

Sildenafil—a possible treatment for acute pulmonary hypertension during cardiac surgery

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Primarily pulmonary hypertension has an annual incidence of 1 to 2 cases per million people in the general population and an onset in the third to fourth decades of life (1). It is a progressive disease that affects women twice as frequently as men; the mean survival time from diagnosis is 2.5 years (2). Patients with chronic congestive heart failure may develop secondary pulmonary hypertension, and this may become a limiting factor for acceptance into a cardiac transplantation program. The new cardiac graft will have a normal-sized right ventricle that may fail when exposed to the increased workload of a preexisting elevated pulmonary vascular resistance (PVR). It is vitally important to prevent acute elevations in PVR intraoperatively in patients undergoing cardiac transplantation with marginally acceptable levels of pulmonary hypertension. The mechanisms to treat an acute rise in pulmonary artery pressures in these circumstances are limited.

A new therapy being examined for the treatment of primary and secondary pulmonary hypertension is the administration of oral sildenafil (3–5). Sildenafil is a selective vasodilator that prolongs the action of cyclic guanosine monophosphate (cGMP) by selective inhibition of phosphodiesterase (PDE) type 5, of which the lung has a rich supply. This action potentiates the effect of endogenously produced nitric oxide in the lung with resulting pulmonary vasodilatation. This report describes an early experience of administering sildenafil to a patient with pulmonary hypertension and right ventricular dysfunction who was undergoing cardiac transplantation surgery at Baylor University Medical Center.

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A 54-year-old man was admitted to Baylor University Medical Center complaining of shortness of breath. He had a history of progressively decompensating heart failure caused by ischemic cardiomyopathy; a previous extensive anterior wall myocardial infarction; and percutaneous transluminal coronary angioplasty with stenting of the left anterior descending coronary artery. On admission he underwent a right heart catheterization that showed severe pulmonary hypertension and poor cardiac output. Hemodynamic data obtained included a pulmonary artery pressure of 82/39 mm Hg with a mean of 53 mm Hg, a pulmonary artery occlusion pressure of 24 mm Hg, and a calculated PVR of 584 dynes·sec·cm⁻⁵. The cardiac output was measured at 3.97 L/min with an index calculated at 1.93 L/min/m². The systemic blood pressure was 122/72 mm Hg, the heart rate 62 beats per minute, and the oxygen saturation 95% breathing room air. The

medical history was further complicated by the presence of adult-onset diabetes mellitus, hyperlipidemia, hypertension, and chronic renal insufficiency. The patient was treated with diuretics and antihypertensives and continued taking digoxin. He initially showed some improvement but developed atrial fibrillation that did not convert back to sinus rhythm despite attempted cardioversion and the administration of amiodarone. He was transferred to the coronary care unit for more intensive intravenous inotropic therapy, including dobutamine 2.5 µg/kg/min, milrinone 0.75 µg/kg/min, and nitroglycerine 1 µg/kg/min, and clinically improved. He was listed for a cardiac transplant as a level 1A (emergent) candidate.

A suitable cardiac donor was found, and the patient was taken to the operating room to undergo orthotopic cardiac transplantation. On arrival in the operating room, initial hemodynamic data were obtained. The pulmonary artery pressures were 70/20 mm Hg with a mean of 41 mm Hg and a PVR of 494 dynes·sec·cm⁻⁵; the cardiac output was measured at 3.4 L/min with an index of 1.7 L/min/m². These elevated pulmonary artery pressures and resistance placed this patient at increased risk for failure of the right heart of the new cardiac graft upon weaning from cardiopulmonary bypass. Therefore, the infusions of dobutamine and milrinone were continued through this period and increased to 5 µg/kg/min and 1 µg/kg/min, respectively.

