

التأثير العلاجى المحتمل لعقار السيلادينافيل لمرضى فشل القلب المزمن بعد عمليات جراحة القلب

رسالة مقدمة من الصيدلانية:
رضوى أحمد محمد قرنى
بكالوريوس العلوم الصيدلانية- جامعة القاهرة (2004)

للحصول على درجة الماجستير فى العلوم الصيدلانية (صيدلة إكلينيكية)
مقدمة إلى كلية الصيدلة – جامعة عين شمس

تحت إشراف:
أ.د/ منال حامد الحمامصى
أستاذ الصيدلة الإكلينيكية و القائم بأعمال عميد كلية الصيدلة
جامعة عين شمس

أ.د/ أحمد سامى طه
أستاذ جراحة القلب و الصدر - كلية الطب
جامعة عين شمس

د/ باسمه فوزى محمد عوض
زميل مدرس رعاية مركزة- موجات فوق صوتية على القلب - كلية الطب
جامعة عين شمس

كلية الصيدلة
جامعة عين شمس

2015

Therapeutic Potential of Sildenafil in Patients with Chronic Heart Failure after Cardiac Surgery

**A Thesis for the Fulfillment of Master Degree in Pharmaceutical Sciences
(Clinical Pharmacy)
Submitted to Faculty of Pharmacy, Ain Shams University**

By the pharmacist:
Radwa Ahmed Mohamed Korany
B.Pharm.Sci, (2004) Cairo University

Supervised by:
Prof. Dr. Manal Hamed El-Hamamsy
Professor of Clinical Pharmacy and acts as Dean of Faculty of
Pharmacy,
Ain Shams University

Prof. Dr. Ahmed Samy Taha
Professor of Cardiac & Thoracic Surgery, Faculty of Medicine,
Ain Shams University

Dr. Basemah Fawzy Mohammed Awad
Fellow of cardiac & Thoracic Surgery, Faculty of Medicine,
Ain Shams University

**Faculty of Pharmacy
Ain Shams University
2015**

List of Abbreviations

2D.....	Two-Dimensional
ACCF.....	American College of Cardiology Foundation
ACE.....	Angiotensin-converting enzyme
ACEI.....	Angiotensin converting enzyme inhibitor
AHA.....	American Heart Association
ANOVA.....	Analysis of variance
ATPase.....	Adenosine triphosphatase
AV node.....	Atrioventricular node
AVR.....	Aortic valve replacement
Ca ²⁺	Calcium ion
CABG.....	Coronary Artery Bypass Grafting
CamKII.....	Calcium/calmodulin-dependent protein kinase II
c-AMP.....	Cyclic adenosine monophosphate
c-GMP.....	Cyclic guanosine monophosphate
CICU.....	Cardiac Intensive Care Unit
Cl ⁻	Chloride ion
Cmax.....	Maximum plasma concentration
CO.....	Cardiac output
CPB.....	Cardiopulmonary bypass
CYP.....	Cytochrome P450 enzyme
DIC.....	Drug Information Center
DVR.....	Double valve replacement
ECG.....	Electrocardiogram
EDV.....	End diastolic volume
EF.....	Ejection fraction
ESV.....	End systolic volume
FS.....	Fractional shortening
GC.....	Guanylatecyclase enzyme
GMP.....	Guanosine monophosphate
GTP.....	Guanosine triphosphate
Hemoglobin A1c.....	Glycated hemoglobin
HR.....	Heart rate
Hz.....	Hertz

IC50.....	Half maximal inhibitory concentration
K ⁺	Potassium ion
LA.....	Left atrium
LV.....	Left ventricle
LVFS.....	Left ventricular fractional shortening
LVIDd.....	Left ventricular internal diastolic diameter
LVIDs	Left ventricular systolic internal diameter
Mg ²⁺	Magnesium ion
MHz.....	Megahertz
MVR.....	Mitral valve replacement
Na ⁺	Sodium ion
NE.....	Norepinephrine
nmol.....	Nanomole
NO.....	Nitric oxide
NYHA.....	New York Heart Association
PDE.....	Phosphodiesterase enzyme
RA.....	Right atrium
RHD.....	Rheumatic Heart Disease
RV.....	Right ventricle
RVP	Right ventricular pressure
SV.....	Stroke volume
V _{O2}	Oxygen consumption
.	
V _{ss}	Steady state volume of distribution
WHO.....	World Health Organization
α.....	Alpha
β.....	Beta

