SILDENAFIL CITRATE FOR THE TREATMENT OF PATIENTS WITH CARDIOVASCULAR DISEASES WITH EXCLUSION OF CORONARY ARTERY DISEASE AND HYPERTROPHIC SUBAORTIC STENOSIS. ITS BENEFICIAL EFFECT ON PATIENTS CHRONIC CHAGAS´S AND DIABETIC CARDIONEUROMYOPATHIES, HYPERTENSIVE AND HYPERTROPHIC CARDIOMYOPATHIES, WITH OR WITHOUT CHRONIC CONGESTIVE HEART FAILURE *

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ABSTRACT

Sildenafil citrate is a potent donor of nitric oxide that has been proved to be effective for the treatment of male erectil dysfunction, but it has been contraindicated in patients with cardiovascular diseases, because of sudden death occured to some of them. Based on the known vasodilator effect of nitrix oxide, effect that should be beneficial for some cardiomyopathies, this work was carried out in order to prove the cardiovascular effects of sildenafil citrate on : 1) heart rate, rhythm and repolarization changes on the ecg; 2) systolic and diastolic arterial blood pressure; 3) left ventricular systolic function and 4) right and left ventricular diastolic function in 26 patients suffering from the following cardiomyopathies: chronic Chagas's and diabetic cardioneuromyopathies, hypertensive and/or hypertrophic cardiomyopathies with or without chronic congestive heart failure .Results:sildenafil citrate 50 mgr after a single oral dose : 1) improved the ecg findings in some patients, worsening the basal ecg in none of the studied patients; 2) significantly reduced systolic and diastolic arterial blood pressure being such reduction very strong in those with basal high level 3) significantly improved left ventricular systolic function in those patients with basal reduced function and 4) Right ventricular diastolic function evaluation: Sildenafil citrate 50 mgr significantly modified to normal pattern the E/A basal altered ratio in those patients with the inverted pattern as well as in those with restrictive pattern of tricupid diastolic influx to the right ventricle during the echo-duplex interrogation (p< o.oool ,) 5) Left ventricular diastolic function evaluation:Sildenafil citrate 50 mgr significantly modified to normal pattern the E/A basal altered ratio in those patients with the inverted pattern as well as in those with restrictive pattern of mitral diastolic influx to the left ventricle,during the echo-duplex interrogation (p 0<.0001)

.Conclusions:based on the above findings it is feasible to propose the use of sildenafil citrate to treat patients with cardiovascular diseases, with exclussion of severe obstructive coronary artery disease, hypertrophic subaortic stenosis and patients with funduscopic alterations that may be affected by a significant and acute increase of flow within the ophthalmic arteries. The rigfht ventricular diastolic changes observed with Sildenafil Citrate may be usefull in patients with abnormal right ventricular compliance such as pulmonary stenosis or hypertension.

RESUMEN

El citrato de sildenafil es un potente dador de óxido nítrico que ha sido efectivo para el tratamiento de la disfunción eréctil pero ha sido contraindicado en pacientes con enfermedades cardiovasculares debido a la ocurrencia de muerte súbita en algunos sujetos con cardiopatías que habían utilizado la mencionada droga. Basado en los efectos vasodilatadores del óxido nítrico que podría ser beneficioso en determinadas cardiomiopatías, este trabajo se realizó para comprobar los efectos cardiovasculares del citrato de sildenafil en: 1) frecuencia cardíaca, ritmo y trastornos de la repolarización ventricular al electrocardiograma; 2) presión arterial sistólica y diastólica; 3) función sistólica ventricular izquierda y 4) función diastólica ventricular derecha e izquierda en 26 pacientes portadores de las siguientes cardiomiopatias: cardioneuromiopatía de origen chagásica y diabética, cardiomiopatía hipertensiva e hipertrófica con o sin insuficiencia cardíaca congestiva. El citrato de sildenafil 50 mgr. después de una dosis unica oral: 1) mejoró los hallazgos electrocardiográficos en algunos pacientes, sin peoría en ninguno de los pacientes estudiados; 2) redujo significativamente la presión arterial sistólica y diastólica, siendo dicha reducción más intensa en los que presentaban valores altos de presion arterial basal; 3) mejoró significativamente la función sistólica ventricular izquierda en aquellos pacientes con función sistólica basal deprimida; 4) normalizó en forma significativa la función diastólica ventricular derecha e izquierda en los pacientes que presentaban en el registro basal del doppler una relación E/A invertida o de tipo restrictiva a la interrogación duplex color de las válvulas tricúspide y mitral, respectivamente. Conclusiones: basado en los hallazgos arriba mencionados es posible proponer el uso del citrato de sildenafil para el tratamiento de enfermedades cardiovasculares con exclusión de las obstrucciones coronarias, de la cardiomiopatía hipertrófica obstructiva o estenosis muscular subaórtica y de pacientes con alteraciones en el fondo de ojo que pueden ser afectados por un significativo aumento del flujo vascular de la arteria oftálmica. Los hallazgos sobre la función diastólica ventricular derecha pueden ser útiles en pacientes con alteraciones de la complacencia ventricular derecha como la estenosis pulmonar o la hipertensión pulmonar.

