Clinical Use of Phosphodiesterase-5 Inhibitors in Chronic Heart Failure

Marco Guazzi, MD, PhD

Nowadays, the inhibitors of the phosphodiesterase enzyme type 5 (PDE5), thanks to a sustained relaxant activity on smooth muscles of the corpus cavernosum, are a widely used remedy for erectile dysfunction in man. This class of compounds was originally developed for the treatment of angina pectoris, based on the ability of oversignaling the pathway originated from nitric oxide (NO) and pursued via cGMP signaling. Because the clinical effects were not as promising as initially reported by experimental studies, PDE5 inhibitors were not regarded as a remarkable advancement of angina pectoris, based on the ability of oversignaling the pathway originated from nitric oxide (NO) and pursued via cGMP signaling. Subsequently, however, it was realized that the clinical applicability of the enhanced NO/cGMP pathway by inhibiting the PDE5 activity could be realized that the clinical applicability of the enhanced NO/cGMP pathway by inhibiting the PDE5 activity could be larger than previously thought. Over the last few years, the use of PDE5 inhibitors has been expanded to the therapeutic management of other cardiovascular disorders, including chronic heart failure (CHF). Their clinical applicability to CHF is the subject of this review.

Phosphodiesterases
The homeostatic role of phosphodiesterases (PDEs) as related to the intracellular levels of cAMP and cGMP was first described by Sutherland, who, because of this, was awarded the Nobel Prize for Physiology and Medicine in 1971. These enzymes hydrolyze the phosphodiester bond of cAMP and cGMP to form the inactive 5'-AMP and 5'-GMP. In optimizing the intracellular levels of cAMP and cGMP, breakdown is predominant over synthesis. PDEs comprise a superfamily with 11 subfamilies, which have been characterized on the basis of amino acid sequence, substrate specificity, pharmacological properties and allosteric regulation. Within these families, more than 40 isoforms are expressed either by different genes or as expression of the same gene through alternative splicing. The substrate specificities include the enzymes that are specific for cAMP hydrolysis, those for cyclic GMP hydrolysis, and those that hydrolyze both. The importance of PDEs as regulators of signaling is evident from their development as drug targets in diseases such as asthma and obstructive pulmonary disease, cardiovascular diseases such as heart failure and atherosclerotic peripheral disease, neurological disorders, erectile dysfunction. Table 1 summarizes the functions of each PDE and the cardiovascular effects of specific inhibitors.

Among all PDEs, PDE5, which is influenced by sildenafil and other inhibitors of clinical use, has been widely investigated. Three PDE5 isoforms have been described, identified as PDE5 A1, A2, and A3. PDE5 A1 and A2 isoforms are expressed in several tissues, including brain, lung, heart, kidney, bladder, prostate, urethra, penis, uterus, and skeletal muscle. The A3 isoform is located in tissues having a cardiac or smooth muscle constituent, like heart, bladder, prostate, urethra, penis, uterus, and skeletal muscle.

PDE5 Inhibitors
Three specific PDE5 inhibitors are in clinical use: sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis). Sildenafil is the agent more extensively investigated in experimental and clinical cardiology. The 3 PDE5 inhibitors have similar although not identical mechanisms of action and structural similarity, but present some significant difference regarding potency and selectivity. For instance, vardenafil is 32-fold more potent than sildenafil to inhibit PDE5; in the rat aorta, vardenafil, but not sildenafil or tadalafil, affects Ca2+ handling to produce relaxation, in addition to the typical increase of cGMP mediated by PDE5 inhibition. Sildenafil, although very selective for PDE5 shows some cross-reactivity with PDE6 which is predominant in photoreceptors. Because of this, in individuals taking high doses of sildenafil the color vision perception may be transiently disturbed. Another cross-reactivity is with PDE11 which might be responsible for development of back pain and myalgia as side effects of tadalafil because of the low selectivity of the compound for PDE5 over PDE11.

The onset of action of sildenafil is rapid and plasma half-life is of 4 hours. Empirical testing shows that the duration of action of sildenafil may reach 12 hours. The results of numerous studies consistently suggest that more commonly used drugs do not disturb the pharmacokinetics of sildenafil, and that the compound is well tolerated without interaction with the physiological effects of most drugs.

