Is Inhibition of Phosphodiesterase Type 5 by Sildenafil a Promising Therapy for Volume-Overload Heart Failure?

Wangde Dai, MD; Robert A. Kloner, MD, PhD

Phosphodiesterase type 5 (PDE5) is an enzyme that belongs to a large family of cyclic nucleotide PDEs that catalyze cAMP and cGMP. cAMP and cGMP are 2 essential intracellular second messengers regulating many different cellular functions of living cells. PDE5 specifically breaks down the substrate cGMP. Inhibition of PDE5 increases intracellular cGMP levels by inhibiting its degradation. Sildenafil (Viagra) is a potent and selective inhibitor of cGMP-specific PDE5 and is the first oral treatment for men with erectile dysfunction; it was approved by the Food and Drug Administration on March 27, 1998. Sildenafil binds to the catalytic site of PDE5 and inhibits the degradation of intracellular cGMP in smooth muscle within the corpus cavernosum, resulting in increased levels of cGMP, which cause smooth muscle cell relaxation and vasodilation and improve erectile function.1,2

Cardioprotection of PDE5 Inhibitors in Experimental Acute Myocardial Infarction

In recent years, there has been growing interest in therapeutic applications of PDE5 inhibitors for cardiovascular diseases other than erectile dysfunction. Some experimental studies demonstrated direct cardioprotective effects of inhibition of PDE5 in experimental acute myocardial infarction models. In 2002, Ockaili et al3 treated rabbits with sildenafil (0.7 mg/kg given as an intravenous bolus) either 30 minutes or 24 hours before coronary occlusion. The rabbits were then subjected to 30 minutes of left anterior descending coronary occlusion followed by 3 hours of reperfusion, and the infarct size was measured by tetrazolium staining. The results demonstrated for the first time that sildenafil had a powerful preconditioning-like effect against myocardial ischemia/reperfusion injury. Our research group4 injected 1.45 mg/kg intravenous sildenafil or saline 30 minutes before ischemia in anesthetized open-chest rabbits subjected to 30 minutes of left anterior descending coronary occlusion followed by 3 hours of reperfusion. Compared with saline, sildenafil significantly decreased coronary resistance in the ischemic risk area, slightly increased regional myocardial blood flow, and significantly decreased left ventricular end-diastolic pressure, although it did not attenuate acute ischemic left ventricular dilation or reduce infarct size. However, in another study, we5 demonstrated that the PDE5 inhibitor tadalafil, which was administered by gastric gavage (10 mg/kg) 2 hours before coronary occlusion, reduced myocardial infarct size in a rat myocardial ischemia/reperfusion model. Moreover, Salloum et al6 and Elrod et al7 reported that treatment with sildenafil at 5 minutes before coronary reperfusion significantly reduced myocardial infarct size in rabbits or mice subjected to ischemia induced by 30 minutes of left coronary artery occlusion followed by coronary reperfusion. In a cell culture experiment, Das et al8 treated cultured adult mouse ventricular myocytes with sildenafil for 1 hour before 40 minutes of simulated ischemia followed by 18 hours of reoxygenation. The expression of PDE5 was detected in mouse cardiomyocytes. Sildenafil significantly reduced necrosis and apoptosis of cultured myocytes. These data suggested that sildenafil has a direct protective effect against myocyte necrosis after ischemia/reperfusion that is independent of the vascular effects of sildenafil. Therefore, inhibition of PDE5 may be a useful adjunctive therapy in patients undergoing coronary artery reperfusion therapy in the setting of acute myocardial infarction.2

Beneficial Effects of PDE5 Inhibitors in Different Experimental Ventricular Remodeling Models

Inhibition of PDE5 exhibited beneficial effects on ventricular remodeling and heart failure in several different models. Salloum et al9 induced myocardial infarction by left coronary artery ligation in mice. The mice received treatment with sildenafil or saline starting immediately after coronary artery ligation and continuing for 4 weeks. Sildenafil reduced cardiac necrosis and apoptosis, attenuated ischemic cardiac hypertrophy, prevented pulmonary edema, and preserved left ventricular function. To determine whether late treatment with sildenafil had benefits, Chau et al10 started sildenafil treatment at day 3 after left coronary artery ligation in mice and treated them continuously for 25 days. Sildenafil treatment attenuated cardiac fibrosis and apoptosis, improved cardiac function, and reduced heart failure progression. Therefore, long-term sildenafil treatment attenuated left ventricular dysfunction independently of its infarct-sparing effect.