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INTRODUCTION:

Sildenafil citrate has been proved to be effective for the treatment of erectil dysfunction.

It was used in male patients with erectil dysfunction from 19 to 87 years old, with excellent results againts placebo, with a rate of success of 70 to 90%, in different ethiologies - organic, psycological or combined dysfunction - (1)

Erectil dysfunction is widely spread around the world and affect more than 100 millons males. The National Institute of Health has reported that the above mentioned dysfunction affects more than 30 millons males in the USA alone (2)

It is well known that erectil dysfunction is frequently associated with cardiovascular diseases, such as Chagas´s and diabetic cardioneuromyopathies — because of microvascular and autonomic nervous system dysfunction —, and with hypertensive and hypertrophic cardiomyopathies, with or without chronic congestive heart failure, because of the negative effects, over the erectil function, of the drugs used for the treatment of these pathologies, as well as, for its own microvascular alterations. (3-9)

In the Massachusetts Male Aging Study it was found a strong and significant correlation between erectil

dysfunction and three treated medical conditions: cardiovascular diseases, hypertension and diabetes.(9)

Sildenafil citrate was produced and patent by Pfizer Inc USA, with a special warning for its use in patients with cardiovascular diseases and reported the following cardiovascular adverse reactions: angina pectoris, av block, migraña, sincope, tachicardia, palpitations, postural hypotension, myocardial ischemia, cerebral thrombosis, heart arrest, heart failure, abnormal ecg and cardiomyopathies. (10).

After the release of the drug, it was reported a number of acute myocardial infarction, serious eyes damages, and sudden death among others cardiovascular adverse reactions (11, 12), it was clear that patients with a strong need of using the drug were almost excluded or prevented from doing it.

Based on the necessity of knowing the real effects of sildenafil citrate on patients with cardiovascular diseases, this study was conducted in order to evaluate four well accepted parameters of cardiovascular function and dysfunction before and after 60 minutes of a single oral dose of sildenafil citrate 50 mgr.

Those parameters were: 1) heart rate, rhythm and repolarization changes on the ecg.; 2) systolic and diastolic arterial blood pressure meassured with a calibrated sphyngomanometer; 3) left ventricular systolic function and 4) right and left ventricular diastolic function by a complete color echo-duplex evaluation, accordingly to the recommendations of the American Society of Echocardiography, and the Canadian Consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography. (13-15)

MATERIAL AND METHODS

26 patients were studied , mean aye 58.9 + 1.5 years old, 21 males and 5 females. Males patients suffered cardiovascular diseases such us Chagas' and NID diabetes cardioneuromyopathy, hypertensive and/or hypertrophic cardiomyopathy with or without different degrees of heart failure from group I to III of the New York Heart Association Clasification (16) and concomitant moderate to severe erectil dysfunction accordingly to the International Index of Erectil Function and the National Institute of Health Consensus on Impotence.

Female patients suffered from Chagas' disease, hypertension with or without congestive heart failure as mentioned above and one of them with concomitant NID diabetic.

All patients were instructed about the drug to be used, were prohibited from taking nitrates or alcohol 24 hs before the test and signed informed consent following the principles of the declaration of Helsinki. All patients under cardiovascular medications, such as diuretics, cardiotonic, beta blockers, enzime converting inhibitors, calcium blocking agents, mexiletin or amiodarone ramained in their usual dosage up to the test' day breakfast. All tests were carried out around 1 to 3 pm without previous meals in the last 6 hours. Routine serum and urine chemistry profile and a complete blood count were obtained prior to the drug administration. The day of the tests, a complete physical examination, including systolic and diastolic arterial blood pressure meassurement, with a calibrated sphygmomanometer, - accordingly to the W.H.O. criteria -, and bilateral fundoscopy were carried out in all patients. (18) Thereafter, a Tele x ray, ECG of 12 leads with rythm control in lead DII, and a complete color echo-duplex systolic and diastolic fuction evaluation was performed, before receiving a single oral dose of sildenafil citrate 50 mgr.

Sixty minutes later, all patients went through the same procedure with exception made of the laboratory and Tele x ray.

INCLUSION-EXCLUSION CRITERIA:

In order to participate in the study, patients had to be between 35 and 80 years old inclusive. All males had to suffer erectil dysfunction and all patients had to suffer a cardiovascular disease in wich a vasodilator effects of a drug would have beneficial effects on their pathologies. Patients were excluded if they:

1) have any evidence of acute tripanozoma cruzi infection as demonstrated by Romagña' sign, a chagoma and or evidence of t. cruzi parasitemia in the blood smear.