PDE5 Inhibition in Heart Failure: Rationales and Evidences
When inside the smooth muscle cell, NO binds to the iron core of soluble guanylyl cyclase enabling faster conversion of GTP into cGMP. cGMP initiates a cascade of reactions that decrease intracellular Ca2+ concentration and produce relaxation. Thus, the NO/cGMP pathway is fundamental to the control of smooth muscle tone and contractility, and an
optimal synergism between NO and cGMP is required for a regular intracellular Ca\(^{2+}\)/H\(^{+}\) release\(^{17}\) (Figure 1). Vasoconstriction is a pathophysiological hallmark of CHF, which involves the systemic and the pulmonary circulation, and results in an increased impedance to the left and the right ventricular (RV) ejection. A defective NO release is one of the major factors involved in vasoconstriction in CHF.

Among strategies to enhance in vivo the NO-based mechanisms, inhibition of PDE5, the predominant isoenzyme that metabolizes cGMP,\(^{18}\) has attracted interest as a potential therapeutic tool in CHF. Experience accumulated in patients with pulmonary vascular hypertension\(^{19}\) was the original background for a therapeutic attempt in CHF. Soon after, the favorable effects on cardiac remodeling, lung function, secondary pulmonary hypertension, RV function, lung diffusion capacity, systemic blood flow distribution have prospected the possibility that PDE5 inhibition may be a beneficial adjunct therapy for patients with CHF.\(^{20}\)

**Lung**

In CHF, dysfunction of vascular endothelium and reduction of NO bioavailability and activity are involved in the development of pulmonary vascular remodeling and overreactivity to vasoconstrictor stimuli.\(^{21}\) This may translate into rise of blood pressure, inequality of lung perfusion and fluid leakage into the alveolar interstitium, whose functional correlates are a ventilatory restrictive pattern\(^{22}\) and impairment in gas diffusion.\(^{23}\) Given the high selectivity of PDE5 for the pulmonary microvessels, lung hemodynamics should reasonably be regarded as a primary target of PDE5 inhibition in CHF.

Studies performed by Guazzi et al\(^{24}\) and by Lewis et al\(^{25}\) in patients with CHF and secondary pulmonary hypertension, have shown that acute oral sildenafil (50 mg) lowers the pulmonary vascular pressure and resistance, without significantly affecting the systemic arterial pressure and the wedge pulmonary pressure. The response of cardiac output is variable and in part related to the severity of the disease. The ability to reduce pulmonary vascular resistance at rest is also evident during exercise.\(^{26}\) Recently, the same authors have reported that the PDE5 inhibitor maintains efficacy during long-term administration.\(^{26,27}\)

An additional effect of sildenafil on the lung\(^{24}\) is an improvement of the diffusion capacity for carbon monoxide by more than 10% in patients with CHF, through a selective increase of the alveolar-capillary membrane gas conductance.

### Table 1. Functions of PDEs and Cardiovascular Effects of Specific Inhibitors

<table>
<thead>
<tr>
<th>Family</th>
<th>Enzyme Main Functions</th>
<th>Selective Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE1</td>
<td>Regulates smooth muscle contraction, sperm function, immune cell activation, neuronal signaling</td>
<td>Heart: ... Systemic: ... Lung: ... Corpus Cavernosum: ...</td>
</tr>
<tr>
<td>PDE2</td>
<td>Regulates aldosterone secretion, long-term memory, endothelium barrier function under inflammation</td>
<td>Vessel Tone: ↑ ...</td>
</tr>
<tr>
<td>PDE3</td>
<td>Regulates platelet aggregation, cardiac and vascular smooth muscle contractility, renin release, oocyte maturation; mediates insulin signaling (anti-lipolitic effects)</td>
<td></td>
</tr>
<tr>
<td>PDE4</td>
<td>Has a role in brain function, vascular smooth muscle proliferation, fertility, vasodilation, cardiac contractility, macrophage activation</td>
<td>... ↓</td>
</tr>
<tr>
<td>PDE5</td>
<td>Is a well-established regulator of vascular smooth muscle contraction especially in lung and corpus cavernosum; is involved in the control of platelet aggregation; may regulate cGMP signaling in the brain</td>
<td>↑ ↓ ↓ ↓</td>
</tr>
<tr>
<td>PDE6</td>
<td>Is involved in the transduction of signal of the eye fotoreceptor and in melatonin release regulation</td>
<td>Not investigated as a therapeutic target</td>
</tr>
<tr>
<td>PDE7</td>
<td>Has a role in T-cells and other inflammatory cells activation</td>
<td>Inhibitors investigated as anti-inflammatory agents in vitro</td>
</tr>
<tr>
<td>PDE8</td>
<td>May be involved in T-cell activation and sperm function</td>
<td>No selective inhibitor available</td>
</tr>
<tr>
<td>PDE9</td>
<td>Has been postulated to regulate the NO-cGMP signaling in the brain</td>
<td>Inhibitor in preclinical development for Alzheimer disease treatment</td>
</tr>
<tr>
<td>PDE10</td>
<td>Is considered a regulator of cGMP in the central nervous system and may be involved in the learning and memory processes</td>
<td>No selective inhibitor available</td>
</tr>
<tr>
<td>PDE11</td>
<td>May play a role in sperm development and function</td>
<td>Inhibited by tadalafil; interest received as a potential source for side effects</td>
</tr>
</tbody>
</table>

