International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

*Original Research Article.*

# Cardiopulmonary Efficacy of a Single Dose of Sildenafil in Patients with Chronic Heart Failure

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## ABSTRACT

**Back Ground:** Chronic Heart Failure is Associated with secondary hypertension, impaired vascular reactivity and permeability and reduced alveolar capillary membrane conduction. Sildenafil is a potent and selective inhibitor of cGMP phosphodiestrase 5 which is responsible for degradation of cGMP, Stabilisation of cGMP result in increasing NO at the tissue level leading to pulmonary vessel vasodilatation.

**Methods:** This study was conducted in Benha University Hospital, it included 30 patients with chronic heart failure, they were divided into two groups, Group (1) was the control group consisted of 15 patients and received the standard therapy, Group (2) was the active group consisted of 15 patients received single dose of Sildenafil 50 mg in addition to standard therapy.

**Results:** In current Study the mean pulmonary artery systolic pressure (PASP) before giving Sildenafil was 58.4 mmhg and after two hours of use Sildenafil it became 51.7 mmhg. Also Sildenafil caused significant improvement of peak minute ventilation (VE), peak oxygen uptake (VO2), peak carbon dioxide output (VCO2).

**Conclusion:** So Sildenafil is Safe in Stable congestive heart failure as it reduces pulmonary hypertension, improve exercise performance, ventilatory efficiency and oxygen uptake kinetics.

**Keywords:** Sildenafil, Heart Failure, Pulmonary Hypertension, Oxygen Uptake.

**Abbreviations**

Pulmonary Artery Systolic Pressure (PASP); Peak Minute Ventilation (VE); Peak Oxygen Uptake (VO2); Peak Carbon Dioxide Output (VCO2); Congestive Heart Failure (CHF); Cardiac Output (cop).

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**Article History:**

**Received:** 04-01-2019, **Revised:** 03-02-2019, **Accepted:** 26-02-2019

| Access this article online | |
|---|---|
| Website: www.ijmrp.com | Quick Response code |
| DOI: 10.21276/ijmrp.2019.5.2.002 | |

## INTRODUCTION

Despite multiple pharmacological and non-pharmacological strategies for management of chronic heart failure most patient will experience some limitation of their exercise capacity.[1]

Multiple Mechanisms seem to interfere with exercise performance in CHF including central and peripheral vascular components. In particular pulmonary hypertension as an important predictor of fuctional disability.

Inhibition of 5 phosphodiestrase by Sildenafil has proven to be beneficial in different Scenarios where endothelial function and vascular tone can be positively influenced.[2]

Similarly, acute administration of Sildenafil has been shown to improve parameters of endothelial, pulmonary, and cardiac function in patients with CHF.[3]

## AIM OF THE STUDY

The aim of the present study is to investigate whether a single oral dose 50 mg of Sildenafil could improve exercise performance, ventilatory efficiency, oxygen uptake kinetics, pulmonary hypertension after two hours in outpatients with stable CHF.

## PATIENTS AND METHODS

This study was conducted at Benha Univercity Hospital during the period from October 2008 till May 2009. It Included 30 patients who had CHF and received Standard medical therapy. These patients were divided into two groups.

**Group (1):** included 15 patients who received only the standard therapy.

**Group (2):** included 15 patients who received a single oral dose of Sildenafil 50 mg in addition to the standard therapy.

**Inclusion Criteria**

1. Patients had chronic Left ventricular systolic dysfunction (LVEF 30% - 50%) and received the standard therapy.
2. All included patients were more than 20 years and clinically stable for at least 2 months and able to perform exercise.

**Exclusion Criteria**

1. Systolic arterial pressure less than 90 mmhg.
2. Concomitant use of Nitrates.
3. History of intolerance to Sildenafil.
4. Patients with Advanced Disease (NYHA class 4).

All included patients undergone careful history taking, physical examination and Transthoracic Echocardiography with measurement of PASP and Right Atrial Pressure.

**Table 1: Demographic baseline and clinic characters**

| | | No. | % |
|---|---|---|---|
| **Age** | **>60y** | 11 | 36% |
| | **<60y** | 19 | 64% |
| **Sex** | **Male** | 20 | 66% |
| | **Female** | 10 | 33% |
| **HTN** | **Yes** | 13 | 43% |
| | **No** | 17 | 57% |
| **DM** | **Yes** | 17 | 56% |
| | **No** | 13 | 44% |
| **Smoking** | **Yes** | 17 | 56% |
| | **No** | 13 | 44% |

**Table 2: Aetiology of heart failure of studied patients**

| Aetiology | No. | % |
|---|---|---|
| **Ischemic** | **14** | **46%** |
| **HTN** | **9** | **30%** |
| **Valvular** | **3** | **10%** |
| **Other** | **4** | **13%** |

**Table 3: ECG rhythm of studied patients**

| | Group II | | Group I | |
|---|---|---|---|---|
| | **No** | **%** | **No** | **%** |
| **Sinus rhythm** | **11** | **73%** | **13** | **38%** |
| **AF** | **2** | **13%** | **4** | **26%** |