2) have used any experimental theraphies within 30 days of the study.

3) have evidence of other systemic illness that might interfere with data interpretation, such as malignancy or renal failure.

4) were pregnant or lactating.

5) were suffering a decompensation of diabetic or have an abnormal fundoscopy such as retinal edema, microaneurism or hemorrage.

6) have history of alcohol or drug abuse.

7) have evidence of primary valvular disease or hypertrophic subaortic stenosis.

8) have a history of acute or chronic coronary artery disease .

9) have a history of acute or chronic myocardial infarction and / or active ischemia.

Cardiovascular parameters were analized tacking into account that each patient was its own control, before and after a single oral dose of sildenafil citrate 50 mgr. The non-parametric Wilcoxon signed rank test for paired observations was used for the statistical analysis of the data . In all cases it was studied the nule hypotesis – :there is no difference- ,-against the oposite :- there is difference- , two tailed and a p less than 0.05 was considered to be significant.

RESULTS:

ECG PARAMETERS:

1) Sildenafil citrate 50 mgr had no significant effect on the heart rate, except in 4 patients with Chagas'disease and sick sinus syndrome with severe bradyarrhythmia, in which after 60 minutes of a single oral dose, the heart rate became normal.

2) Sildenafil citrate 50 mgr had an acute and unexpected effect on two patients with Chagas'disease and a basal ECG findings of sick sinus syndrome, one with second degree av block type 11: after 60 minutes both patients had normal sinus rhythm.

3) Sildenafil citrate 50 mgr reduced or turned to normal the basal presence of arrhythmias such as ventricular premature beats or supraventricular premature beats as well as repolarization changes in some patients.

4) Sildenafil citrate 50 mg did not induce a worsening of the basal ecg findings in the studied patients.

ARTERIAL BLOOD PRESSURE MEASUREMENTS:

1) Sildenafil citrate 50 mgr significantly reduced systolic and diastolic arterial blood pressure ($p< 0.001$ and $p< 0.001$ respectively)

2) The above mentioned reduction was more strong in those patients with basal high level of arterial blood pressure , but very mild in those with normal values.

LEFT VENTRICULAR SYSTOLIC FUNCTION EVALUATION:

1) Sildenafil citrate 50 mgr significantly improved left ventricular ejection fraction meassured by the bidimensional echocardiographic teichholtz -formula. ($p< 0.001$)

2) The above mentioned improvement was specially higher in those with basal depressed ejection fraction.

3) Sildenafil citrate 50 mgr significantly improved left ventricular fraction shortening ($p< 0.001$) specially in those patients with basal depressed function.

RIGHT VENTRICULAR DIASTOLIC FUNCTION EVALUATION:

1) Sildenafil citrate 50 mgr significantly modified to normal pattern the E/A basal altered ratio in those patients with the inverted pattern as well

as in those with restrictive pattern of tricupid diastolic influx to the right ventricle during the echo-duplex interrogation (p< o.oool ,) (Fig 1)

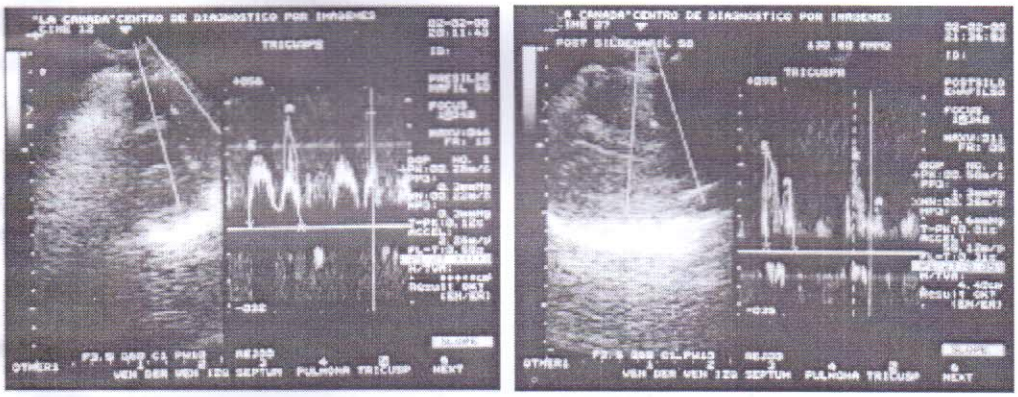

Figure 1: a typical inverted tricuspid pattern before sildenafil citrate (left pannel) turned to normal after 60 minutes of a single oral dose (right pannel).