PDE indicates phosphodiesterase.

Guazzi PDE5 Inhibition in Heart Failure

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Cyclic GMP (cGMP) and NO are crucial for cardiovascular function. cGMP is generated from GTP by soluble guanylyl cyclase (sGC) and acts as a second messenger for vasorelaxation in the cardiovascular system. NO, produced by the endothelium, binds to the heme group of sGC, initiating a cascade that leads to faster conversion of GTP into cGMP, which is then deactivated by PDE5.

**Figure 1.** Schematic diagram of endothelial molecular pathways that control NO activity and smooth muscle relaxation, and site of action of PDE5 inhibitors. Once inside the smooth muscle cell, NO binds to the iron core of soluble guanylyl cyclase enabling faster conversion of GTP into cGMP. cGMP initiates a cascade of reactions in part mediated by protein kinase G (PKG) and subsequent K⁺ channel opening leading to reductions in intracellular Ca²⁺ concentration.

**Heart**

In the heart, inhibition of PDE5 signaling can be protective against ischemia-reperfusion and antracycline toxicity, attenuate adrenergic inotropic stimulation, modulate myocardial hypertrophy, and dysfunction secondary to pressure overload. Despite early documentation of PDE5 gene expression in the myocardium, its enzyme activity is rather low compared with lung and has been currently considered as physiologically not significant. However, more recent studies have provided evidence of PDE5 expression in isolated myocytes, of myocyte physiological effects of sildenafil and tadalafil, and of whole heart effects of PDE5 inhibitors. PDE5 inhibition exerts little influence on cardiac function in the baseline, but inhibits acute β-adrenergic stimulation. The adrenergic effect of sildenafil is lacking in myocytes deficient in endothelial NO synthase or with NOS inhibited by Nω-nitro-L-arginine methyl ester, suggesting a main role of NO-generated cGMP. In a number of chronic cardiovascular diseases, cGMP increases often in response to sustained release of natriuretic peptides, and PDE5 is upregulated in pulmonary hypertension, RV hypertrophy, congestive heart failure. A correlate of PDE5 upregulation is that effects of its counteraction can be emphasized. In the hypertrophied human right ventricle, PDE5 is highly expressed and its inhibition improves contractility, thus showing that this upregulation is physiologically significant. Ockaili et al. first demonstrated that sildenafil induces acute and delayed protective effects against ischemia-reperfusion injury, which are mediated by opening of mitochondrial potassium adenosine triphosphate (KATP) channels: the infarct size in treated rabbits was reduced from the value in control animals by 68%, during the acute phase, and by 41% during the delayed phase. Salloum et al. have shown that endothelial NO synthase and inducible NO synthase are prominent players in protection mediated by sildenafil. The same group has reported similar results with vardenafil in rabbits. Elrod et al. however, have then observed in a murine model that reduction of myocardial ischemia/reperfusion injury by sildenafil may be independent of both endothelial NO synthase and inducible NO synthase, because protection is also seen in null animals and at doses of sildenafil that do not alter cGMP levels. These authors have also reported that sildenafil is not effective in diabetic mice subjected to myocardial ischemia/reperfusion injury, and have suggested that delineation of the mechanisms involved in sildenafil-mediated cardioprotection requires further research, mainly for translation to the clinical setting. Recently, Salloum et al. have demonstrated that acute and prolonged treatment with sildenafil during myocardial infarction is associated with myocardial salvage from necrosis during the first 24 hours, reduction of apoptosis at 7 and 28 days, prevention of severe cardiac remodeling and heart failure, and improved survival. In this study, PDE5 inhibition has been prospected as a promising means for heart failure prevention in acute postmyocardial infarction patients.
Landmark experiments by Takimoto et al. performed in mice exposed to sustained pressure overload, have documented that chronic PDE5 inhibition can prevent and reverse cardiac and myocite hypertrophy and interstitial fibrosis. Mechanistic insights provided by this study suggest that sildenafil deactivates multiple hypertrophy signaling pathways triggered by pressure overload (the calcineurin/fatty acid transport protein, extracellular signal regulated kinase/mitogen-activated protein kinase, and Akt). This modulatory activity was not observed in cases of hypertrophy induced in vitro, suggesting upstream targeting of these pathways. A simplified diagram depicting the potential molecular pathways involved in the antihypertrophic effects of PDE5 inhibition is reported in Figure 2.