**Table 4: Baseline characters of Group I**

| | | No | % |
|---|---|---|---|
| **Age** | **>60y** | **6** | **40%** |
| | **<60y** | **9** | **60%** |
| **sex** | **Male** | **10** | **66%** |
| | **Female** | **15** | **44%** |
| **HTN** | **Yes** | **8** | **53%** |
| | **No** | **7** | **47%** |
| **DM** | **Yes** | **8** | **53%** |
| | **No** | **7** | **47%** |
| **Smoking** | **Yes** | **8** | **53%** |
| | **No** | **7** | **47%** |

**Table 5: Baseline characters of Group II**

| | | No | % |
|---|---|---|---|
| **Age** | **>60y** | 5 | 33% |
| | **<60y** | 10 | 77% |
| **sex** | **Male** | 10 | 66% |
| | **Female** | 5 | 44% |
| **HTN** | **Yes** | 5 | 33% |
| | **No** | 10 | 77% |
| **DM** | **Yes** | 9 | 60% |
| | **No** | 6 | 40% |
| **Smoking** | **Yes** | 9 | 60% |
| | **No** | 6 | 40% |

**Table 6: Comparison between Group I Group II**

| | GROL PS | | | | | |
|---|---|---|---|---|---|---|
| **Variable** | **Group I** | | **Group II** | | **T** | **p** |
| | **Mean** | **Sd** | **Mean** | **sd** | | |
| **Age** | 58.60 | 7.09 | 58.93 | 8.67 | 0.1 | >0.05 |
| **SPB** | 133.27 | 16.08 | 130.6 | 21. 86 | 0.3 | >0.05 |
| **HR** | 78.40 | 9.46 | 78.80 | 13.19 | 0.2 | >0.05 |
| **LVEF** | 37.60 | 4.54 | 37.46 | 6.27 | 0.1 | >0.05 |
| **LVDD** | 73.06 | 8.82 | 72.53 | 12.14 | 0.2 | >0.05 |

**Table 7: Functional class of studied patients**

| Functional class | All patients | Group I | Group II | P |
|---|---|---|---|---|
| **NYHA1_11** | 27 | 13 | 14 | >0.05 |
| **NYHA 111** | 3 | 2 | 1 | >0.05 |

**Table 8: Medications Used by studied patients**

| Functional class | All patients | Group I | Group II |
|---|---|---|---|
| **Diuretics** | 30 | 15 | 15 |
| **Beta_blockers** | 27 | 13 | 14 |
| **ACE_inhibitor** | 30 | 15 | 15 |
| **Digoxin** | 25 | 10 | 15 |

**Table 9: Comparison between Group I Group & II after two hours**

| | GROL PS | | | | | |
|---|---|---|---|---|---|---|
| **Variable** | **Group I** | | **Group II** | | **T** | **p** |
| | **Mean** | **Sd** | **Mean** | **sd** | | |
| **SPB** | 128.47 | 16.44 | 125.2 | 21.86 | 0.65 | >0.05 |
| **HR** | 77 | 8.22 | 84.76 | 10.79 | 0.37 | >0.05 |
| **LVEF** | 37.60 | 4.54 | 39.66 | 7.62 | 0.1 | >0.05 |

**Table 10: Comparison between Group I & Group II as regard to PASP**

| | GROL PS | | | | | |
|---|---|---|---|---|---|---|
| **Variable** | **Group I** | | **Group II** | | **t** | **p** |
| | **Mean** | **Sd** | **Mean** | **sd** | | |
| **PASP before** | 58.80 | 9.90 | 58.40 | 10.62 | 0.1 | >0.05 |
| **PASP after 2 hours** | 58.20 | 9.960 | 51.70 | 8.50 | 2.01 | <0.05 |

**Table 11: Comparison between Group I Group & II baseline Maximal cardiopulmonary exercise test parameters**

| | GROL PS | | | | | |
|---|---|---|---|---|---|---|
| **Variables** | **Group I n= 15** | | **Group II n= 15** | | **T** | **P** |
| | **Mean** | **SD** | **Mean** | **SD** | | |
| **VE peak, L/ min** | 49.40 | 8.09 | 49.93 | 8.17 | 0.8 | >0.05 |
| **Vo2 peak, ml/kg/min** | 19.47 | 3.44 | 19.20 | 4.16 | 0.2 | >0.05 |
| **Vco2 peak, L/min** | 19.80 | 3.49 | 17.53 | 2.29 | 2.1 | <0.05 |
| **VE/voc2 slope** | 45.15 | 4.11 | 39.85 | 5.30 | 3.6 | <0.05 |
| **T $^{1/2}$ VE (min)** | 2.51 | 0.64 | 2.19 | 0.34 | 1.7 | >0.05 |
| **T $^{1/2}$ Vo2 (min)** | 2.57 | 0.52 | 2.01 | 0.33 | 3.5 | <0.05 |
| **T $^{1/2}$ Vco2 (min)** | 2.45 | 0.73 | 2.02 | 0.29 | 2.3 | <0.05 |