The surgery was performed uneventfully, and the new heart reperfused after a short cross-clamp time of 55 minutes. Following implantation of the new graft and weaning from cardiopulmonary bypass, the cardiac output was measured at 6.6 L/min, the systemic blood pressure was 70/45 mm Hg, and the pulmonary artery pressures gradually increased from an initially normal range of 20 to 30 mm Hg systolic pressure to 54/22 mm Hg, with a mean of 36 mm Hg and a PVR of 278 dynes·sec·cm⁻⁵. This elevation in afterload increased the work of the “naïve” new right ventricle, and it could be seen, directly in the surgical field, to dilate and begin to function poorly. Therapy with increasing amounts of intravenous dobutamine and milrinone failed to

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improve the right heart function or decrease the pulmonary hypertension.

Therefore sildenafil 100 mg was crushed into 60 cc of saline, and the slurry thus produced was administered via a syringe through the nasogastric tube. Over the next 30 minutes the pulmonary artery pressures declined to 38/19 mm Hg, with a mean of 32 mm Hg and a PVR of 154 dynes·sec·cm⁻⁵, and cardiac output increased from 6.6 L/min to 13.5 L/min. Systemic arterial blood pressure increased from 78/39 mm Hg to 91/46 mm Hg. The patient's oxygenation was maintained at 99% saturation. This improvement was sustained postoperatively in the intensive care unit, as measured by a pulmonary artery catheter, with no further administration of sildenafil required.

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Pulmonary hypertension is defined as a resting mean pulmonary arterial pressure of ≥ 25 mm Hg with a normal pulmonary capillary wedge pressure of < 15 mm Hg (1). An acute or chronic increase in pulmonary arterial pressure may lead to right ventricular dysfunction or failure. Pulmonary hypertension is the third most frequent cause of cardiac dysfunction, after coronary artery and hypertensive heart disease, in patients older than 50 years (6). The etiology of primary pulmonary hypertension is unknown. It may present acutely at birth as persistent pulmonary hypertension of the newborn or present more gradually in the adult. The causes of secondary pulmonary hypertension include parenchymal lung disease, pulmonary embolism, congestive heart failure, collagen vascular disease, congenital heart disease, AIDS, and anorexic agent use, and it is also associated with portal hypertension and liver cirrhosis (6, 7).

The pathogenesis of pulmonary hypertension includes endothelial injury in the pulmonary arterioles, vasoconstriction caused by reduced production of endogenous nitric oxide by the pulmonary endothelium, and thrombosis (1). The pathological changes seen in the pulmonary arterioles include plexogenic arteriopathy, medial and intimal hyperplasia, fibrosis, and thrombosis. Similar changes may be seen in the pulmonary venous circulation (8, 9).

Endogenous nitric oxide production is one of the most important modulators of microvascular tone and may protect against the development of pulmonary hypertension. It is produced by the action of the enzyme nitric oxide synthase on the substrate L-arginine found in the endothelium of the pulmonary microvasculature. Symptoms of pulmonary hypertension include dyspnea on exertion, chest pain, fatigue, hemoptysis, and syncope (2). However, up to 60% of patients with pulmonary hypertension may be symptom free (2). On clinical examination the following signs may be present: systemic hypertension, a loud P2 sound heard on auscultation of the chest, and a prominent right ventricular heave. The chest radiograph may reveal prominent pulmonary arteries and the electrocardiogram, a right heart strain pattern. A transthoracic echocardiogram may show right ventricular dilatation together with right ventricular systolic hypertension. The diagnosis is confirmed by right heart catheterization (10, 11).

Pulmonary hypertension is treated by administering pulmonary vasodilators. The limiting factor for most of these therapies is that they are not specific for the pulmonary vasculature but also cause systemic vasodilatation and hypotension (12). The

administration of calcium channel antagonists and the anticoagulant warfarin will prolong survival in responding patients with chronic pulmonary hypertension (13). Milrinone, a selective inhibitor of PDE type 3, is the mainstay therapy for acute elevations in pulmonary blood pressure accompanied by right ventricular dysfunction during cardiac surgery. Epoprostenol is another very potent intravenous vasodilator that inhibits platelet aggregation and smooth muscle proliferation, markedly prolongs survival, and in some cases causes vascular remodeling. However, it has to be administered as a long-term intravenous infusion (14–16). An aerosolized preparation, iloprost, a stable prostacyclin analogue, provides vasodilatation in ventilated areas of the lung, but the action lasts for only approximately 1 hour (17, 18).