Interestingly enough, an antiproliferative effect has also been reported in both human and animal models of RV hypertrophy and pulmonary hypertension.

Other investigators have reported that PDE5 inhibition suppresses hypertrophy induced by catecholamine stimulation. Reversal of hypertrophy may stem from myocyte and, in intact animals, also from nonmyocyte effects of PDE5 inhibition. Nonmyocyte effects may include systemic, pulmonary and renal vascular changes, hormone and cytokine release from different cell types, myofibroblast, inflammatory responses, and antifibrotic activity. The molecular mechanisms, however, whereby PDE5 inhibitors produce antihypertrophic effects remain basically unclear.

Systemic and Pulmonary Hemodynamics and Endothelium

Vasoconstriction and endothelial dysfunction are hallmarks of CHF that promote an increase in systemic vascular resistance. Hirata et al. investigated the acute effects of oral sildenafil (50 mg) on systemic vascular resistance, stiffness of large arteries and wave reflection, 3 major determinants of impedance to left ventricular ejection. These authors described a modulatory effect on these variables and an improvement in cardiac performance. A similar effect on aortic pressure augmentation index has been observed in patients with hypertensive heart disease. On these bases, sildenafil has been suggested to have a possible indication in the management of systemic hypertension, especially of the isolated systolic form. The prolonged (3 months) administration of sildenafil (50 mg 3 times a day) to patients with high blood pressure modulated the arterial wave reflection and lowered systolic and diastolic ambulatory pressure by an average of 8 and 6 mm Hg, respectively.

More than two thirds of patients with severe left ventricular systolic function impairment have secondary pulmonary pressure elevation and impaired RV performance. These are significant determinants of functional status and prognosis, because RV dysfunction increases by more than 2-folds mortality compared with patients with similar left ventricular function and preserved RV performance. With the exception of the combination of isosorbide dinitrate and hydralazine, use of drugs with pulmonary vasodilatory properties, including endothelin receptor antagonists and prostacyclin analogues, has not been effective for the treatment of heart failure due to left ventricular systolic dysfunction. Thus, based on the high prevalence of pulmonary vasoconstriction and secondary pulmonary hypertension in heart failure, new strategies to reduce pulmonary vascular tone and impedance to RV ejection are quite desirable. Sildenafil is a selective pulmonary vasodilator that in CHF reduces secondary pulmonary pressure elevation, increases RV systolic function, possibly due to reduced afterload and improves contractility and exercise capacity to an extent proportional to the baseline level of the pulmonary vascular resistance. Thus, PDE5 inhibition seems very attractive for patients in whom CHF selectively targets the pulmonary vascular tone.

