Sildenafil and Phosphodiesterase-5 Inhibitors for Heart Failure

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Treatment of heart failure (HF) is a challenging task. An impaired nitric oxide pathway contributes to several abnormal cardiac and vascular phenotypes typical of the failing cardiovascular system. Inhibition of phosphodiesterase-5 (PDE5) is a new therapeutic strategy for overexpressing nitric oxide signaling by increasing the availability of cyclic guanosine monophosphate (cGMP). A number of background studies support the use of PDE5 inhibitors in HF. Treatment of pulmonary hypertension secondary to left ventricular dysfunction appears to be a primary target by virtue of the high PDE5 selectivity for the pulmonary circulation. Basic studies suggest that increased cGMP activity by PDE5 inhibition has potentially favorable direct myocardial effects that may block adrenergic, hypertrophic, and proapoptotic signaling. Furthermore, studies in humans have underscored the benefits of acute PDE5 inhibition on lung diffusion capacity, systemic endothelial function, muscle perfusion, and exercise performance. Despite promising initial data, larger controlled trials are necessary to define the safety, tolerability, and potential impact of PDE5 inhibitors on morbidity and mortality across the wide spectrum of patients with HF.

Introduction

Heart failure (HF) is a significant health care concern that is evolving to epidemic proportions. The development of new strategies for intervention is a challenging task [1].

An abnormal nitric oxide (NO) pathway is involved in some basic abnormalities of HF syndrome [2]. NO is a ubiquitous signaling molecule synthesized from L-arginine and oxygen. The process is catalyzed by NO synthase (NOS), an enzyme expressed in constitutive (endothelial, neuronal) and inducible forms, whose uncoupling leads to overproduction of superoxide and peroxynitrite, two potent oxidants. By activating soluble guanylate cyclase in target cells, endothelium-derived NO stimulates the production of cyclic guanosine monophosphate (cGMP), increases the activity of cGMP-dependent protein kinases, and activates a variety of intracellular mechanisms, the most prominent of which are related to relaxation of smooth muscles, vasodilation of coronary arteries, and attenuation of vascular remodeling in the pulmonary vessels [3]. Among strategies to enhance in vivo the NO-based mechanisms, inhibition of phosphodiesterase-5 (PDE5), the predominant isoenzyme that metabolizes cGMP [3], plays an important role in the pulmonary vasculature [4•], where its inhibition provides documented therapeutic properties for patients with pulmonary vascular hypertension [5]. Based on experience accumulated thus far, use of PDE5 inhibitors appears to be a new therapeutic approach for patients with HF [6].

This article addresses the currently available evidence for considering PDE5 inhibition an emerging opportunity in HF syndrome.

Cardiac Remodeling and PDE5 Inhibition

In the heart, PDE5 is compartmentalized, and its inhibition can exert a cardioprotective activity against hypertrophy, ischemia-reperfusion injury, and adrenergic contractile stimulation [4•]. Research on experimental HF has demonstrated that chronic PDE5 inhibition by sildenafil may reverse left ventricular hypertrophy resulting from pressure overload remodeling by a cGMP-mediated effect [7••,8]. Specifically, in hearts exposed to sustained pressure overload, sildenafil shows a direct antihypertrophic effect in a protein kinase G_1-dependent manner by deactivation of many cardiac hypertrophy signaling pathways (calcineurin/nuclear factor of the activated T cell, phosphoinositide-3 kinase/Akt, and extracellular signal-related kinase 1/2) [7••]. Consistently, in a rat model of isoproterenol-induced cardiac hypertrophy, cGMP levels were inversely correlated with cardiac hypertrophy [8]. Other observations in animals demonstrate that cGMP catabolism by PDE5 regulates adrenergic cardiac contractility [9].

Table 1. Acute changes in pulmonary hemodynamics after oral sildenafil administration (50 mg) at rest and during exercise in patients with stable heart failure

	Rest			Exercise		
	PVR, *dyne* × *sec* × *cm*$^{-5}$	SPAP, *mm Hg*	PCWP, *mm Hg*	PVR, *dyne* × *sec* × *cm*$^{-5}$	SPAP, *mm Hg*	PCWP, *mm Hg*
Guazzi et al. [16••]	-70.0*	-7.2*	-1.2	—	—	—
Lewis et al. [17••]	-75.0*	-6.0*	-2.0	-98.0*	-5.0*	-1.0

*$P < 0.05$ versus before sildenafil administration.
PCWP—pulmonary capillary wedge pressure; PVR—pulmonary vascular resistance; SPAP—systolic pulmonary arterial pressure.