List of Figures

<i>Figure Number</i>	<i>Figure Title</i>	<i>Page Number</i>
Figure. 1	<i>The Frank-Starling Mechanism</i>	 22
Figure. 2	<i>The Molecular Structures of Sildenafil and c-GMP</i>	 35
Figure. 3	<i>Change in New York Heart Association classes after 1, 2 and 3 months of sildenafil treatment</i>	 53
Figure. 4	<i>Change in pulmonary hypertension after 1, 2 and 3 months of sildenafil treatment</i>	 61
Figure. 5	<i>Adverse effects and mortality after 1, 2 and 3 months of sildenafil treatment</i>	 62

List of Tables

<i>Table Number</i>	<i>Table Title</i>	<i>Page Number</i>
Table. 1	<i>Types and effective orifice area of artificial mitral valves</i>	 7
Table. 2	<i>Types and effective orifice area of artificial aortic valves</i>	 9
Table. 3	<i>The New York Heart Association Functional Classification of Heart Failure Patients</i>	 31
Table. 4	<i>Isoforms of human phosphodiesterases</i>	 36
Table. 5	<i>Demographic data of the study patients</i>	 50
Table. 6	<i>Heart failure symptoms pre and post sildenafil treatment of the study patients</i>	 52
Table. 7	<i>NYHA classification pre and post sildenafil treatment of the study patients</i>	 53
Table. 8	<i>Heart failure signs pre and post sildenafil treatment of the study patients</i>	 55
Table. 9	<i>Hemodynamic parameters pre and post sildenafil treatment of the study patients</i>	 56
Table. 10	<i>Comparison of hemodynamic parameters which gives positive results with ANOVA test by the post Hoc test to identify the variable that made the significant change</i>	 57
Table. 11	<i>Echocardiographic parameters pre and post sildenafil treatment of the study patients</i>	 59
Table. 12	<i>Comparison of echocardiographic parameters which gives positive results with ANOVA test by the post Hoc test to identify the variable that made the significant change</i>	 60
Table. 13	<i>Pulmonary hypertension pre and post sildenafil treatment of the study patients</i>	 61

Abstract

Background: Previous studies have demonstrated hemodynamic and clinical benefits associated with chronic inhibition of 5-phosphodiesterase with sildenafil therapy for heart failure patients. However, its effects in refractory heart failure following cardiac surgery are unknown.

Objective: To evaluate the clinical benefits of sildenafil addition to standard therapy in patients with advanced (refractory) heart failure after cardiac surgery.

Methods: A prospective single-arm study which was conducted from September 2012 to June 2013 on 26 adult patients (mean age 44.57 ± 11.93 years, 73.1% females) with refractory heart failure after cardiac surgery despite receiving the standard anti-failure treatment. A baseline evaluation (Signs and symptoms of heart failure, NYHA class, hemodynamic and echocardiographic parameters) was performed and repeated after addition of sildenafil to the standard treatment at 1, 2 and 3 months intervals.

Results: Add-on sildenafil treatment resulted in significant increase in cardiac output (p -value 0.01), ejection fraction (p -value 0.0001) and fractional shortening (p -value 0.0001), with significant decrease in left ventricular systolic internal diameter (p -value 0.0001), end systolic volume (p -value 0.009), right ventricular pressure (p -value 0.007), and pulmonary hypertension. Consistently, there were significant improvements in signs and symptoms of heart failure, New York Heart Association (NYHA) class, with marked improvement in the patients' clinical status. There were no significant changes in heart rate, left ventricular diastolic internal diameter (LVIDd) and end diastolic volume (EDV). There were no significant adverse effects and the reported four cases of mortality (15.4%) were died due to different causes and none was associated with sildenafil therapy.