More than one study suggest that sildenafil may reverse endothelial dysfunction in heart failure. In a report in which sildenafil was tested in patients with stable CHF, at the doses of 12.5, 25, and 50 mg, flow-mediated dilatation in the forearm circulation increased in a dose-dependent fashion and the lower effective dose was shown to be 25 mg. When combined with the ACE inhibitor ramipril, sildenafil produced an additional benefit on endothelial function in patients with heart failure.
Table 2. Clinical Trials Investigating the Acute Cardiovascular, Respiratory, and Neurohormonal Effects of PDE5-Inhibition in Stable CHF Patients

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>No. Patients</th>
<th>Design</th>
<th>Drug</th>
<th>Inclusion Criteria</th>
<th>End Points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz et al&lt;sup&gt;17&lt;/sup&gt;</td>
<td>48</td>
<td>Single-center; randomized, placebo-controlled; double-blind</td>
<td>Sildenafil randomization to single doses (12.5, 25, 50 mg orally)</td>
<td>CHF in stable hemodynamic conditions; no history of unstable angina, stroke, MI or open heart surgery within the previous 12 mo; no treatment with long-acting nitrate preparations</td>
<td>Brachial artery endothelial flow-mediated dilatation (FMD)</td>
<td>No effect of placebo and 12.5 mg of sildenafil. Significant FMD improvement after treatment with 25 and 50 mg of sildenafil (P&lt;0.05)</td>
</tr>
<tr>
<td>Piccirillo et al&lt;sup&gt;18&lt;/sup&gt;</td>
<td>20</td>
<td>Single-center; randomized, placebo-controlled</td>
<td>Sildenafil single dose (50 mg orally)</td>
<td>Stable CHF with no worsening symptoms in the 3 mo before the study; no atrial fibrillation, frequent extrasystole and branch block; no treatment with long-acting nitrate preparations</td>
<td>QT dispersion, R-R and systolic blood pressure variability</td>
<td>No direct effect on QT dispersion. Significant changes in autonomic control with a decrease in high frequency component (P&lt;0.01)</td>
</tr>
<tr>
<td>Bocchi et al&lt;sup&gt;19&lt;/sup&gt;</td>
<td>23</td>
<td>Single-center; randomized, placebo-controlled; double-blind</td>
<td>Sildenafil single dose (50 mg orally)</td>
<td>CHF with stable hemodynamic conditions; no unstable angina or MI in the 3 mo before the study; absence of atrial and/or ventricular arrhythmias</td>
<td>Systemic hemodynamics (HR, BP); resting and exercise norepinephrine concentration; peak exercise oxygen uptake (V&lt;sub&gt;O2&lt;/sub&gt; peak) and ventilation efficiency (W/VA&lt;sub&gt;O2&lt;/sub&gt; slope)</td>
<td>Significant decrease in resting HR (P&lt;0.02) and BP (P&lt;0.01); no changes in resting and peak exercise norepinephrine; significant increase in peak V&lt;sub&gt;O2&lt;/sub&gt; (P=0.025) and decrease in W/VA&lt;sub&gt;O2&lt;/sub&gt; slope (P=0.04)</td>
</tr>
<tr>
<td>Guazzi et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>16</td>
<td>Single-center; randomized, placebo-controlled; double-blind</td>
<td>Sildenafil single dose (50 mg orally)</td>
<td>CHF with stable hemodynamic conditions and mild pulmonary hypertension; no pulmonary disease or history of smoking; systemic hypertension; nitrate use and ischemia during exercise</td>
<td>Systemic hemodynamics (cardiac index, LV ejection fraction, vascular resistance); pulmonary hemodynamics (arterial pressure, wedge pressure, arterial resistance) alveolar gas diffusion (DLCO); peak exercise oxygen uptake (V&lt;sub&gt;O2&lt;/sub&gt; peak) and ventilation efficiency (W/VA&lt;sub&gt;O2&lt;/sub&gt; slope)</td>
<td>No significant changes in LV ejection fraction, cardiac index, vascular resistance and wedge pressure. Significant decrease in mean pulmonary pressure and arterial resistance and V&lt;sub&gt;O2&lt;/sub&gt; peak (P&lt;0.01); significant increase in DLCO and peak V&lt;sub&gt;O2&lt;/sub&gt; (P&lt;0.01)</td>
</tr>
<tr>
<td>Lepore et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>11</td>
<td>Single-center; randomized, case series study</td>