Furthermore, Das et al. [10] reported that, in mice, sildenafil exerts a direct protective activity on myocyte apoptosis, an effect that was also observed in a chronic model of doxorubicin cardiotoxicity and left ventricular dysfunction [11]. Recent findings by Pérez et al. [12] in rats suggest that PDE5 inhibition with sildenafil may prevent early left ventricular post–myocardial infarction remodeling through Na^+/H^+ exchanger blockade, causing an increase in the activity of phosphoglycerate kinase-1.

Recent observations in rats expressing pulmonary hypertension and right ventricular hypertrophy have highlighted a role for PDE5 inhibition in improving right ventricular contractility in the isolated heart. The observed effects on right ventricle contractility were not observed in normal right ventricles and were due to a combined inhibitory effect on cGMP and cyclic adenosine monophosphate (cAMP) [13].

Most of the effects obtained in murine models await confirmation in patients. In the human heart, PDE5 activity is involved in the cardiac contractile response mediated by the β-adrenergic receptor pathway [14], as suggested by the blunting effect of sildenafil on the β-receptor–mediated inotropic response. Acute administration of sildenafil may also reduce cardiac norepinephrine spillover, suggesting an inhibitory influence on adrenergic outflow to the heart [15]. These findings may have implications in patients with HF with excessive sympathetic activity, but the potential benefits of PDE5 inhibition in HF depend on a variety of actions in addition to those proposed at the cardiac and sympathetic levels. Although evidence of the clinical effects of PDE5 inhibition in patients with HF has been gained primarily after acute sildenafil administration, two recent reports have extended the experience to long-term use [16••,17••].

Effects of PDE5 Inhibition on Pulmonary Hemodynamics and Lung Function in HF

Pulmonary vascular resistance is frequently elevated in patients with chronic left ventricular failure as a result of impaired vascular smooth muscle tone and structural remodeling. These abnormalities are, at least in part, due to pulmonary vascular endothelial dysfunction resulting from impaired NO bioavailability and activity [18]. In HF, the resulting pulmonary hypertension directly yields to inequality of lung perfusion and enhanced interstitial fluid leakage. A restrictive ventilatory pattern [19] and impaired alveolar gas diffusion are functional correlates of the pulmonary involvement in HF [20].

Given the high selectivity of PDE5 for the pulmonary microcirculation, lung hemodynamics and function must be considered a primary target of PDE5 inhibitors.

Similarly to what has been reported for idiopathic pulmonary hypertension, two studies of patients with pulmonary hypertension secondary to HF have shown that 50 mg of acute sildenafil does not cause systemic hypotension. Instead, it lowers pulmonary vascular resistance and systolic pulmonary arterial pressure without a detectable effect on pulmonary capillary wedge pressure, and it produces a variable effect on cardiac output that is in part related to the severity of disease [21,22•]. The effects on pulmonary hemodynamics observed at rest also were detected during exercise [22•] (Table 1).

Moreover, Guazzi et al. [21] have reported that 50 mg of sildenafil significantly improved lung diffusion capacity for carbon monoxide (DLCO) by 11%. This effect is determined by a specific increase in the alveolar-capillary membrane conductance properties (DM) in the absence of changes in the capillary blood volume. Interestingly, DM improvement was still evident after normalization for alveolar volume. These findings suggest that an increased NO availability is also important in the modulation of the tissue component of resistance to O_2 transfer from alveoli to hemoglobin.

The same authors recently demonstrated that the effects observed in an acute setting persist in long-term treatment [16••,17••].

Effects on Systemic Hemodynamics, Vascular Tone, and Endothelial Function

Abnormal systemic vascular tone and endothelial dysfunction, hallmarks of HF syndrome, contribute to heightened systemic vascular resistance. Hirata et al. [23] investigated the effects of 50 mg of sildenafil on peripheral resistance, large artery stiffness, and wave reflection as major components of cardiac afterload. They found an acute improvement in cardiac performance due to a combined decrease of all peripheral determinants of impedance to left ventricular ejection. A similar effect on