Conclusion: We demonstrated that sildenafil use improves signs and symptoms of heart failure, NYHA class, echocardiographic parameters and quality of life in patients with refractory heart failure following cardiac surgery.

Key Words: Cardiac surgery, refractory heart failure, sildenafil, clinical pharmacy.

ANATOMY AND PHYSIOLOGY OF THE HEART

Heart is a muscular pump located in the chest, between the pleural cavities (**Boulpaep, 2005**). About one-third of the heart lies to the right of the median plane of the body, and two-thirds to the left (**Mahadevan, 2004**).

I- ANATOMY OF THE HEART:

1- **Pericardium:** It is the sac which encloses the heart. It is composed of an outer layer which is inelastic and the serous pericardium. The serous pericardium consists of two layers with a fluid between them to enable the heart to glide within the pericardium. (**Mahadevan, 2004**)

2- **Wall of the heart:** It is composed of three layers;

The epicardium: is the outer layer. It is formed by the inner layer of the serous pericardium.

The myocardium: is the intermediate layer. It consists of cardiac muscles.

The endocardium: is the inner layer. It is formed of endothelium cells. (**Tortora et al., 1996**)

3- **Cardiac chambers and valves:**

3.1. Cardiac chambers:

a. *The right atrium (RA):* RA receives the superior and inferior vena cava, together with the venous drainage of the heart from the coronary sinus.

b. *The right ventricle (RV):* RV joins the RA by the tricuspid valve and joins with the pulmonary trunk through the pulmonary valve.

c. *The left atrium (LA):* Entering the wall of LA are the upper and lower pulmonary veins.

d. *The left ventricle (LV):* LV communicates with LA via the mitral valve. (**Ellis, 2006**)

3.2. Cardiac valves:

a. *The mitral valve:* Mitral valve connects LA to LV. It is composed of five components (annulus, two leaflets, commissures, chordae tendineae, papillary muscles) (**Boulpaep, 2005**).

b. *Aortic valve:* Aortic valve (semilunar valve) opens between LV and aorta. It is composed of three components (annulus, three semilunar cusps, commissures) (**Boulpaep, 2005**).

c. *The pulmonary valve.*

d. *The tricuspid valve.*

4- Blood supply and venous drainage of the heart:

The heart derives its arterial supply from the right and left coronary arteries. Most of the venous return from the heart drains into RA via coronary sinus. (Mahadevan, 2004)

II- PHYSIOLOGY OF THE HEART:

1- Cardiac function:

The overall function of the cardiovascular system is to deliver oxygen and nutrients to the tissues and carries away waste materials to be eliminated by organs such as lungs, liver and kidneys (Boulpaep, 2005).

2- Cardiac cycle:

The cardiac cycle is a term referring to all events related to the flow of blood that occurs from the beginning of one heartbeat to the beginning of the next one (Pramme et al., 2014).

Stages:

1. *Early diastole*: The heart is relaxed with passive ventricular filling. Semilunar valves (aortic and pulmonary valves) close and atrio-ventricular valves (mitral and tricuspid valves) open.
2. *Atrial systole*: The atrial contraction forces blood flow to ventricles.
End diastolic volume (EDV): Maximum amount of blood in ventricles at the end of diastole.
3. *Isovolumic ventricular contraction*: Ventricles begin to contract. Ventricular contraction pushes the atrio-ventricular valves to close. There is no change in volume.
4. *Ventricular ejection*: Ventricles are contracting, semilunar valves open and blood is ejected.
End systolic volume (ESV): Minimum amount of blood in ventricles at the end of systole.
5. *Isovolumic ventricular relaxation*: Ventricles begin to relax and blood flows back into cusps of the semilunar valves and snaps them closed. (Widmaier et al., 2006)

3- Cardiac function determinants:

Cardiac output (CO): It is the volume of blood ejected from the heart per one minute. It depends on the stroke volume and heart rate (Papaioannou et al., 2014).

Stroke volume (SV): It is the volume of blood ejected from the heart per one beat (Papaioannou et al., 2014).