<td>Sildenafil single dose (50 mg orally) vs inhaled NO (80 ppm) and their combination</td>
<td>CHF in stable hemodynamic conditions; mean pulmonary artery pressure &gt;25 mm Hg; no acute decompensated HF, severe valvular disease and COPD</td>
<td>Systemic hemodynamics (cardiac index, vascular resistance); pulmonary hemodynamics (mean arterial pressure, wedge pressure, vascular resistance)</td>
<td>Sildenafil alone promoted a significant decrease in mean pulmonary pressure, arterial resistance, and wedge pressure and a significant increase in O&lt;sub&gt;2&lt;/sub&gt; uptake (P&lt;0.05). Additive effects of the sildenafil/inhaled NO combination vs placebo (P&lt;0.03)</td>
</tr>
<tr>
<td>Hryniewicz et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>64</td>
<td>Single-center; randomized, placebo-controlled; double-blind</td>
<td>Sildenafil single dose (50 mg orally) vs ramipril (10 mg orally) and their combination</td>
<td>CHF in stable hemodynamic conditions; no history of unstable angina, stroke, MI or open heart surgery within the 12 mo before the study; no treatment with long-acting nitrate preparations</td>
<td>Brachial artery endothelial flow-mediated dilatation (FMD)</td>
<td>Significant FMD improvement after sildenafil 50 mg vs placebo (P&lt;0.02) and additive effect of ramipril and sildenafil combination vs placebo (P&lt;0.03)</td>
</tr>
<tr>
<td>Al-Hesayen A et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>10</td>
<td>Single-center; open-label study</td>
<td>Sildenafil single intravenous dose (bolus of 0.5 mg/5 min followed by a maintenance infusion)</td>
<td>CHF in stable hemodynamic conditions free of nitrate therapy</td>
<td>Systemic hemodynamics (cardiac index, LV ejection fraction, vascular resistance); pulmonary hemodynamics (mean arterial pressure, wedge pressure, arterial resistance); cardiac and total body norepinephrine spillover</td>
<td>No significant changes in pulmonary wedge pressure. Significant decrease in mean pulmonary arterial pressure, pulmonary and systemic vascular resistances (P&lt;0.05); significant increase in cardiac index (P&lt;0.05); significant decrease in cardiac (P&lt;0.02) but no changes in total body norepinephrine spillover</td>
</tr>
<tr>
<td>Lewis et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>13</td>
<td>Single-center; open-label study</td>
<td>Sildenafil single dose (50 mg orally)</td>
<td>CHF with stable hemodynamic conditions and moderate pulmonary hypertension; no COPD or ongoing nitrate therapy</td>
<td>Resting and exercise systemic (cardiac index, vascular resistance); pulmonary hemodynamics (mean arterial pressure, wedge pressure, arterial resistance); peak exercise O&lt;sub&gt;2&lt;/sub&gt; uptake (V&lt;sub&gt;O2&lt;/sub&gt; peak) and ventilation efficiency (W/VA&lt;sub&gt;O2&lt;/sub&gt; slope)</td>
<td>Significant decrease in resting exercise mean pulmonary arterial pressure, arterial resistance and (P&lt;0.05); significant decrease in resting exercise pulmonary vascular resistance; significant increase in peak V&lt;sub&gt;O2&lt;/sub&gt; (P=0.005) and decrease in W/VA&lt;sub&gt;O2&lt;/sub&gt; slope (P&lt;0.05)</td>
</tr>
<tr>
<td>Guazzi et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>16</td>
<td>Single-center; randomized, placebo-controlled; double-blind</td>
<td>Sildenafil single dose (50 mg orally)</td>
<td>CHF with stable hemodynamic conditions and mild pulmonary hypertension; no pulmonary disease or history of smoking; systemic hypertension; nitrate use and ischemia during exercise</td>
<td>Brachial artery endothelial flow-mediated dilatation (FMD); metabolic assessment; peak exercise aerobic (ΔV&lt;sub&gt;O2&lt;/sub&gt;/ΔWR) and ventilation (ΔV&lt;sub&gt;O2&lt;/sub&gt;/ΔVR) efficiency</td>
<td>Significant improvement in FMD, ergoreflex assessment, ΔV&lt;sub&gt;O2&lt;/sub&gt;/ΔWR and ΔV&lt;sub&gt;O2&lt;/sub&gt;/ΔVR slope (P&lt;0.01)</td>
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</table>

MI indicates myocardial infarction; LV, left ventricular; COPD, chronic obstructive pulmonary disease; DLCO, diffusion capacity for carbon monoxide; CHF, chronic heart failure; HR, heart rate; BP, blood pressure; ΔV<sub>O2</sub>, change in O<sub>2</sub> uptake; ΔWR, change in work rate.
a canine model of cardiac failure, the hemodynamic influences of sildenafil were similar to those of the B-type natriuretic peptide and potentiated the pulmonary pressure lowering effect. An additional reason why PDE5 inhibition may be beneficial in CHF is that resistance to natriuretic peptide in the syndrome is in part related to an increased PDE5 activity.

**Exercise Performance and Gas Exchange**

Maximal exercise capacity and oxygen consumption are improved by sildenafil in heart failure. Several interpretations of this effect may be offered: a) the cGMP-mediated decrease of pulmonary arterial pressure and vascular resistance lowers the RV afterload and improves RV output and lung perfusion; b) the increased NO availability may facilitate the DM; c) a better RV function and a diminished peripheral resistance improve left ventricular output and systemic perfusion. Sildenafil is not effective on arterial-venous O₂ content difference and maximal O₂ extraction is preserved in heart failure; however, an upward shift of the relationship oxygen consumption/work rate, and a faster decay in oxygen consumption time constant in the recovery phase of ischemia during exercise ventilatory inefficiency reflected by an increased VE/VCO₂ slope is commonly seen in patients with left ventricular dysfunction and represents a significant prognostic indicator. This may be because of

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**Table 3. Clinical Trials Investigating the Chronic Cardiovascular, Respiratory, and Neurohormonal Effects of PDE5-Inhibition in Stable CHF Patients**

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>No. Patients</th>
<th>Design</th>
<th>Drug</th>
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<th>End Points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al²⁷</td>
<td>13</td>
<td>Singlecenter; randomized, placebo-controlled; double-blind</td>
<td>Sildenafil (from 25 to 50 mg 3 times per day orally) for 3 mo</td>
<td>CHF with stable hemodynamic conditions and mild pulmonary hypertension; no COPD or ongoing nitrate therapy</td>
<td>Resting and exercise systemic (stroke volume, vascular resistance) and pulmonary hemodynamics; peak exercise O₂ uptake (VO₂) and ventilation efficiency (Ve/VCO₂ slope); 6-min walk test distance and quality-of-life score</td>
<td>Significant decrease in resting and exercise pulmonary arterial resistance without altering wedge pressure; significant improvement in exercise cardiac output, peak VO₂, and quality-of-life score (P&lt;0.05); significant decrease in hospitalization rate and Ve/VCO₂ slope (P&lt;0.05)</td>
</tr>
<tr>
<td>Guazzi et al²⁶</td>
<td>16</td>
<td>Singlecenter; randomized, placebo-controlled; double-blind</td>
<td>Sildenafil (50 mg 2 times per day orally) for 6 mo</td>
<td>CHF with stable hemodynamic conditions and mild pulmonary hypertension; no pulmonary or valvular disease; neuromuscular disorders, atrial fibrillation, claudication or peripheral vascular disease</td>
<td>Pulmonary hemodynamics (systolic arterial pressure); brachial artery endothelial flow-mediated dilatation (FMD); ergoreflex assessment; peak exercise O₂ uptake (VO₂) and ventilation efficiency (Ve/VCO₂ slope); quality-of-life score</td>
<td>Significant improvement in FMD, quality-of-life score and reversal of ergoreflex overactivation (P&lt;0.01) which correlated with improvement in FMD; significant increase in peak VO₂ (P&lt;0.05) and decrease in Ve/VCO₂ slope and dyspnea sensation (P&lt;0.01)</td>
</tr>
<tr>
<td>Behling et al²⁶</td>
<td>19</td>
<td>Singlecenter; randomized, placebo-controlled; double-blind</td>
<td>Sildenafil (50 mg 3 times per day orally) for 3 mo</td>
<td>CHF with stable hemodynamic conditions; no hypertension, bradycardia and chronic atrial fibrillation, nitrate use and ischemia during exercise</td>
<td>Pulmonary systolic pressure; peak exercise O₂ uptake (VO₂) and ventilation efficiency (Ve/VCO₂ slope), endothelial function</td>
<td>Significant decrease in pulmonary systolic pressure and Ve/VCO₂ slope (P&lt;0.01); significant increase in peak VO₂ (P&lt;0.01) and no significant changes in forearm blood flow</td>
</tr>
</tbody>
</table>

