Targeting Heme-Oxidized Soluble Guanylate Cyclase Solution for All Cardiorenal Problems in Heart Failure?

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Increased peripheral vascular resistance is a hallmark of advanced chronic congestive heart failure (CHF) and contributes to the phenomenon of increased afterload that complicates that condition. Multiple factors have been proposed to contribute to this phenomenon, such as increased sodium water content of the vasculature, increased activation of neurohormonal vasoconstrictor forces, and intrinsic abnormalities of the vasculature. During the past decade, it has also been shown that CHF is associated with a severe degree of endothelial dysfunction in experimental animals, as well as in humans. Given that the endothelium, as well as endothelium-dependent vasodilation, plays a crucial role in the control of systemic hemodynamics, this phenomenon is probably an important reason for increased vascular resistance and afterload in heart failure. Because the NO–cGMP–cGMP-dependent kinase-1 relaxation pathway is predominantly responsible for the regulation of vascular tone (Figure), numerous studies have examined abnormalities of this pathway in heart failure. Experimental and clinical studies revealed that NO production is decreased because of decreased expression of endothelial NO synthase and diminished endothelial NO synthase–mediated NO production. A further related mechanism related to this is increased production of vascular superoxide anions, which may react with NO in a diffusion-limited reaction to form the highly reactive intermediate peroxynitrite (Figure). Increased superoxide production, however, is clearly not limited to the endothelium, because more recent experimental studies revealed increased oxidative stress throughout the vasculature, including the media and adventitia.1 Oxidative stress within the media reacts with NO formed as it diffuses from the endothelium and also inhibits NO signaling, thereby causing a state of vascular NO resistance. Theoretically, the decrease in vascular NO bioavailability may be used as an argument to initiate therapy in CHF with nitroglycerin, which improves systemic hemodynamics and renal function when given acutely. There is, however, a marked degree of “nitrate resistance” in the setting of CHF,2 and its therapeutic usefulness is also limited because of the development of nitrate tolerance3 and the induction of oxidative stress and endothelial dysfunction,4 all of which can decrease sensitivity of the NO target enzyme, soluble guanylyl cyclase (sGC). It is important to note that sGC is a heterodimeric enzyme containing a prosthetic heme group and that oxidation of this ferrous heme to its ferric form (from Fe²⁺ to Fe³⁺) completely prevents NO-mediated activation of sGC5 (Figure). This seems to be an important mechanism underlying altered vascular function caused by oxidant stress and nitrate tolerance.

To avoid these disadvantages of oxidant stress and nitrate therapy, direct heme-independent sGC activators have been developed (for review see Reference 6). These compounds are NO-independent sGC activators (Figure) with unique biochemical and pharmacological properties. They are capable of causing vasodilation even when the prosthetic heme iron of sGC is oxidized and, in fact, seems to selectively activate the enzyme when it is in the oxidized state.6

In this issue of Hypertension, Boerrigter et al7 demonstrate that 1 such compound, Bay 58-2667, dose-dependently reduces mean arterial pressure, lowers central venous filling pressures, increases cardiac output, and enhances renal blood flow in an animal model of heart failure because of rapid ventricular pacing. Glomerular filtration rate and sodium and water excretion were improved. Consistent with cardiac unloading, this agent also lowered plasma levels of ANP and BNP. Interestingly, although this agent caused vasodilatation and reduced mean arterial pressure, it did not cause an increase in either plasma renin activity or aldosterone. These data indicate that direct activation of oxidized sGC with drugs such as Bay 58-2667 could represent a novel therapeutic strategy for the treatment of CHF and perhaps other cardiovascular diseases.

Our current therapeutic options might also address some of the issues related to sGC oxidation and nitrate tolerance. The Vasodilator in Heart Failure Trial I and II trials showed that a combination of isosorbide dinitrate and the arteriolar dilator hydralazine was very effective in improving both exercise tolerance and prognosis in patients with severe CHF.8 Importantly, the recently published A-HeFFT trial reported huge reductions in mortality in black Americans treated with the combination of these 2 compounds.9 There are likely several mechanisms that are important: (1) the combination of hydralazine and isosorbide dinitrate provides both preload (isosorbide dinitrate) and afterload (hydralazine) reduction that favorably influences hemodynamics in CHF; and (2) more recent studies show that hydralazine can scavenge reactive oxygen species, such as superoxide and peroxynitrite,10 and could, therefore, potentially prevent oxidation of the heme iron of sGC. Finally, hydralazine inhibits the reduced nicotinamide-adenine dinucleotide phosphate oxido-
oxygen species, which are activated in response to nitroglycerin treatment. Thus, the combinations of isosorbide dinitrate and hydralazine or similar agents could prevent sGC oxidation and preserve vascular responsiveness. Likewise, angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists can reduce tissue oxidant stress by inhibiting signaling events leading to activation of several reactive oxygen species generating enzymes. These agents might also prevent sGC oxidation and preserve responsiveness to organic nitrates. Head-to-head comparisons between these agents and drugs like Bay 58-2667 will be very helpful.

Compared with nitrate therapy, sGC activators such as Bay 58-2667 seem to have several advantages. Most importantly, these agents preferentially and very effectively activate sGC when it is in the oxidized state. This actually promotes vasodilatation in vessels where endogenous NO fails to function. To date, there is no evidence that they promote oxidative stress, as do organic nitrates. They do not need to be bioactivated like organic nitrates, and, thus, impairments to organic nitrate activation caused by oxidant stress would not alter their effectiveness. They do not induce endothelial dysfunction and do not seem to promote reflex neurohumoral vasoconstriction. Taken together, these direct sGC activators would seem to avoid many of the untoward effects of long-term nitrate therapy.

Endothelial dysfunction to dysfunctional sCG, because the latter is likely most important in the vascular smooth muscle. It would be ideal to determine the intracellular ratio of sGC in the ferrous versus ferric state in vessels from animals with CHF. This would allow a more specific application of these agents. Moreover, understanding this biochemical property would help us determine whether the preferential effect of these drugs is really dependent on this ratio.

Although Boerrigter et al. did not observe an increase in plasma renin or aldosterone levels, this does not reflect all of the neurohumoral responses to heart failure or vasodilator therapy. The effect of this drug on catecholamine or vasopressin levels or fluid shifts from the extravascular to intravascular spaces needs further investigation. Another potential compensatory mechanism is activation of phosphodiesterases, which could degrade cGMP distal to sGC activation, preventing the effects of these drugs during chronic therapy. Despite these concerns, the results of this study are encouraging and support the substantial therapeutic potential of these new vasodilators. These agents could revolutionize the treatment of not only CHF but also other conditions, such as coronary artery disease, systemic hypertension, and pulmonary hypertension.

**Disclosures**

None.
References