Inhaled nitric oxide is undergoing clinical trials; among its advantages, it affects only the pulmonary circulation and does not cause systemic hypotension. Nitric oxide also affects only the microvasculature of ventilated alveoli (19, 20). This is an advantage in that oxygenation is improved and shunt fraction reduced.

Cardiac surgical patients who do not respond to medical therapy may be candidates for mechanical support with a right ventricular assist device. It has been observed that patients with primary pulmonary hypertension who have a patent foramen ovale have a better survival rate than patients with an intact septum. In an effort to create the more favorable condition of intra-atrial communication, the technique of atrial septostomy for congenital cardiac defects such as transposition of the great arteries has been applied to patients with severe pulmonary hypertension and right heart failure. This also has been utilized as a bridge to lung transplantation for patients with severe primary pulmonary hypertension (10).

Lung transplantation may be the only treatment available for some patients. However, the scarcity of donors limits the use of this therapy to a minority of patients. Experience with bilateral lung transplantation has demonstrated immediate and sustained reduction in PVR and recovery of right ventricular systolic function in the majority of patients (21).

The treatment of pulmonary hypertension remains very challenging because of the many different etiological factors; the range of pathophysiological changes, including vasoconstriction, vascular hyperplasia, thrombosis, and fibrosis; and the side effects of therapeutic agents that limit doses. Early observational studies on the actions of sildenafil in the management of pulmonary hypertension suggested a role for the drug in both short-term and long-term management. Sildenafil has been shown in an animal model of acute pulmonary hypertension to reduce pulmonary artery pressures in a dose-dependent manner (3). There are now several anecdotal reports of the efficacious actions of sildenafil in humans (4, 5). The addition of oral sildenafil to inhaled iloprost therapy has recently been demonstrated to prolong the action of iloprost in reducing pulmonary hypertension (22).

The vascular endothelium produces nitric oxide that rapidly diffuses into the surrounding vascular smooth muscle cells, where it binds to and activates guanylate cyclase. This results in smooth muscle relaxation. The action of cGMP is terminated by PDE, which converts cGMP to the inactive 5-GMP. Thus, PDE inhibitors such as milrinone and sildenafil should be capable of affecting vasodilatation by prolonging the action of cGMP.

At least 11 isoenzymes of PDE have now been identified in various tissues, each expressed in a tissue-dependent manner. The specificity of sildenafil for PDE type 5 has been used to produce vasodilatation in the corpus cavernosum while avoiding adverse side effects of generalized vasodilatation. Because PDE type 5 is also found in high concentrations in the lung, sildenafil should, in theory, potentiate pulmonary vasodilatation and thus may find use as a treatment for pulmonary hypertension.

The pharmacokinetics of nasogastric sildenafil administration to critically ill patients has not been studied. The information from a case report demonstrated a sildenafil plasma concentration of 7.7 ng/mL 30 minutes after administration of 25 mg via a nasogastric tube. The initial hemodynamic effect occurred within 15 minutes of administration of the sildenafil, indicating a rapid absorption in this critically ill patient (5). In healthy male volunteers, a 100-mg oral dose produced a sildenafil plasma concentration of >300 ng/mL at 30 minutes. The maximum plasma concentration of sildenafil was reached in 30 to 120 minutes (median, 60 minutes) (23). This suggests that even though absorption may occur rapidly in the critically ill patient, it may be impaired.

This case report provides further data to support many other anecdotal reports on the efficacy of sildenafil in the treatment of pulmonary hypertension in human patients, together with convincing data from animal trials (24–30).

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