PDE indicates phosphodiesterase; CHF, chronic heart failure.
lung ventilation/perfusion mismatch, or of hyperresponsiveness of the reflexogenic areas of the cardiovascular system, causing overstimulation of the centers that control ventilation, or to excessive signaling from the metaboreceptors in the exercising muscles.

Sildenafil has been shown, both in acute\textsuperscript{24,25} and long-term studies,\textsuperscript{26,27,65} to properly reduce breathlessness sensation and Ve/V\textsubscript{CO}2 slope on exercise. This effect seems to depend on a combination of favorable mechanisms. First, a decrease of waste ventilation (ie, reduced dead space to tidal volume ratio) and a facilitated DM.\textsuperscript{24,26} In addition, it has been recently reported that sildenafil intake can produce an endothelium-mediated attenuation of the ergoreflex stimulus to hyperventilation and breathlessness.\textsuperscript{26,62}

Tables 2 and 3 summarize the clinical studies investigating the effects of acute and chronic use of PDE5 inhibitors in CHF patients.

Safety and Tolerability

Although studies are consistent with safety and good tolerability of PDE5 inhibitors in CHF, some caution is advisable. In fact, most trials were performed in single centers and on small cohorts of patients. An inconvenience might be the elicitation of sympathetic activity, which has been reported to occur with sildenafil both in healthy subjects\textsuperscript{67} and in patients with heart failure.\textsuperscript{68} However, after 50 mg oral sildenafil no changes in plasma norepinephrine have been reported in heart failure at rest\textsuperscript{69,70} or on exercise.\textsuperscript{68} An unexplored issue is safety of sildenafil in cases of acute cardiac dysfunction or advanced decompensated CHF. It should also be remarked that the increase in myocardial cAMP with stimulation of myocardial contractility and fall in systemic vascular resistance produced by the PDE3 inhibitor milrinone has been shown to increase the risk of sudden death in patients with moderate-to-severe CHF. For these reasons, the drug was withdrawn from the market. Even if the PDE5 inhibitors in clinical use are highly selective for the type 5 isofrom, direct effects on myocardial cAMP and myocardial contractility cannot be ruled out.\textsuperscript{71}

Thus far there are no published data on safety or efficacy of other PDE5 inhibitors, vardenafil and tadalafil, in patients with heart failure. Differences in pharmacokinetics and selectivity among PDE5 inhibitors in clinical use suggest that safety and efficacy should be evaluated for each single preparation.

Conclusions and Perspectives

Heart failure treatment is a challenging task. An impaired NO pathway contributes to several abnormal cardiac and vascular phenotypes typical of the failing cardiovascular system. Inhibition of PDE5 is a novel therapeutic strategy for overexpressing NO signaling by increasing cGMP availability. A number of theoretical backgrounds and progressively accumulating evidence support the usefulness of NO potentiating compounds in CHF. Reduction of impedance to RV ejection and increase of RV output is an innovative way of treatment of CHF and patients with predominant pulmonary vasoconstriction and pressure elevation may be those who mostly benefit from prescription of PDE5 inhibitors. This is one of the main topics that deserve definitive evidence from large-scale clinical trials.

Initial promising perspectives await definition of safety, tolerability and potential impact of PDE5 inhibition on morbidity and mortality across the wide spectrum of heart failure populations. The first multicenter trial examining the clinical use of PDE5 inhibitors in heart failure (RELAX) will test the efficacy of chronic sildenafil to treat heart failure patients without dilatation and preserved ejection fraction (referred to as diastolic heart failure). Affected patients are generally more elderly, are more frequently females, often have high blood pressure and left ventricular hypertrophy, and nearly 40% have pulmonary hypertension. The main end points of the trial will include metabolic exercise capacity, left ventricular mass and function changes.

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Disclosures

None.

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