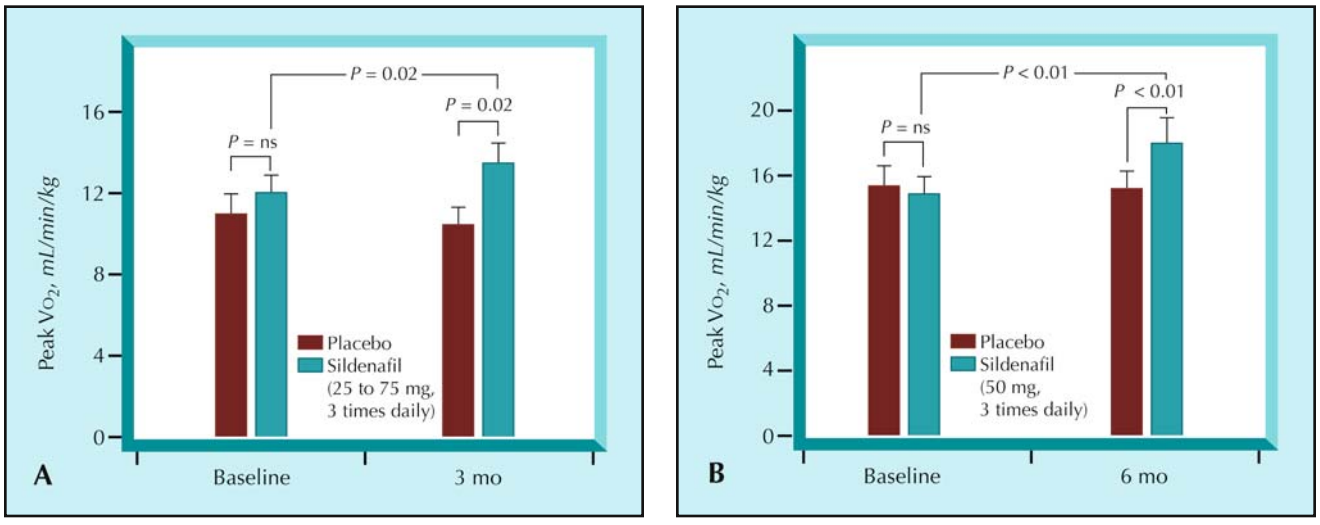

Figure 1. Data from Lewis et al. [22•] (**A**) and Guazzi et al. [21] (**B**) show an improvement in peak oxygen consumption (Vo_2) after chronic sildenafil therapy. ns—nonsignificant.

the aortic pressure augmentation index has been reported in patients with hypertensive heart disease [24], suggesting that, by virtue of its effects on large systemic arteries, sildenafil could have a role in the management of systemic hypertension, especially in the isolated systolic form.

Remarkably, chronic treatment (3 months) with sildenafil, 50 mg 3 times daily, modulated arterial wave reflection and decreased systolic (-8 mm Hg) and diastolic (-6 mm Hg) ambulatory blood pressure [25].

Data suggest that sildenafil may be of use in reversing systemic endothelial dysfunction typical of HF patients [26,27]. Katz et al. [26] studied the effect of PDE5 inhibition at three doses of sildenafil (12.5, 25, and 50 mg) on flow-mediated endothelium-dependent vasodilation in the forearm circulation of 48 patients with stable HF and found a dose-dependent favorable effect starting with 25 mg. These data were confirmed by subsequent observations that showed an additive effect of 50 mg of sildenafil on top of 10 mg of the angiotensin-converting enzyme inhibitor ramipril on endothelial function [28].

The influences of PDE5 inhibitors on coronary hemodynamics in HF are poorly investigated. In an animal model of pacing-induced HF, sildenafil failed to show any effect on endothelium-dependent coronary vasodilation in response to acetylcholine. In addition, sildenafil did not alter the increase in coronary flow in response to the increased oxygen demands during exercise [29].

Interestingly, recent observations by Forfia et al. [30••] in a canine model of HF suggest that sildenafil exerts similar cardiovascular hemodynamic effects as B-type natriuretic peptide (BNP), and their combination was additive in reducing pulmonary pressures.

Considering that part of the natriuretic peptide resistance in HF relates to increased PDE5 activity, findings support a potential combined approach and an additional therapeutic role for PDE5 inhibition.

Effects on Cardiopulmonary Exercise Performance

The improvement in maximal exercise capacity and oxygen uptake at peak exercise (Vo_2) observed with PDE5 inhibition (Fig. 1) may be attributable to more than one mechanism.

An important role is played by the pulmonary cGMP-mediated reduction in pulmonary arterial pressure and pulmonary vascular resistances and consequent improved pulmonary perfusion [16••,17••]. The increased NO availability in lung capillaries may then improve endothelial permeability and promote a more efficient alveolar gas exchange [16]. An additional mechanism that may contribute to the augmented peak Vo_2 is the increased cardiac index, due to reduction of conduit vessel afterload [22•].

Despite the fact that sildenafil has not been shown to improve maximal oxygen extraction in HF patients, an improvement in aerobically regenerated adenosine triphosphate during exercise has been reported, given an upward shift in the relation between the Vo_2 and work rate and a faster decay in Vo_2 time constant during the recovery phase after maximal exercise [21]. These effects may be attributed to the improved vessel ability to accommodate incremental increases in blood flow and a more proficient redistribution to working muscles [16••,26].

An exaggerated ventilatory response (VE) to CO_2 output (Vco_2) is a common feature in HF patients and provides relevant prognostic information [31,32]. Possible explanations for the inefficient ventilation may be excessive stimulation of the central controller of VE due to an overactive chemoreflex and metaboreflex response or a ventilation–perfusion (V/Q) mismatching.

Studies have consistently shown that sildenafil reduces the slope of VE/Vco_2 on exercise during both acute [16••,17••] and chronic administration [21]. A number of mechanisms may be at work in reducing the exertion

ventilatory requirement. Certainly, a decrease of waste ventilation, as suggested by the acute reduction in the exercise dead space–tidal volume ratio, and an increase in DLCO indicate that improved V/Q matching may be a mechanism [16••,21].

However, we have provided evidence that specific modulation of peripheral skeletal muscle oversignaling (ergoreflex) is an additional factor whereby chronic treatment with sildenafil may further improve exercise breathlessness sensation and ventilation inefficiency. This effect derives from reduced neurogenic vasoconstriction during exercise and improved endothelial responsiveness leading to upregulation of the working muscle perfusion [16••].

Considerations on Safety and Tolerability of PDE5 Inhibition in Chronic HF

Although the cited studies have involved single centers and small numbers of patients, they are consistent with a high safety and tolerability of PDE5 inhibition in HF. However, a note of caution is appropriate. We do not know whether reflex sympathetic activation due to the vasodilating effects of PDE5 inhibition may be detrimental. Phillips et al. [33] reported increased sympathetic nerve activity in response to acute administration of 100 mg of sildenafil in healthy subjects. Similarly, in 10 healthy subjects and 10 patients with congestive heart failure (CHF), Piccirillo et al. [34] reported reflex sympathetic activation in response to 50 mg of oral sildenafil, with a decrease in systolic blood pressure of 7 to 9 mm Hg. However, Bocchi et al. [35] observed no acute changes in plasma norepinephrine at rest or during exercise after patients with CHF took 50 mg of sildenafil. Similarly, norepinephrine spillover does not seem to change [15]. Another important concern is related to the safety of sildenafil in patients with acute left ventricular dysfunction or advanced decompensated HF.

With regard to long-term safety, it must be recognized that increased myocellular cAMP levels produced with long-term use of the PDE3 inhibitor milrinone in patients with moderate to severe CHF have been associated with increased mortality risk.

Although clinically available PDE5 inhibitors are highly selective for the type 5 isoform, direct effects on myocellular cAMP levels and myocardial contractility would be anticipated [36], and previous experimental and clinical studies on the effects of PDE5 inhibition on myocardial levels of cyclic nucleotides and cardiac contractility have yielded conflicting findings (4). Divergent findings may be partly attributable to species-related differences in phosphodiesterase isoform tissue distribution, complex cyclic nucleotide regulatory crosstalk, and/or differences in pharmacologic agents and dosing regimens [4•].

There are no published data on the safety or efficacy of other PDE5 inhibitors, such as vardenafil and tadalafil, in patients with HF. Given the differences in pharmacokinetics and isoform selectivity among the clinically available PDE5 inhibitors, the safety and efficacy of each individual compound must be tested in the HF population.

Conclusions

Building on a solid foundation of translational research, evidence is mounting on the potentially favorable impact of sildenafil on clinical end points in HF. Accordingly, the National Institutes of Health is sponsoring the first multicenter trial (RELAX) aimed at testing the effects of chronic sildenafil on cardiopulmonary performance, left ventricular function, and mass in elderly patients with diastolic HF.

Disclosure

No potential conflict of interest relevant to this article was reported.

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