Therapeutic Potentials of Phosphodiesterase-5 Inhibitors in Cardiovascular Disease

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Phosphodiesterase-5 (PDE5) inhibitors have been approved by the US Food and Drug Administration for the treatment of erectile dysfunction and more recently for pulmonary arterial hypertension (World Health Organization functional class I). PDE5 inhibitors can induce vasodilation; in addition, through a complex pathway involving nitric oxide, cyclic guanosine monophosphate, and protein kinase G, it can reduce apoptosis and suppress cell proliferation. The presence of PDE5 inhibitors in various tissues and systemic vasculature make them potential targets in a variety of cardiovascular diseases. In many in vitro and in vivo studies, PDE5 inhibitors have been shown to have positive effects in systolic and diastolic congestive heart failure, ischemic heart disease, doxorubicin cardiomyopathy, and pulmonary arterial hypertension. They also improved vasoconstriction in Raynaud phenomenon, peripheral artery disease, and hypoxic brain conditions. This article reviews the therapeutic potentials of PDE5 inhibitors in different cardiovascular diseases.

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KEY WORDS

Phosphodiesterase-5 inhibitors • Sildenafil • Vardenafil • Tadalafil • Cardiovascular disease • Pulmonary arterial hypertension

The effects of phosphodiesterases (PDEs) have been observed since the 9th century, when coffee was first discovered. However, not until the 1950s was the mechanism of PDE elucidated. Since they were first described in the late 1950s and early 1960s by Sutherland and Rall[1] and Ashman and colleagues,[2] at least 11 subtypes of PDEs (PDE1-PDE11) have been identified in mammals. PDEs can be found ubiquitously in various tissues and are involved in many signaling pathways. Each of them is distinctive in tissue distribution, as well as intracellular interactions and target proteins. Among them, PDE5, with its potential clinical applications and therapeutic uses, has been studied

extensively. This article reviews the therapeutic potentials of PDE5 inhibitors in cardiovascular disease.

PDE5 is expressed in several tissues, corpus cavernosum smooth muscle, vascular and visceral smooth muscle, cardiomyocytes, skeletal muscle, platelets, kidney, lung, cerebellum, and pancreas. Its main intracellular activities are mediated via the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP)/protein kinase G (PKG) pathway.

NO/cGMP/PKG Pathway

NO is synthesized from the precursor L-arginine through the activities of NO synthase (NOS). NO is produced in response to different stimuli, which can be mechanical, hormonal, or neurologic. After being synthesized, it enters target cells and functions as the first signal to the NO/cGMP/PKG pathway, which causes subsequent intracellular changes. After permeating the cellular membrane, NO binds to guanylyl cyclase (GC) and activates this enzyme. NO-GC accelerates the conversion of guanosine triphosphate to cGMP.

cGMP has different intracellular interactions with PKGs, cGMP-gated cation channels, cGMP-hydrolyzing PDEs, and cGMP-binding cGMP-hydrolyzing PDEs. Phosphorylation of different proteins by PKGs, especially the PKG I isoenzyme, mediates activities of membrane channels/pumps and therefore causes decreased calcium influx through L-type calcium channels[3,4] and increased calcium sequestration by its inhibitory effect on the sarcoplasmic reticulum calcium/adenosine triphosphatase pump.[5,6] This results in vasodilation and smooth muscle relaxation. cGMP-dependent PKGs were also shown to increase apoptosis and decrease cell proliferation.[7,8]

