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. Because the clinical effects were not as promising as initially reported by experimental studies, PDE5 inhibitors were not regarded as a remarkable advancement.

Nonetheless, 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 A3.5 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).6 Silde-

nafil is the agent more extensively investigated in experimen-
tal 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.8 Sildenafil, although very selective for PDE5 shows some cross-reactivity with PDE6 which is predominant in photoreceptors.9 Because of this, in individuals taking high doses of sildenafil the color vision perception may be transiently disturbed.10 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.11–13 Empirical testing shows that the duration of action of sildenafil may reach 12 hours.14 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.15 cGMP initiates a cascade of reactions that decrease intracellular Ca2+ concentration and produce relaxation.16 Thus, the NO/cGMP pathway is fundamental to the control of smooth muscle tone and contractility, and an

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optimal synergism between NO and cGMP is required for a regular intracellular Ca\textsuperscript{2+}/H\textsubscript{11001} release\textsuperscript{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,\textsuperscript{18} has attracted interest as a potential therapeutic tool in CHF. Experience accumulated in patients with pulmonary vascular hypertension\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{22} and impairment in gas diffusion.\textsuperscript{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\textsuperscript{24} and by Lewis et al\textsuperscript{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.\textsuperscript{25} Recently, the same authors have reported that the PDE5 inhibitor maintains efficacy during long-term administration.\textsuperscript{26,27}

An additional effect of sildenafil on the lung\textsuperscript{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.
sildenafil and tadalafil, which have been shown to provide evidence of PDE5 expression in isolated myocytes, clinically not significant. More recent studies, however, have demonstrated that sildenafil is effective on alveolar-capillary diffusion impairment in heart failure. It is clinically significant, therefore, that sildenafil is effective on alveolar-capillary conductance and that the improvement of DM with sildenafil is tightly related with that of VE/VCO₂. This proves that PDE5 inhibition can affect one of the lung function abnormalities produced by CHF, also suggests that a defective NO/cGMP pathway may have a putative role in the excessive resistance to gas transfer across the blood gas barrier. On a clinical setting, a debated issue is whether impairment in gas transport at the alveolar-capillary junction is significantly involved in exercise intolerance in CHF. The correlations of baseline diffusion capacity for carbon monoxide with peak exercise oxygen uptake, and of DM with the ventilatory reaction to exercise in relation to the carbon dioxide output (VE/VCO₂) and with the arterial oxygen saturation at peak exercise, support a lung diffusion limitation as one of the mediators of exercise impairment in heart failure. It is clinically significant, therefore, that sildenafil is effective on alveolar-capillary conductance and that the improvement of DM with sildenafil is tightly related with that of VE/VCO₂.

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, enzyme activity is rather low compared with that of VE/VCO₂. This proves that PDE5 inhibition can affect one of the lung function abnormalities produced by CHF, also suggests that a defective NO/cGMP pathway may have a putative role in the excessive resistance to gas transfer across the blood gas barrier. On a clinical setting, a debated issue is whether impairment in gas transport at the alveolar-capillary junction is significantly involved in exercise intolerance in CHF. The correlations of baseline diffusion capacity for carbon monoxide with peak exercise oxygen uptake, and of DM with the ventilatory reaction to exercise in relation to the carbon dioxide output (VE/VCO₂) and with the arterial oxygen saturation at peak exercise, support a lung diffusion limitation as one of the mediators of exercise impairment in heart failure. It is clinically significant, therefore, that sildenafil is effective on alveolar-capillary conductance and that the improvement of DM with sildenafil is tightly related with that of VE/VCO₂.

Nitric Oxide

PDE₅ inhibitors

Endothelium

(SM), without affecting the pulmonary capillary volume of blood available for gas exchange (DM and pulmonary capillary volume of blood are the 2 components of diffusion capacity for carbon monoxide). This proves that PDE5 inhibition can affect one of the lung function abnormalities produced by CHF, also suggests that a defective NO/cGMP pathway may have a putative role in the excessive resistance to gas transfer across the blood gas barrier. On a clinical setting, a debated issue is whether impairment in gas transport at the alveolar-capillary junction is significantly involved in exercise intolerance in CHF. The correlations of baseline diffusion capacity for carbon monoxide with peak exercise oxygen uptake, and of DM with the ventilatory reaction to exercise in relation to the carbon dioxide output (VE/VCO₂) and with the arterial oxygen saturation at peak exercise, support a lung diffusion limitation as one of the mediators of exercise impairment in heart failure. It is clinically significant, therefore, that sildenafil is effective on alveolar-capillary conductance and that the improvement of DM with sildenafil is tightly related with that of VE/VCO₂.