*Heart rate (HR):*The frequency of cardiac cycles or beats per one minute(**Yi et al., 2014**).

Ejection fraction (EF): It is the percentage ratio of SV to EDV. Normally it averages at rest between 55%to65% (**Veldhuisen et al., 2013**).

*Fractional shortening (FS):*The percentage change in diameter from diastole to systole (**Movahed et al., 2006**).

4- The Circulatory System(Systemic and Pulmonary Circulation):

The deoxygenated blood from the superior and inferior vena cava and the coronary sinuses reaches RA. The RA is filled with deoxygenated blood, increasing pressure in the atrial chamber. When the pressure exceeds the pressure in RV, tricuspid valve opens allowing the blood to enter the RV. As the RV starts to contract the pressure increases and forces the tricuspid valve to close and the pulmonary valve to open, thereby ejecting the blood into the pulmonary arteries and lungs where the gas exchange takes place (**Boulpaep, 2005**).

The oxygenated blood from the lungs reaches the LA via the pulmonary veins, and as a result, pressure in LA builds up and when it exceeds that of the LV, the mitral valve opens, allowing the blood to enter the LV. As the LV starts to contract, the LV chamber pressure increases and forces the mitral valve to close and aortic valve to open, thus ejecting blood into the aorta, to be distributed through arteries, arterioles and capillaries to the whole body (**Thibodeau and Patton, 1996**).

5- The Conduction System:

The cardiac myocytes have a unique ability of automatic impulse generation. Normally, the electrical impulse begins in the sinoatrial node in the RA. The impulse then spreads to the rest of the right atrial walls directly, to the LA and the AV node, then propagates through the ventricular myocardium via the bundle of His and Purkinje fibers(**Quinn and Kohl, 2012**).

6- Regulation of cardiac function:

There are many factors that determine the performance of the heart:

6.1. Preload:

It is the degree of myocardial distension prior to contraction. The greater the stretch, the greater the force of contraction which will increase CO(**Pingitore et al., 2013**).

The major determinants of ventricular preload are:

- a. *Total blood volume:* When blood volume is depleted, venous return to the heart declines and EDV and preload fall. This results in decrease of SV and CO (**Sabatier et al., 2012**).
- b. *Atrial contraction:* As it augments ventricular filling and EDV (**Pingitore et al., 2013**).

6.2. Afterload (Outflow resistance):

It is the resistance against which ventricle contracts (**Struthers and MacDonald, 2004**).

The major determinants of afterload are:

- a. *Arterial pressure:* An increase in arterial pressure (induced by vasoconstriction for example) augments afterload, and reduces SV (**Pingitore et al., 2013**).
- b. *Left ventricular volume and wall thickness:* The afterload on a dilated LV of normal thickness is higher than that on a normal-sized ventricle. Conversely, the afterload of a hypertrophied ventricle is lower than of a normal chamber (**Dupont and Wilson, 2013**).

6.3. Myocardial Contractility (The Inotropic State):

The major factors affecting contractility are:

- a. *Adrenergic nerve activity:* The quantity of norepinephrine (NE) released by adrenergic nerve endings in the heart is the most important factor that acutely modifies myocardial contractility. NE acts on the β -adrenergic receptors in the myocardium increasing both force and rate of contraction.
- b. *Force-Frequency relation:* Myocardial contractility is also influenced by the rate and rhythm of cardiac contraction. The contractility of the heart is augmented by an increase in frequency of contraction.
- c. *Exogenously administered inotropic agents:* Sympathomimetic agents, cardiac glycosides, and the phosphodiesterase inhibitors; all improve the contractility and therefore may be used to stimulate ventricular performance. (**Borlaug et al., 2009**)
- d. *Myocardial depression:*

Physiologic depressants: As severe myocardial hypoxia, ischemia, and acidosis. These conditions depress myocardial contractility and left ventricular work.

