Res-Erection of Viagra as a Heart Drug

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In 1998, the world was formally introduced to Viagra (sildenafil), the first oral agent to be approved in the United States for the treatment of erectile dysfunction. Developed by Pfizer chemists, sildenafil inhibited phosphodiesterase type 5 (PDE5), one of the 11-member superfamily of enzymes that hydrolyze cyclic nucleotide monophosphates and among the first discovered that was selective for cGMP. PDE5 had been identified more than 2 decades earlier, first as a protein that bound cGMP and later as one that hydrolyzed it (the binding function turning out to be a mechanism to regulate activity).1 Sildenafil induces vasorelaxation by blocking PDE5-cGMP hydrolysis, raising cGMP levels in smooth muscle to activate protein kinase G (also known as cGK). In platelets, this blunts thrombosis; together, the effects suggested a potential use for coronary vascular disease and hypertension. Pfizer initiated trials targeting coronary ischemia, but, although antianginal effects were disappointing, the study gave a whole new meaning to the term “side effect,” effectively hijacking sildenafil from cardiovascular development to a rather different indication.

There were still some cardiovascular studies performed, but essentially all were limited assessments of volunteer populations, mostly normal and at rest and some with cardiovascular disease; the results were interpreted to support safety for patients taking the drug. In particular, blood pressure changes were slight if present at all, and cardiac function appeared unaltered. Well into the mid 2000s, PDE5 was thought to be expressed in selective vascular beds, lung and corpus cavernosum being dominant, and to have a minor cardiovascular profile elsewhere, with a negligible role in the heart.

Sildenafil reemergence as a cardiovascular medicine came with evidence that it was effective for treating primary pulmonary hypertension.2 PDE5 is highly expressed in lung, and this expression rises further in patients with pulmonary vascular disease. Other studies started examining secondary pulmonary hypertension such as that associated with heart failure,3–5 and again sildenafil appeared to offer benefits. Potential cardiac effects, however, were thought secondary to vascular unloading.

Sildenafil was shown to enhance exercise cardiac output while reducing pulmonary but not systemic vascular resistance. It improved endothelial function and suppress the peripheral skeletal ergoreflex (ventilatory stimulation associated with skeletal muscle contraction), suggesting improved

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delivery of blood to exercising muscles. In both studies, systemic blood pressures were unaltered.

In this issue of Circulation: Heart Failure, a new and important study from the Guazzi laboratory critically extends these observations—providing intriguing evidence that sildenafil’s impact on the failing heart involves improvement of both systolic and diastolic function and can trigger reverse remodeling. The study size and design was similar to their 2007 trial (slightly higher sildenafil dose this time) but doubled the follow-up duration. Improved exercise capacity and symptoms and lack of change in systemic arterial pressure but decline in noninvasive estimated pulmonary systolic pressure, all similar to that observed after 3 to 6 months of therapy, were sustained to 1 year. What is new is the evidence that myocardial function was also altered. The rise in left ventricular ejection fraction from 30% to 36.3% over 1 year was accompanied by a fall in diastolic volume index. The study particularly focused on diastolic function examined by echo and tissue Doppler methods. Although none of the parameters change in the placebo group, sildenafil treatment shortened estimated isovolumic relaxation rate and lowered estimated left ventricular diastolic pressure (E/E’). Atrial volume index declined accompanied by a reduction of circulating amino-terminal fragment of B-type natriuretic peptide.

These left ventricular functional changes occurred without any obvious vascular afterload reduction, nor were they replicated by acute sildenafil administration, suggesting that they resulted from a more chronic reversal of maladaptive chamber remodeling. The authors did not report heart rate, cardiac output, stroke volume, or left ventricular end-systolic volumes, making it a bit more difficult to dissect the hemodynamics further. If indeed stroke volume was preserved yet volumes, this would mirror dynamics further. If indeed stroke volume was preserved yet volumes, making it a bit more difficult to dissect the hemodynamics further. If indeed stroke volume was preserved yet volumes, making it a bit more difficult to dissect the hemodynamics further. If indeed stroke volume was preserved yet volumes, making it a bit more difficult to dissect the hemodynamics further. If indeed stroke volume was preserved yet volumes, making it a bit more difficult to dissect the hemodynamics further. If indeed stroke volume was preserved yet volumes, making it a bit more difficult to dissect the hemodynamics further.

Where does this leave us? For one, the current and other recent small-scale single-center trials cry out for more definitive multicenter studies to determine if these benefits can be reproduced in a broad population with congestive heart failure. The National Institutes of Health is presently supporting a multicenter trial of sildenafil for the treatment of heart failure patients with preserved ejection fraction—RELAX (Clinicaltrials.gov:NCT00763867). This was founded on the preclinical data focusing on pressure-overload hypertrophy, a common feature in many heart failure patients with a preserved ejection fraction. Another study is examining cardiac benefits in younger patients with Duchenne muscular dystrophy and associated heart disease (Reverse-DMD: NCT01168908). However, the current and other recent studies in dilated heart failure support larger studies into this population as well. The initial hunch that benefits would be limited to patients with marked pulmonary hypertension does not appear to be the case, as more evidence highlights integrative effects on exercise physiology, peripheral circulatory reserve, and now cardiac effects. Twelve years after its introduction, sildenafil is poised for resurrection as a heart drug—with longer-lasting effects than those associated with its initial approved indication, we hope.

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**Disclosures**

None.

**References**


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