**Table 12: Comparison between Group & I Group II Maximal cardiopulmonary exercise test parameters after 2 hours**

| | GROL PS | | | | | |
|---|---|---|---|---|---|---|
| **Variables** | **Group I n= 15** | | **Group II n= 15** | | **T** | **P** |
| | **Mean** | **SD** | **Mean** | **SD** | | |
| **VE peak, L/ min** | 50.10 | 8.24 | 51.53 | 8.08 | 2.2 | <0.05 |
| **Vo2 peak, ml/kg/min** | 20.00 | 3.39 | 20.87 | 2.24 | 2.4 | <0.05 |
| **Vco2 peak, L/min** | 19.87 | 3.20 | 16.2 | 2.73 | 2.1 | <0.05 |
| **VE/voc2 slope** | 45.79 | 3.79 | 36.48 | 2.73 | 5.5 | <0.05 |
| **T $^{1/2}$ VE (min)** | 2.47 | 0.55 | 1.99 | 0.27 | 1.1 | >0.05 |
| **T $^{1/2}$ Vo2 (min)** | 2.63 | 0.55 | 1.87 | 0.31 | 3.7 | <0.05 |
| **T $^{1/2}$ Vco2 (min)** | 2.44 | 0.74 | 1.82 | 0.28 | 2.1 | <0.05 |

**Table 13: Comparison between Group II before and after two hours**

| | GROL PS | | | | | |
|---|---|---|---|---|---|---|
| **Variables** | **Group I n= 15** | | **Group II n= 15** | | **T** | **P** |
| | **Mean** | **SD** | **Mean** | **SD** | | |
| **VE peak, L/ min** | 49.93 | 8.17 | 51.53 | 8.08 | 2.14 | <0.05 |
| **Vo2 peak, ml/kg/min** | 19.2 | 4.16 | 20.87 | 4.24 | 2.1 | <0.05 |
| **Vco2 peak, L/min** | 17.53 | 2.29 | 16.2 | 2.73 | 2.1 | <0.05 |
| **VE/voc2 slope** | 39.85 | 5.30 | 36.48 | 3.24 | 2.1 | <0.05 |
| **T $^{1/2}$ VE (min)** | 2.19 | 0.34 | 1.99 | 0.27 | 2.1 | <0.05 |
| **T $^{1/2}$ Vo2 (min)** | 2.0 | 0.33 | 1.87 | 0.31 | 2.14 | <0.05 |
| **T $^{1/2}$ Vco2 (min)** | 2.0 | 0.29 | 1.82 | 0.28 | 2.1 | <0.05 |

## RESULTS AND DISCUSSION

It is clear that nitric oxide (NO) secretion by pulmonary arterial and venous endothelium plays an important role in lung physiology.[4]

At the lung level, congestive heart failure (CHF) is typically associated with secondary hypertension, impaired vascular reactivity and permeability and reduced alveolar capillary membrane conductance.[5]

Sildenafil is specific inhibitor for phosphodiestrase 5 that increases Nitric Oxide availability and NO mediated vasodilatation in CHF Patients.[3]

In a heamodynamically invasive acute study, Lepore and coworkers showed that, Sildenafil alone, inhaled NO, and combination of both produced positive and synergistic effect in terms of reducing pulmonary artery systolic pressure (PASP) and increasing cardiac output (COP) in patients with CHF dependent pulmonary hypertension.[6]

Also Sildenafil was found to restore NO availability by promoting cyclic guanosine monophosphate accumulation via inhibition of phosphodiestrase activity.[7]

Recently demonstrated in an elegantly Last, Lewis and colleages designed study that acute use of Sildenafil improves exercise capacity and haemodynamics in patients with CHF. Possibly through a reduction in right ventricular afterload, secondary to reduced pulmonary artery pressure values.[8] Patients with CHF peculiarly exhibit an abnormal ventilatory response to exercise characterized by a steep VE/ VCO2 slope, the increase in this slope may be multifactorial through increase of the ventilation required to overcome a large dead space, augmented central drive to ventilation originating from J receptors activation in consequence of the interstitial space distension, bicarbonate buffering of accumulating lactic acid, reduced perfusion of ventilating lung, abnormal chemosensitivity, overactive ergoreceptors, and abnormal autonomic and baroreceptor control of the circulation.[9]

A better exercising muscle perfusion may also explain well the benefits of Sildenafil on Peak VO2.[10]

## SUMMARY & CONCLUSION

Sildenafil is Safe and beneficial in patients with stable Chronic Heart Failure in terms of reducing pulmonary hypertension, improve exercise performance, ventilatory efficiency, and oxygen uptake kinetics.

## ACKNOWLEDGMENTS

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**Source of Support:** Nil.

**Conflict of Interest:** None Declared.



**Cite this article as:** Osama Saad Arafa, Hesham Mohamed Abo Elenein, Neima Ali El Melegy, Hesham Drwesh, Ahmed Mohamed El Saied. Cardiopulmonary Efficacy of a Single Dose of Sildenafil in Patients with Chronic Heart Failure. Int J Med Res Prof. 2019 Mar; 5(2):6-9. DOI:10.21276/ijmrp.2019.5.2.002