Pharmacologic depressants: These include many drugs as antiarrhythmic drugs, calcium antagonists, and β -adrenergic blockers. (**Meijer et al., 2011**)

ADULT HEART DISEASES AND THEIR SURGICAL CORRECTION

I- VALVULAR HEART DISEASES:

INTRODUCTION:

Rheumatic Heart Disease (RHD):

Rheumatic fever is an inflammatory disease that occurs following a *Streptococcus pyogenes* infection, such as streptococcal pharyngitis. (*Henningham et al., 2012*).

Pathophysiology: Group A streptococcus pyogenes has a cell wall contains M protein that is highly antigenic. The antibodies which the immune system generates against M protein may cross react with myocardium and joints causing tissue destruction (*Henningham et al., 2012*).

In acute rheumatic fever: The inflammation may cause a serofibrinous pericardial exudate which usually resolves without sequelae. However, Involvement of the endocardium results in fibrinoid necrosis and verrucae formation in the left-sided heart valves (*Guzman-Cottrill et al., 2004*).

In chronic RHD: It is characterized by repeated inflammation. The anatomic changes of the valve can result in valvular damage and abnormalities in function (*Marijon et al., 2012*).

A. MITRAL VALVE DISEASES:

1- Mitral Stenosis: It is a condition of pathological narrowing of mitral valve (*Devi, 2008*).

Etiology: Mitral stenosis usually results from RHD (*Devi, 2008*).

Pathophysiology and consequences:

Rheumatic mitral stenosis develops slowly after initial RHD which may progress to valvular fibrosis (*Kirklin and Barratt-Boyes, 2013*), this causes a backflow to the LA and subsequent rise in LA pressure and LA enlargement. The raised LA pressure is transmitted back to pulmonary veins, thus increasing pressure in pulmonary capillaries, fluid transudate into interstitial space causing pulmonary edema and pulmonary venous congestion. The rise in pulmonary venous pressure leads to constriction of pulmonary arterioles causing elevated pulmonary vascular resistance and pulmonary arterial hypertension. (*Devi, 2008*)

Atrial fibrillation usually develops and becomes persistent due to disintegration of the architecture of the atrial muscle (**Kirklin and Barratt-Boyes, 2013**).

Clinical features: Patients complaint from dyspnea, peripheral coldness, cyanosis, hepatic enlargement, and sometimes ascites and peripheral edema (**Devi, 2008**).

2- Mitral Regurgitation: It is the systolic retrograde flow of blood from the LV into the LA due to impairment of coaptation between the leaflets of the mitral valve (**Pedrazzini et al., 2011**).

Etiology: Mitral regurgitation may be due to numerous causes as:

- a. *Rheumatic mitral regurgitation:* Mitral regurgitation occurs due to anular dilatation during the acute rheumatic process (**Kirklin and Barratt-Boyes, 2013**).
- b. *Mitral valve prolapse:* It is a billowing of leaflets into LA during ventricular systole. Familial prolapse is inherited as an autosomal trait (**Kirklin and Barratt-Boyes, 2013**).
- c. *Ischemic papillary muscle dysfunction or rupture (ischemic mitral regurgitation):*
It is a mitral regurgitation caused by ischemic heart disease (**Kirklin and Barratt-Boyes, 2013**). Types:
 - i. *Acute mitral regurgitation complicating myocardial infarction:* Rupture of papillary muscle as an acute complication of myocardial infarction results in failing mitral leaflets (**Eagle et al., 2004**).
 - ii. *Chronic mitral regurgitation from ischemic heart disease:* Papillary muscle ischemic dysfunction and scarring, and LV remodeling, all of which can result from an earlier myocardial infarction (**Jacob et al., 2011**).
- d. *Infective endocarditis:* It is an endovascular infection of cardiovascular structures (primarily the valves) caused by bacteria. It can cause mitral regurgitation through chordal rupture or leaflet perforation (**Pedrazzini et al., 2011**).

Pathophysiology and consequences:

The compensated phase:

The volume overload causes LA enlargement and the filling pressure in the LA to decrease. This improves the drainage from pulmonary veins, and symptoms of pulmonary congestion will decrease. The LV develops hypertrophy to better manage the decreased SV and

CO. So, patients are often asymptomatic for many years, during which time left ventricular size may steadily increase and left ventricular contractility decrease (**Kliger and Ruiz, 2012**).

