympathetic activation. Furthermore, in contrast to the experience of Lechin et al, our experience indicates that the ratio of plasma norepinephrine to epinephrine is not attenuated in chronic heart failure. Our findings2 that the clinical effects of moxonidine seem to differ from those of β-blockers surprised us, and we would propose that much remains to be learned about the optimal way to correct sympathetic dysregulation in chronic heart failure.

Karl Swedberg, MD
Department of Medicine
Sahlgrenska University Hospital/Ostra
Gotteborg, Sweden

Michael R. Bristow, MD
Division of Cardiology
University Hospital
University of Colorado Health Sciences Center
Denver, Colo

Jay N. Cohn, MD
Cardiovascular Division
University of Minnesota Medical School
Minneapolis, Minn

Henry Dargie, MD
MRC Clinical Research Initiative in Heart Failure
University of Glasgow
Glasgow, UK

Matthias Straub, MD
Solvay Pharmaceuticals
Hanover, Germany

Curtis Willse, PhD
Eli Lilly and Company
Lilly Research Laboratories
Indianapolis, Ind