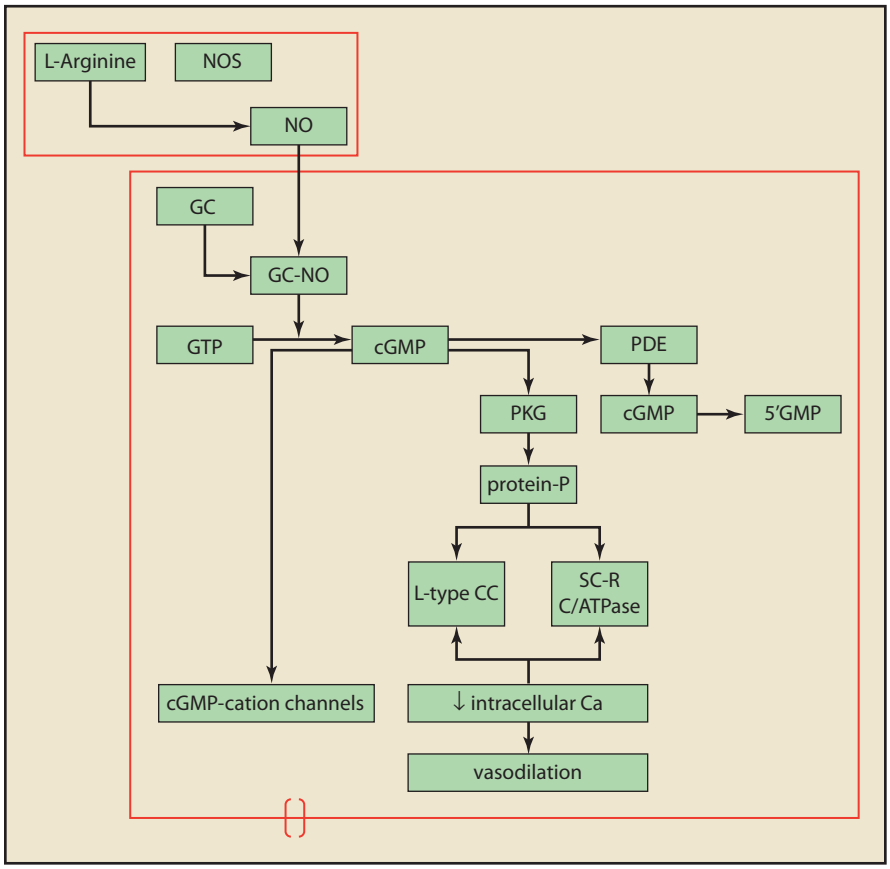

Figure 1. NO/cGMP/PKG pathway. Ca, calcium; cGMP, cyclic guanosine monophosphate; GC, guanylyl cyclase; GTP, guanosine triphosphate; L-type CC, L-type calcium channels; NO, nitric oxide; PDE, phosphodiesterase; PKG, protein kinase G; SC-R C/ATPase, sarcoplasmic reticulum calcium/adenosine triphosphatase pump.

cGMP-hydrolyzing PDEs degrade cGMP to its inactive form, 5'-GMP, when cGMP binds to the enzyme catalytic site. PDE5 is considered cGMP specific due to its considerably higher affinity to cGMP compared with cyclic adenosine monophosphate (Figure 1).[9]

The *PDE5* gene encodes three distinct proteins: PDE5A1, PDE5A2, and PDE5A3.[10,11] These three isoforms are different in the N terminus of the mitochondrial RNA and accompanying amino acid sequence. The regulation and expression of PDE5A1, PDE5A2, and PDE5A3 varies in tissues, yet no functional difference has been reported.

Our understanding of the NO/cGMP/PKG pathway and molecular activity of PDEs—theoretically, inhibiting PDE5 and thus blocking the hydrolysis of cGMP—led to other ways to increase cGMP activity. A substantial amount of work has been conducted on drugs targeting different points of action in this pathway. Among them, PDE5 inhibitors have emerged as a topic of very strong interest for the past decade. Nonselective and selective PDE5 inhibitors (sildenafil, vardenafil, and tadalafil) have been introduced with several therapeutic applications. PDE5 inhibitors compete with the natural substance, cGMP, to bind PDE catalytic sites. These drugs are powerful, with a 1000-fold higher affinity than cGMP to catalytic sites. Moreover, unlike cGMP, they are not degraded once bound to those sites, leading to durable effects that have been seen clinically. These drugs have a similar structure to that of cGMP, which is important in their mechanism as competitive binding agents with

TABLE 1

Pharmacokinetics of Sildenafil, Vardenafil, and Tadalafil

	Sildenafil	Vardenafil	Tadalafil
Onset of action	60 min	60 min	60 min
Half-life	4 h	3-6 h	15-17.5 h
Metabolism	Hepatic via CYP3A4 and CYP2C9	Hepatic via CYP3A4 and CYP2C and 3A5	Hepatic, via CYP3A4 to metabolites
Cross interaction with other PDE inhibitors	PDE6	Not known	PDE11
Consequences of PDEs cross interaction	Visual disturbances	QTc prolongation	Unknown

PDE, phosphodiesterase.

cGMP. The pharmacokinetics of each drug is described in Table 1.