The decompensated phase:

Ventricular myocardium begins to dilate and is no longer able to contract, leading to decreased SV and CO and increased ESV. The increased ESV translates to increased filling pressures of the LV and increased pulmonary venous congestion. Secondary tricuspid regurgitation (and subsequent enlarged RA) is usually evident (**Lancellotti et al., 2010**).

Clinical features: Symptoms of pulmonary venous hypertension (dyspnea, orthopnea, paroxysmal nocturnal dyspnea, pulmonary edema) and fluid retention (**Lancellotti et al., 2010**).

3- Surgical Management:

a. Mitral Valve Repair:

Technique: The technique includes inserting a cloth-covered ring around the valve to bring the leaflets into contact with each other (**Kirklin and Barratt-Boyes, 2013**).

Outcomes: Early and long-term results have been good, but a recurrent mitral regurgitation may occur due to either progression of RHD or inadequate operation. Also, regression of LV hypertrophy may occur with decreased heart size and muscle mass (**Yamano et al., 2009**).

b. Mitral Valve Replacement:

Technique: Mitral valve is replaced by artificial valve which may be of either two types:

1. *Mechanical valves:* which are made from metal and pyrolytic carbon, and can last a lifetime. Patients must take blood-thinning medications to prevent clotting.
2. *Bioprosthetic (biological) valves:* which are made from animal tissues. Patients can avoid blood thinners. It only lasts 10 to 15 years. (**Rajbanshi et al., 2014**)

Table 1: Types and effective orifice area of artificial mitral valves: (Yoganathan et al., 1997)

<i>Prosthesis</i>	<i>Type</i>	<i>Effective orifice area at rest (cm²)</i>	<i>Effective orifice area at exercise (cm²)</i>
1-Starr-Edwards 6120	25mm device	1.6	1.6
	27 mm device	1.7	2.2
2- St.Jude Medical	25mm device	2.1	2.3
	27 mm device	2.3	3.6
3-Bjork-Shiely Monostrut	25mm device	2.3	

27 mm device	1.8
31 mm device	2.5

Note: The normal effective orifice area at rest equals 4 – 6 cm², and the desired postoperative value must be greater than 1.5 cm² (*Kirklin and Barratt-Boyes, 2013*).

Outcomes:

Generally, symptoms are reduced in most patients. However, in patients who had severe LV hypertrophy preoperatively, LV size is reduced in early postoperative period but increases late postoperatively. LV wall hypertrophy does not regress (*Otto, 2001*). In such patients, the preoperative LV structure and contractile abnormalities progress and account for recurrence of symptoms 2 to 5 years postoperatively (*Kirklin and Barratt-Boyes, 2013*). LV dysfunction can lead to hypo-perfusion of the RV and right ventricular failure (*Itagaki et al., 2012*).

Also, most prostheses result in an orifice area smaller than the natural valve. In some cases, this leads to an unacceptably high pressure gradient across the valve, valve deterioration, extra heart work and reduced survival (*Abu-Omar and Ratnatunga, 2008*).

B. AORTIC VALVEDISEASES:

1- Aortic Stenosis: It is the narrowing of the aortic valve with consequent increase in valvestiffness and progressive reductions in valve area (*Zigelman and Edelstein, 2009*).

Etiology:

- a. *Rheumatic aortic stenosis:* It is almost always accompanied by mitral valve involvement. It is characterized by fibrous cusp thickening.
- b. *Degenerative aortic stenosis:* It is often present in elderly patients. The cusps are held by deposits of diffuse calcification. (*Zigelman and Edelstein, 2009*)

Pathophysiology and consequences:

In early stages:

When the aortic valve becomes stenosed, the blood can't be pumped adequately and the pressure in LV increases. LV compensates by thickening its walls to maintain adequate pumping (*Morris et al., 2009*). So, patients are asymptomatic for many years (*Linefsky and Otto, 2014*).

In later stages: