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

Running title: Dai et al.; Sildenafil therapy for heart disease

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Phosphodiesterase type 5 (PDE5) is an enzyme that belongs to a large family of cyclic nucleotide PDEs that catalyze cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). cAMP and cGMP are two 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 males with erectile dysfunction, which was approved by 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 that causes smooth muscle cell relaxation, vasodilation, and improves erectile function. 

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 al treated rabbits with sildenafil (0.7 mg/kg, given as an intravenous bolus) at either 30 minutes or 24 hours before coronary occlusion. The rabbits were then subjected to 30 minutes of left anterior descending coronary artery 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 group injected 1.45 mg/kg intravenous sildenafil or saline at 30 minutes prior to ischemia in anesthetized open-chest rabbits that were
subjected to 30 minutes of left anterior descending coronary occlusion followed by 3 hours of reperfusion. Compared with saline,ildenafil 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 and reduce infarct size. However, in another study, we demonstrated that PDE5 inhibitor tadalafil, which was administrated by gastric gavage (10 mg/kg) at 2 hours before coronary occlusion, reduced myocardial infarct size in a rat myocardial ischemia/reperfusion model. Moreover, Salloum et al and Elrod et al reported that treatment with sildenafil at 5 min 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 al treated cultured adult mouse ventricular myocytes with sildenafil for 1 hour before 40 min 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 following ischemia/reperfusion that is independent of 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.

**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 al 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. In order to determine whether late treatment with sildenafil had benefits, Chau et al.\textsuperscript{10} started sildenafil treatment at day 3 after left coronary artery ligation in mice and continuously treated for 25 days. Sildenafil treatment attenuated cardiac fibrosis and apoptosis, and improved cardiac function and reduced heart failure progression. Therefore, chronic sildenafil treatment attenuated left ventricular dysfunction independent of its infarct-sparing effect.

Takimoto et al.\textsuperscript{11} induced left ventricular hypertrophy and pathological remodeling in mice by transverse aortic constriction in order 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 chronic isoproterenol infusion in rats\textsuperscript{12}.

While 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\textsuperscript{9,10}, there had been a lack of data regarding the effect of sildenafil in a non-ischemic or non-infarct model of volume overload. In this issue of Circulation, Kim et al.\textsuperscript{13} 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 TUNEL-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 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 - that is, volume overload.

PDE5 as a therapeutic target for patients with heart failure

In a clinical study, Lu et al.\textsuperscript{14} 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 approximately 4.5-fold in tissue samples obtained from congestive heart failure patients compared normal donor hearts. The expression of PDE5 was mainly detected 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\textsuperscript{15}. Katz et al.\textsuperscript{16} reported that sildenafil, compared with placebo, increased endothelium-dependent, flow-mediated vasodilation of the brachial artery in patients with chronic heart failure. This improvement of flow-mediated vasodilation was consistent with the
decrease in systemic vascular resistance and showed that sildenafil was able to improve
endothelial dysfunction of patients with chronic heart failure. Guazzi et al\textsuperscript{17} 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 LV 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 chronic 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 which has led to the use of PDE5 inhibitors for the treatment of
pulmonary arterial hypertension. Both sildenafil and tadalafil are currently approved by the FDA
for the treatment of pulmonary hypertension. Lewis et al\textsuperscript{18} treated 13 patients with New York
Heart Association class III heart failure with 50 mg of oral sildenafil. Sildenafil reduced
pulmonary arterial pressure and pulmonary vascular resistance, and increased cardiac index at
rest and exercise. In the 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 al\textsuperscript{19} reported that long-term (a 5-year period)
use of sildenafil in 25 patients with symptomatic secondary pulmonary hypertension
significantly reduced pulmonary vascular resistance and the mean pulmonary arterial pressure,
and improved cardiac output and six minute walk distance. In a 16-week, double-blind, placebo-controlled study\textsuperscript{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 three major patterns of ventricular remodeling in different loading conditions: (1) a pressure overload induced concentric hypertrophy (myocytes become thickened); (2) a volume overload induced eccentric hypertrophy (myocytes become lengthened), and (3) mixed load post-infarct remodeling with a combination of concentric and eccentric hypertrophy. In this issue of circulation, Kim et al\textsuperscript{13} for the first time demonstrated that 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 three 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 signalling pathways, including nitric oxide, cyclic guanosine monophosphate, protein kinase G, extracellular-signal-regulated kinase, B-cell lymphoma protein-2, Rho kinase inhibition, calcineurin/NFAT, PI3K/Akt and ERK1/2 [for review, see \textsuperscript{2}].

In conclusion, based on the cumulative data, inhibition of PDE5 is a promising approach for treatment of ventricular remodeling induced by pressure or volume overload and heart failure. In order to expand therapeutic use of PDE5 inhibitor in patients with heart disease\textsuperscript{2},
future 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.

**Conflict of Interest Disclosures:** None

**References:**


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