Sildenafil was the first selective PDE5 inhibitor, introduced in 1996 by Pfizer Healthcare Ireland (Dublin, Ireland), and later approved by the US Food and Drug Administration (FDA) in 1998 for erectile dysfunction (ED) as Viagra®, and in 2005 for pulmonary hypertension (World Health Organization [WHO] Group I) as Revatio® (Pfizer, New York, NY). Vardenafil was FDA approved in 2003 and 2010 for ED, marketed as Levitra® (Bayer HealthCare, Pittsburgh, PA) and STAXYN (Bayer HealthCare). The third PDE5 inhibitor, tadalafil (Cialis®; Eli Lilly & Co, Indianapolis, IN), joined the market in 2003 as another drug for the treatment of ED, and was recently revised for a new indication of benign prostatic hyperplasia. In 2009, it was also approved under the name of Adcirca® (Eli Lilly & Co.) for the treatment of pulmonary arterial hypertension (PAH; WHO Group I).

Cardiac Disease

Ischemic Injury

The cardiac-protective mechanism of PDE5 inhibitors has been investigated substantially. Several studies have found that PDE5 inhibitors reduced myocardial infarct and ischemia through a PKG-dependent pathway. It was hypothesized that the administration of PDE5 inhibitors mediated the release of endogenous vasodilators, which may trigger the phosphorylation of endothelial and inducible NOS and subsequently generate NO. NO then activates the cGMP/PKG pathway, in which PKG opens mitochondrial and sarcolemmal adenosine triphosphate (ATP)-sensitive potassium channels.[12,13] The opening of these channels plays a key role in stabilizing membrane potentials, and maintaining ATP synthesis and calcium homeostasis, all of which are essential for cell survival.[14] In a mouse model, sildenafil exhibited a preconditioning effect to protect the heart against necrosis and apoptosis, for which the NO signaling pathway was demonstrated to have an essential role.[15]

Salloum and colleagues[16] added to our understanding of the cardioprotective effects of PDE5 inhibitors by demonstrating that tadalafil protected the heart through hydrogen sulfide (H_2S) signaling in a PKG-dependent fashion. H_2S is a product synthesized continuously at micromolar levels in mammals. Interestingly, both PKG and H_2S open mitochondrial ATP-sensitive potassium channels. Tadalafil's cardioprotective effect was blocked by the PKG inhibitor KT5823 and cystathionine-γ-lyase (CSE), the H_2S-producing enzyme inhibitor in CSE-knockout mice.

However, the acute cardioprotection of sildenafil appears to be independent of the NO/cGMP pathway.[17] Low-dose sildenafil given before reperfusion significantly reduced myocardial infarct size in NOS-null mice. This finding was contrary to the results of other studies. It could be explained that this study was conducted to focus on the acute effect of sildenafil on cardiomyocytes, whereas other studies investigated delayed preconditioning, which could allow upregulation of NOS. When a second series in diabetic mice was performed, the protective effect of sildenafil no longer existed. However, NO donor therapy maintained the cardioprotection in both

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nondiabetic and diabetic mice. This suggested that the cardioprotection of sildenafil and other PDE5 inhibitors could vary depending on coexisting conditions in study subjects.

The protective effects of PDE5 inhibitors against cardiac ischemic and reperfusion injury were duplicated in many in vitro studies with sildenafil,[14,18] tadalafil,[19,20] and vardenafil.[21] These agents were reported to reduce infarct size, which is an important prognostic factor of mortality and progression to heart failure from cardiac ischemia. In a dog model, fewer and less serious ventricular arrhythmias occurred during occlusion of the anterior descending coronary artery in the sildenafil-treated group.[22] However, reperfusion ventricular fibrillation was not modified by the drug.