Takimoto et al11 induced left ventricular hypertrophy and pathological remodeling in mice by transverse aortic constriction to create chronic cardiac pressure overload. Pressure overload–stimulated hypertrophy increased PDE5 activity, which increased cGMP catabolism in the pressure-loaded...
hearts. Treatment with sildenafil suppressed chamber and myocyte hypertrophy and improved in vivo heart function in mice. Sildenafil also reversed pre-established hypertrophy induced by pressure overload secondary to transverse aortic constriction and restored chamber function back to normal. PDE5 inhibition by sildenafil has also been reported to attenuate left ventricular remodeling induced by long-term isoproterenol infusion in rats.12

Although previous studies used models of volume overload of myocardial infarction with subsequent left ventricular eccentric hypertrophy and dilatation of the left ventricle to investigate the effects of sildenafil on ventricular remodeling.9,10 there had been a lack of data regarding the effect of sildenafil in a nonischemic or noninfarct model of volume overload. In this issue of Circulation, Kim et al13 have extended the concept that PDE5 inhibition can improve experimental left ventricular remodeling and heart failure by studying a model of volume-overloaded heart failure by creating a hole in the mitral valve that causes chronic mitral regurgitation, which is independent of myocardial ischemia or infarction. At 2 weeks after induction of mitral regurgitation, left ventricular dilatation was confirmed by echocardiography. The rats were randomly assigned to sildenafil or normal saline treatment for 4 months. Pathological analysis showed that sildenafil reduced perivascular fibrosis and the percentage of terminal deoxynucleotidyl transferase dUTP nick-end labeling–positive cells. Sildenafil significantly improved left ventricular ejection fraction, attenuated left ventricular remodeling, and prevented exercise intolerance. These benefits were hypothesized to be associated with the antiapoptotic and anti-inflammatory effects of sildenafil. The results of this study suggest a potential new clinical application of PDE inhibitors: the treatment of left ventricular remodeling induced by chronic mitral regurgitation, ie, volume overload.

PDE5 as a Therapeutic Target for Patients With Heart Failure

In a clinical study, Lu et al14 determined myocardial PDE5 expression and cellular distribution in left ventricular samples from patients with end-stage congestive heart failure and normal donor hearts. Expression of PDE5 protein was increased 4.5-fold in tissue samples obtained from congestive heart failure patients compared with normal donor hearts. The expression of PDE5 was detected mainly in vascular smooth muscle in normal donor hearts, but its expression was increased in both cardiac myocytes and vascular smooth muscle in congestive heart failure hearts. Several clinical studies showed that PDE5 inhibition might be a useful approach for treating heart failure.15 Katz et al16 reported that, compared with placebo, sildenafil increased endothelium-dependent, flow-mediated vasodilatation of the brachial artery in patients with chronic heart failure. This improvement of flow-mediated vasodilatation was consistent with the decrease in systemic vascular resistance and showed that sildenafil was able to improve endothelial dysfunction in patients with chronic heart failure. Guazzi et al17 randomly assigned 45 heart failure patients (New York Heart Association class II–III) to receive placebo or sildenafil for 1 year. Compared with placebo, sildenafil significantly improved left ventricular ejection fraction, diastolic function, cardiopulmonary exercise performance, ventilation efficiency, and quality of life. These improvements were accompanied by a reverse remodeling of left atrial volume index and left ventricular mass index. Only minor adverse effects, including flushing in 4 and headache in 2 sildenafil-treated patients, were noted. This study provided evidence to support the concept that long-term PDE5 inhibition might benefit left ventricular diastolic function and cardiac geometry in heart failure patients.

Heart failure may result in secondary pulmonary hypertension, which subsequently leads to right ventricular remodeling in patients. Inhibition of PDE5 can lead to pulmonary arterial vasodilation, a property that has led to the use of PDE5 inhibitors for the treatment of pulmonary arterial hypertension. Both sildenafil and tadalafil are currently approved by the Food and Drug Administration for the treatment of pulmonary hypertension. Lewis et al18 treated 13 patients with New York Heart Association class III heart failure with 50 mg oral sildenafil. Sildenafil reduced pulmonary arterial pressure and pulmonary vascular resistance and increased cardiac index at rest and exercise. In patients with secondary pulmonary hypertension, right heart hemodynamics and exercise capacity were improved. The data indicated that sildenafil acted as a selective pulmonary vasodilator during rest and exercise in patients with heart failure and secondary pulmonary hypertension. Chapman et al19 reported that long-term (5-year) use of sildenafil in 25 patients with symptomatic secondary pulmonary hypertension significantly reduced pulmonary vascular resistance and mean pulmonary arterial pressure and improved cardiac output and 6-minute walk distance. In a 16-week, double-blind, placebo-controlled study,20 405 patients with pulmonary arterial hypertension were randomized to placebo or tadalafil treatment. Tadalafil improved exercise capacity and quality-of-life measures and reduced clinical worsening related to pulmonary arterial hypertension.

There are 3 major patterns of ventricular remodeling in different loading conditions: pressure-overload–induced concentric hypertrophy (myocytes become thickened), volume-overload–induced eccentric hypertrophy (myocytes become lengthened), and mixed-load postinfarct remodeling with a combination of concentric and eccentric hypertrophy. In this issue of Circulation, Kim et al13 have demonstrated for the first time that a PDE5 inhibitor directly decreased remodeling associated with left ventricular volume overload caused by mechanically induced mitral regurgitation (preload). Thus, PDE5 inhibition becomes a therapeutic target of all 3 types of ventricular remodeling. The mechanisms of myocardial effects of PDE5 inhibition have not been fully understood. PDE5 inhibitors might protect the myocardium through an indirect action by reducing ventricular preload and afterload via enhancing smooth muscle relaxation and vasodilation of the pulmonary and systemic vasculature or through direct actions on myocytes through increasing intracellular cGMP levels. It has been hypothesized that inhibition of PDE5 protects the heart through complex multiple signaling pathways, including nitric oxide, cGMP, protein kinase G, B-cell...
Dai and Kloner Sildenafil Therapy for Heart Disease 1343

lymphoma protein-2, Rho kinase inhibition, calcineurin/nuclear factor of activated T cell, PI3K/Akt, and extracellular-signal–regulated kinase 1/2 (see the work of Schwartz et al\(^2\) for a review).

In conclusion, cumulative data indicate that inhibition of PDE5 is a promising approach for the treatment of ventricular remodeling induced by pressure or volume overload and heart failure. To expand the therapeutic use of PDE5 inhibitor in patients with heart disease,\(^2\) carefully controlled clinical trials are needed. The time has come to test PDE5 inhibitors in a large population of patients with heart failure to determine whether the therapy will have a long-term effect on reducing major adverse cardiac events and ventricular remodeling in this population.

Disclosures
Dr Kloner has served on the speakers’ bureau for Pfizer.

References

KEY WORDS: Editorials heart failure myocardial infarction phosphodiesterase inhibitors
Is Inhibition of Phosphodiesterase Type 5 by Sildenafil a Promising Therapy for Volume-Overload Heart Failure?
Wangde Dai and Robert A. Kloner

_Circulation_. 2012;125:1341-1343; originally published online February 8, 2012; doi: 10.1161/CIRCULATIONAHA.112.094912

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/125/11/1341

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/