Nitric Oxide

PDE₅ inhibitors

Endothelium

(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 hyper-trophied human right ventricle, PDE5 is highly expressed and its inhibition improves contractility, thus showing that this upregulation is physiologically significant. Okcaili 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.

Nitric Oxide

PDE₅ inhibitors

Endothelium

Smooth muscle

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.
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 myocyte 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-Inhibiton 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 al21</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;0.005)</td>
</tr>
<tr>
<td>Piccolito et al22</td>
<td>20</td>
<td>Single-center; randomized, placebo-controlled</td>
<td>Sildenafil single dose (50 mg orally)</td>
<td>Stable CHF with no warning symptoms in the 3 mo before the study; no atrial fibrillation, frequent extrastyle 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 al23</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 (VO2) and ventilation efficiency (W/FIO2 slope)</td>
<td>Significant decrease in resting HR (P=0.02) and BP (P&lt;0.01); no changes in resting and peak exercise norepinephrine; significant increase in peak VO2 (P=0.025) and decrease in W/FIO2 slope (P=0.04)</td>
</tr>
<tr>
<td>Guazzi et al24</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, arteriolar resistance) alveolar gas diffusion (DLco); peak exercise oxygen uptake (VO2) and ventilation efficiency (W/FIO2 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 Ve/VCO2 slope (P&lt;0.01); significant increase in DLco and peak VO2 (P&lt;0.01)</td>
</tr>
<tr>
<td>Lepore et al25</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 arterial 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 O2 (P&lt;0.03). Additive effects of the sildenafil/inhaled NO combination</td>
</tr>
<tr>
<td>Hryniewicz et al26</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>Systemic hemodynamics; LV ejection fraction, vascular resistance; Cardiac and total body norepinephrine spillover</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 al27</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 (cardiac index, LV ejection fraction, vascular resistance); and 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 al28</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; and pulmonary hemodynamics (mean arterial pressure, wedge pressure, arterial resistance); peak exercise O2 uptake (VO2) and ventilation efficiency (W/FIO2 slope)</td>
<td>Significant decrease in resting and exercise mean pulmonary arterial pressure, arterial resistance and (P&lt;0.05); significant decrease in resting (P&lt;0.05) but no exercise systemic vascular resistance; significant increase in peak VO2 (P&lt;0.05) and decrease in W/FIO2 slope (P=0.05)</td>
</tr>
<tr>
<td>Guazzi et al29</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); metaboloreceptor assessment; peak exercise aerobic (ΔVO2/ΔWR) and ventilation (ΔVe/VCO2 slope) efficiency</td>
<td>Significant improvement in FMD, ergoreflex assessment, (ΔVO2/ΔWR) and Ve/VCO2 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; VO2, change in O2 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 peptide43 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.26,27 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 perfusion27; b) the increased NO availability may facilitate the DM24; 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 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.64,65 This may be because of

<table>
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<tr>
<th>Clinical Trial</th>
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<th>Results</th>
</tr>
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<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 moderate pulmonary hypertension; no COPD or ongoing nitrates therapy</td>
<td>Resting and exercise systemic (stroke volume, vascular resistance) and pulmonary hemodynamics (mean arterial pressure, wedge pressure, vascular resistance); peak exercise O2 uptake (VO2) and ventilation efficiency (VE/VCO2 slope); 6-min walk test; hospitalization; 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, 6-min walk test distance 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, nitrates 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.
Sildenafil has been shown, both in acute and long-term studies, to reduce breathlessness and the Ve/Vco₂ slope on exercise. This suggests a dependence on favorable mechanisms. First, a decrease of waste ventilation (ie, reduced dead space to tidal volume ratio) and a facilitated DM. In addition, it has been reported that sildenafil intake can produce an endothelium-mediated attenuation of the ergoreflex stimulus to hyperventilation and breathlessness.

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

Safeguards 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 in healthy subjects and in patients with heart failure. However, after 50 mg oral sildenafil no changes in plasma norepinephrine have been reported in heart failure at rest or on exercise. 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 isoform, direct effects on myocardial cAMP and myocardial contractility cannot be ruled out.

Thus far there are no published data on safety or efficacy of other PDE5 inhibitors, vardenafil and tadalafl, 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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