The safety of PDE5 inhibitors in coronary artery disease is certainly a concern. Because they are a vasodilator, PDE5 inhibitors were theoretically hypothesized to cause coronary steal phenomenon, where more blood would be shifted toward the nonischemic tissue from the ischemic area and therefore exacerbate ischemia. However, there has been no such evidence from animal models[23] or human studies. The systemic, pulmonary, and coronary hemodynamics were studied in a group of 14 men with severe stenosis of at least one coronary artery.[24] Oral sildenafil had no effect on pulmonary-capillary wedge pressure, right atrial pressure, heart rate, cardiac output, coronary vascular resistance, or coronary arterial blood flow. In another study of 105 men with stable coronary artery disease, sildenafil had no effect on symptoms, exercise duration, or presence or extent of exercise-induced ischemia.[25] Similar results on patients' exercise capacity were found with vardenafil[26] and tadalafil.[27]

PDE5 inhibitors have an effect on platelet aggregation. In a study by Berkels and colleagues,[28] sildenafil, 100 mg, markedly inhibited collagen-induced aggregation and prolonged bleeding time. The coadministration of NO and sildenafil resulted in significant inhibition of ADP- and collagen-induced platelet aggregation. This increased our awareness of a possible increased bleeding risk when sildenafil is given together with other antiplatelet agents such as aspirin or clopidogrel.

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Heart Failure

Congestive heart failure (CHF) is one of the most common causes of death worldwide. Cardiac dysfunction from different causes (volume overload, pressure overload, cardiomyocyte diseases, cardiac injury) leads to an adaptive or maladaptive process called cardiac remodeling.[29] This process results in molecular, cellular, and interstitial changes, manifesting as changes in size, shape, or function of the heart.

As demonstrated in animal studies,[15] sildenafil can induce a preconditioning effect protecting the heart from necrosis and apoptosis. This potentiated the role of PDE5 inhibitors in preventing and/or minimizing ventricular remodeling and thus slowing down the progression to advanced CHF.

The benefits of sildenafil were illustrated in a mouse model of chronic mitral regurgitation in which the authors reported less perivascular fibrosis, smaller left ventricular (LV) size, and greater LV ejection fraction in the sildenafil-treated group.[30] Sildenafil also suppressed chamber and myocyte hypertrophy and reversed preestablished hypertrophy induced by pressure load, and restored chamber function in normal mice exposed to chronic pressure overload induced by transverse aortic constriction.[31] In this study, sildenafil was shown to deactivate multiple hypertrophic signaling pathways triggered by pressure load (the calcineurin/NFAT, phosphoinositide-3 kinase/Akt, and ERK1/2 signaling pathways). However, hypertrophy induced by calcineurin in vitro or Akt in vivo was not suppressed by sildenafil. This may suggest an upstream target of these pathways. This benefit of sildenafil in cardiac conditions of pressure overload was illustrated in a recent human study on patients with severe aortic stenosis. A single oral dose of sildenafil (40 mg or 80 mg) reduced systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR), decreased mean pulmonary artery pressure (PAP) and pulmonary capillary wedge pressures (PCWP), and thus increased the stroke volume index. Sildenafil was well tolerated with no episode of symptomatic hypotension.[32]

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A number of studies have been conducted on the effects of sildenafil in patients with CHF (Table 2); 13 patients with New York Heart Association class III CHF who were given a single oral dose of sildenafil, 50 mg, had reduced PAP and SVR and

TABLE 2

PDE5 Inhibitors and Congestive Heart Failure

Study	Patients (N)	PDE5 Inhibitor	Design	Primary Outcomes
Lewis GD et al[33]	13 systolic CHF	Sildenafil, 50 mg single dose	Prospective	Reduction in resting and exercise PVR, SVR, CI, more selection on pulmonary vessels in exercise
Lewis GD et al[34]	34 CHF with PH	Sildenafil 25-75 mg tid × 12 wk	Randomized, placebo	Reduction in PVR, increase in CO with exercise, improvement in 6-min walk distance, fewer hospitalizations
Guazzi M et al[35]	44 CHF with preserved EF	Sildenafil, 50 mg tid × 6 mo and 1 y	Double-blind, randomized, placebo	Improvement in pulmonary pressure and vasomotility, RV fuction, LV relaxation, and pulmonary interstitial water metabolism
Guazzi et al[36]	16 CHF	Sildenafil, 50 mg single dose	Randomized, placebo	Improvement in endothelial activity and muscle perfusion, ventilator and aerobic efficiencies
Behling A et al[37]	19 systolic CHF	Sildenafil, 50 mg (1 h) and 50 mg tid × 4 wk	Double-blind, randomized, placebo	Both phases: acute and chronic: Improvement in PASP, oxygen uptake, and ventilatory efficiency

CHF, congestive heart failure; CI, cardiac index; CO, cardiac output, EF, ejection fraction; LV, left ventricle; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RV, right ventricle; SVR, systemic vascular resistance; tid, three times daily.

PVR at rest. During exercise, these patients were shown to have reduced exercise PAP, PVR, and PVR/SVR ratio and increased resting and exercise cardiac index. All of these changes occurred without altering mean arterial pressure, heart rate, or PCWP.[33] In 34 patients with CHF and pulmonary hypertension, compared with placebo, 12-week treatment of sildenafil, 25 to 75 mg orally three times daily, improved cardiac output with exercise and 6-minute walk distance, reduced PVR, and was associated with fewer hospitalizations for CHF.[34] Sildenafil, 50 mg orally three times daily, can improve right and LV function, decrease mean PAP, and reduce PCWP in patients with CHF with preserved ejection fraction.[35] Improvement of endothelial function, muscle perfusion, and ventilatory and aerobic efficiencies in 16 patients with CHF was also observed with sildenafil administration.[36] The acute and chronic improvement in pulmonary artery systolic pressure and ventilator efficiency with sildenafil was again demonstrated in a study of 19 systolic CHF patients.[37] These results are suggestive of a novel therapeutic role of sildenafil in CHF from different causes.

Coronary artery disease is a major cause of heart failure. After an acute infarct, the heart undergoes a remodeling process involving both the infarcted and noninfarcted regions.[38] The noninfarcted region develops important lengthening and increases in ventricular size to compensate for the infarcted noncontractile region in order to restore stroke volume. PDE5 inhibitors might be of therapeutic potential in heart failure secondary to ischemic heart disease. In 2008, Salloum and associates[39] demonstrated that sildenafil reduced infarct size and apoptosis following ischemia-reperfusion, attenuated cardiac hypertrophy, and improved LV function. To date, data of vardenafil and tadalafil in heart failure patients are limited.

Doxorubicin Cardiomyopathy

Doxorubicin is a chemotherapeutic agent used in several types of malignancies, including breast cancer, leukemia, Hodgkin and non-Hodgkin lymphoma, and sarcoma. One of its well known side effects is cardiotoxicity, which can occur acutely or chronically after years of treatment. This cardiotoxicity seems to occur mainly through the production of free radicals,[40-42] which is different from its antitumor activity, which takes place by the inhibition of topoisomerase II. Several studies have reported this oxidative stress can affect different levels of intracellular and molecular activities, including the mitochondria,[43] microtubules,[44] and lipid peroxidation.[45]

In addition, doxorubicin administration appeared to decrease endogenous antioxidants.[46] The combination of increased oxidative

stress and decreased antioxidants can induce apoptosis,[47,48] leading to cardiomyocyte death. Patients with doxorubicin cardiotoxicity usually suffer from cardiomyopathy, heart failure, and arrhythmia.

Prophylactic treatment with sildenafil prevented apoptosis and LV failure in a mouse model of chronic doxorubicin-induced cardiomyopathy.[49] The administration of sildenafil with doxorubicin reduced apoptosis and desmin disruption, and maintained LV pressure and ST interval. The exact mechanism of sildenafil's cardiac protection from doxorubicin toxicity is unclear. However, it seemed that the pharmacologic preconditioning with sildenafil could arise from increased phosphorylation of NOS of endogenous vasodilators, which resulted in the generation of NO, formation of cGMP, and subsequent opening of mitochondrial potassium-ATP channels, which play a role in cardioprotection.[50]

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Koka and Kukreja[51] and Koka and associates[52] demonstrated that tadalafil improved cardiac contractile function and survival by attenuating doxorubicin-induced apoptosis and cardiac oxidative stress without interfering with the antitumor efficacy of doxorubicin in both in vitro and in vivo tumor models. In the study, tadalafil treatment increased cardiac cGMP and PKG activity, and preserved GATA4, a transcription factor important to the differentiation and response of cardiac tissue to stress.

Pulmonary Arterial Hypertension

PAH is defined as a mean PAP $>$ 25 mm Hg at rest in the setting of PCWP $\leq$ 15 mm Hg with a PVR $>$ 3 Woods units.[53] This requires confirmation by a complete right heart catheterization because it is primarily a hemodynamic definition. A high pressure in the pulmonary arteries and/or veins restricts blood flow through pulmonary circulation and subsequently results in right heart failure.

PAH is a complex entity with multiple pathogenic pathways that have been studied for the past several decades. Some genetic mutations have been found to be associated with PAH; however, this disease is inherited in fewer than 10% of patients,[53,54] suggesting that a "multi-hit" theory, including genetic abnormalities and environmental factors, is likely. Imbalance in vasoconstriction/vasodilation and decrease in apoptosis/proliferation ratio have been reported in several studies as important pathologic features in PAH.[55-57] Based on these physiologic findings, PAH therapies should aim to enhance vasodilation, suppress cellular hyperproliferation, and induce apoptosis. Several vasodilators targeting the vasoconstrictive properties of PAH have been developed. However, the distinct of elevated pulmonary arterial resistance with a normal systemic vasculature is a challenge to nonselective vasodilators. These agents can cause systemic hypotension in the setting of impaired right ventricular function, which may not fully compensate to increase systemic blood pressure. This prompted the development of vasodilators selective for pulmonary circulation.

Increased expression of PDE5 in models of PAH[58] and right ventricular hypertrophy,[59] and reduced production of endothelial NOS in the lungs of patients with PAH,[60] make PDE5 inhibitors a promising agent in the treatment of this condition. By inhibiting PDE5, these drugs, acting through the NO/cGMP/PKG pathway, inhibit the hydrolysis of cGMP, resulting in decreased calcium influx through L-type calcium channels and increased calcium sequestration, and subsequently induce vasorelaxation. In addition, PDE5 inhibitors were reported by Wharton and colleagues[61] to reduce DNA synthesis and cell proliferation and stimulate apoptosis, which may be significant in reducing pulmonary pressure.

In a double-blind placebo-controlled trial including 278 patients with PAH (mostly of WHO functional class II and III),[62] oral sildenafil at doses of 20 mg, 40 mg, and 80 mg three times daily was shown to increase the distance in a 6-minute walking test, an independent prognostic factor in patients with idiopathic pulmonary hypertension.[63] The drug also reduced the mean PAP and improved the WHO functional class. This effect on exercise capacity was observed after 12 weeks of treatment and sustained in the 1-year extension study. The efficacy of sildenafil in PAH treatment appears to be comparable with that of bosentan, an endothelin receptor antagonist, in a small-sized study.[64]

In the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) study group,[65] tadalafil at the highest dose of 40 mg/d orally over 16 weeks increased the distance walked in 6 minutes compared with baseline, improved the incidence and time to clinical worsening, and improved health-related quality of life. These improvements seemed to be greater in bosentan-naïve patients than in the bosentan-treated group. This might be related to pharmacokinetic interaction, as tadalafil and bosentan are metabolized via the

TABLE 3

PDE5 Inhibitors and Pulmonary Arterial Hypertension

Study	Patients (N)	PDE5 Inhibitors	Design	Primary Outcomes
Galiè N et al[62]	278 PAH with WHO class II and III	Sildenafil, 20 mg, 40 mg, and 80 mg tid	Double-blind, randomized, placebo	Improvement in exercise capacity, WHO functional class, mean PAP
Wilkins MR et al[64]	26 PAH with WHO class III on conventional treatment	Sildenafil, 50 mg bid × 4 wk then 50 mg tid × 16 wk	Double-blind, bosentan	Both groups: improvement in RV mass, cardiac function, and exercise capacity
Galiè N et al[65]	405 PAH	Tadalafil, 40 mg/d × 16 wk	Double-blind, randomized, placebo	Improvement in quality of life, exercise capacity, reduction in clinical worsening
Simonneau G et al[67]	267 PAH on IV epoprostenol	Sildenafil, 20 mg tid, titrate to 80 mg tid over 16 wk	Double-blind, parallel-group, placebo, multicenter	Improvement in exercise capacity, hemodynamic measurements, time to clinical worsening, and quality of life

IV, intravenous; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; RV, right ventricular; tid, 3 times daily; bid, twice daily; WHO, World Health Organization.

cytochrome CYP3A4 pathway, or the result of a ceiling effect.[66]

PDE5 inhibitors can also be used as combination therapy with other PAH-targeted treatments. The combination of sildenafil and long-term intravenous epoprostenol therapy improved exercise capacity, hemodynamic measurements, time to clinical worsening, and quality of life compared with epoprostenol as monotherapy.[67] Increased rates of headache and dyspepsia occurred with the addition of sildenafil. Side effects are usually tolerable, and include flush, headache, myalgia, and digestive symptoms (Table 3).

The short-term impacts of three PDE5 inhibitors were investigated in a small study comprising 60 patients with New York Heart Association class II to IV heart failure. Vardenafil had the most rapid effect on pulmonary vasorelaxation, whereas sildenafil and tadalafil were more selective for pulmonary circulation. Significant improvement in arterial oxygenation was only noted with sildenafil.[68]

Miscellaneous

The potent vasodilation effect of PDE5 inhibitors has prompted a considerable amount of research studying disorders for which improved blood flow might have therapeutic effects. The presence of PDE5 in a wide variety of tissues and vascular beds makes it a potential target of treatment in numerous different conditions.

Raynaud Phenomenon

Raynaud phenomenon manifests as episodic, recurrent acral vasospasm in response to cold weather or stress. It could be primary or secondary to a systemic connective tissue disease. In a small study of 18 patients with regular occurrence of Raynaud attacks and resistance to conventional vasodilation therapy, oral sildenafil, 50 mg twice daily, decreased the frequency and duration of attacks and improved capillary blood flow velocity.[69] Similar results were observed with vardenafil[70] but not tadalafil.[71] It is unclear if the ineffectiveness of tadalafil was dose dependent or related to receptors of PDE5 in the peripheral vascular system. PDE5 inhibitors such as sildenafil and vardenafil might become a novel therapeutic agent for patients with this disorder.

PDE5 inhibitors might be of therapeutic benefit in two pregnancy-related conditions related to small artery vasoconstriction and uteroplacental hypoperfusion: fetal growth restriction and preeclampsia.

Pregnancy

PDE5 inhibitors might be of therapeutic benefit in two pregnancy-related conditions related to small artery vasoconstriction and uteroplacental hypoperfusion: fetal growth restriction[72] and preeclampsia.[73] Wareing and colleagues[72] performed a study in

which myometrial small arteries from pregnancies complicated by fetal growth restriction were dissected and incubated with sildenafil. It confirmed increased vasotone in these arteries and vasodilation after sildenafil administration. It was also hypothesized that the use of selective PDE5 inhibitors could improve outcomes in preeclampsia.[73] This theory is based on the observation that the pathophysiologic changes in preeclampsia are similar to those caused by persistent hypoxemia from high altitude or chronic obstructive pulmonary disease, in which PDE5 inhibitors were shown to improve oxygenation and vasotone.

Peripheral Vascular Disease

PDE5 inhibitors may also be a consideration in peripheral vascular disorders. An in vitro study reported that vardenafil 10 mg/kg/d in mice with induced hindlimb ischemia upregulated the protein expression of vascular endothelial growth factor and enhanced mobilization of endothelial progenitor cells in peripheral blood and bone marrow, contributing to neovascularization. Blood flow recovery and capillary collateral formation were significantly increased in ischemic muscle during the 4 weeks of the study.[74] Sildenafil was shown to increase tissue blood flow and stimulate angiogenesis in ischemic tissue without altering these parameters in the nonischemic tissue. It appeared that this effect was taken through a PKG-dependent pathway that is not related to NO or NOS activity.[75] Further studies in humans are required to explore the role of PDE5 inhibitors as a potential treatment in peripheral vascular disease.

Central Nervous System

To date, PDE5 inhibitors do not appear have any significant effect on cerebral blood flow in normal healthy subjects. However, their capacity to improve cerebral oxygenation and circulation is well reported in hypoxic conditions. Under conditions of high-altitude hypoxia, sildenafil attenuated cerebral blood flow and oxygenation.[76] The authors suggested a hypoxic drive that enhanced the sensitivity and upregulation of PDE5. A group of 11 patients with severe PAH and 22 healthy volunteers were tested for cerebral and pulmonary vascular function while being given inhaled iloprost and oral sildenafil.[77] Both agents significantly reduced PVR with minor change in SVR. However, only sildenafil improved cerebral microvascular reactivity whereas iloprost worsened it.

A study by Zhang and associates,[78] revealed that administration of an NO donor to rats with stroke significantly increased brain levels of cGMP, induced cell genesis, and improved functional recovery. An additional study by Zhang and associates,[79] testing sildenafil in rats subjected to strokes, showed increased cortical levels of cGMP, increased neurogenesis, and reduced neurologic deficit with the use of sildenafil starting 2 or 24 hours after stroke onset and continuing for 7 days.

Al-Amran and coworkers[80] reported that sildenafil improved cerebrovascular reactivity in patients with type 2 diabetes but not in healthy subjects. There was no significant increase of mean flow velocity of the middle cerebral artery at rest in both groups. These findings might suggest improvement or perhaps amelioration of endothelial dysfunction in diabetic patients with sildenafil administration.[80]

In summary, findings from these studies suggest a potential role of PDE5 inhibitors in improving cerebral blood flow in hypoxic conditions, promoting neurogenesis, improving neurologic functions after stroke, and ameliorating endothelial dysfunction in diabetic patients. However, most of the studies were in vitro or conducted in a small group of subjects. Further work involving more participants will be helpful to confirm the validity of these results.

Conclusions

PDE5 inhibitors were first approved by the FDA for the treatment of ED when this urologic disorder was recognized as a side effect in an original study in which angina pectoris was the primary clinical target. Since vasodilation was recognized as a potent effect of PDE5 inhibitors, interest in PDE5 inhibitors and cardiovascular disease has grown extensively, with both in vitro and in vivo studies. To date, PDE5 inhibitors have expanded their therapeutic role to various cardiovascular diseases, including ischemic heart disease, CHF, pulmonary arterial hypertension, Raynaud phenomenon, peripheral vascular disease, and cerebral hypoperfusion. It is promising that the clinical use of PDE5 inhibitors may expand to other cardiovascular disorders. Well-designed clinical trials are needed to confirm findings from animal experiments and small-sized human studies to further explore potential therapeutic roles of PDE5 inhibitors. ■

The authors report no real or apparent conflicts of interest.

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MAIN POINTS

- Phosphodiesterase-5 (PDE5) inhibitors have been shown to have positive effects in systolic and diastolic congestive heart failure, ischemic heart disease, doxorubicin cardiomyopathy, and pulmonary arterial hypertension.
- Several studies have found that PDE5 inhibitors reduced myocardial infarction and ischemia through a protein kinase G–dependent pathway. It was hypothesized that the administration of PDE5 inhibitors mediated the release of endogenous vasodilators, which may trigger the phosphorylation of endothelial and inducible nitric oxide (NO) synthase, and subsequently generate NO. However, there is also evidence that the acute cardioprotection of sildenafil appears to be independent of the NO/cGMP pathway.
- PDE5 inhibitors can induce a preconditioning effect protecting the heart from necrosis and apoptosis.
- In congestive heart failure, PDE5 inhibitors have been shown to result in improvement of endothelial function, muscle perfusion, oxygen uptake, pulmonary artery systolic pressure, pulmonary and systemic vascular resistance, and ventilatory and aerobic efficiencies.
- In pulmonary arterial hypertension, PDE5 inhibitors can be used as a single agent or combination therapy to improve patient's exercise capacity, cardiac function, right ventricular mass, and quality of life.

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