LEFT VENTRICULAR DIASTOLIC FUNCTION EVALUATION:

1) Sildenafil citrate 50 mgr significantly modified to normal pattern the E/A basal altered ratio in those patients with the inverted pattern as well as in those with restrictive pattern of mitral diastolic influx to the left ventricle,during the echo-duplex interrogation (p 0<.0001) (Fig 2)

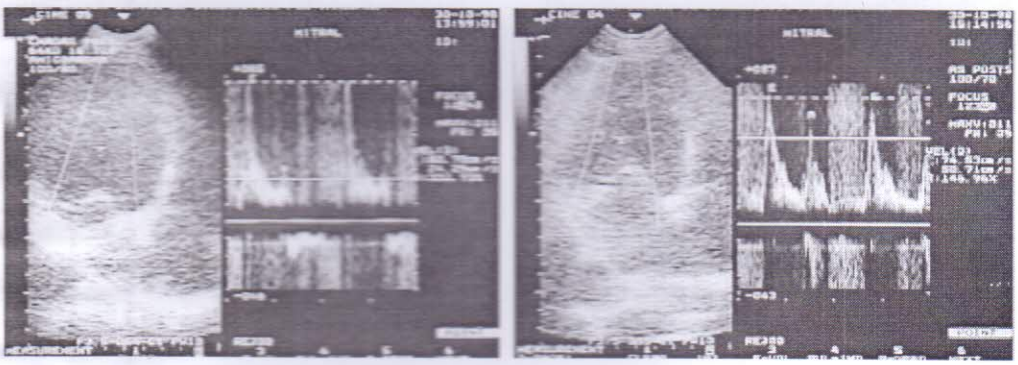

Figure 2: a typical restricted mitral pattern before sildenail citrate (left pannel) turned to normal after 60 minutes of a single oral dose (right pannel).

All male patients recovered their sexual erectil function with the chronic use of sildenafil citrate 50 mgr, except one that had to increase the dose to 100 mgr to get the beneficial effect on his erectil dysfunction. Females patients were not evaluated in relation to sexual function or dysfunction.

Only one male patient , wich fundoscopy was normal previous to the administration of sildefil citrate , refered vision of blue color after a single oral dose of the drug ,phenomeno that the patient never experience before. A retinofluoresceinography was normal in both eyes .The ophthalmic artery was studied by color echo-duplex evaluation : it was found a significant reduction of the pick systolic flow in the right compared to the left one (0.19 m/s vs 0.36 m/s) , that increased almost to equal the normal left artery after 60 minutes of a single dose of sildenafil citrate 50 mgr.(0.36 vs 0.45 m/s ;after 170 minutes the right pick systolic flow surpassed the one of the left side (o.47 m/s vs o.45 m/s).

At this time the patient begun to experience the blue vision and was asked to close his normal left eye and the vision of blue was really intense, when the patient closed the right eye the blue vision dissapeared.

The correlation between the acute enhanced retinal"s blood perfusion and blue vision of color was evident. The vasodilator effect remained on the right artery even though with a lesser pick value , 48 hs latter ,(0.28 m/s vs o.19 m/s in the basal homolateral artery).With the chronic use of sildenafil citrate, even though the author council against its use , the patient experienced a retinal disruption and lasser treatment.

DISCUSSION:

The incidence and prevalence of chronic congestive heart failure have steadily increased in the USA, in the last years, even thought the use of newer and more effective drugs, especially in the elderly (19-21).

In the last decade it has increased the percentage of patients with heart failure with preserved systolic function (22) It is noteworthy that 30 to 40 percent of hospitalized patients with diagnoses of chronic congestive heart failure, have preserved left ventricular systolic function. (22) In this very interesting group - the diastolic heart failure patients - the diagnostic and therapeutic meassurements have been dissapointing and as for the prognosis of these heart failure patients with normal systolic function, the total mortality is similar in some series to those with reduced systolic function. (22-24)

Recent evidences showed that hibernation is a precarious equilibrium between perfusion and cellular viability that can not be indefinitly mantained and will end in myocardial necrosis if perfusion does not increase. (25-28)This protective mechanism -hybernation- leads to a considerable mass of hipocontractil myocardium and lately contributes to a global dysfunction of the ventricle .(29,30). Sildenafil citrate is a selective inhibitor of cyclic guanosine monophosphate (CGMp) -specific phosphodiesterase type 5 (PDE5). It inhances the effect and concentration of nitric oxide in the vascular tree and induces smooth arterial muscle relaxation. It is formulated in tablets equivalent to 25, 50 and 100 mgr of sildenafil citrate.(1,10)

It is important to point out that most of the studies on sildenafil citrate, assesed the efficacy of the drug approximatly post sixty minutes of an oral dose of the above mentioned drug.(1,31,32) ; and that Pfizer Inc USA in the contraindications of the drug clearly stated that its administration to patients who are concurrently using organic nitrates in any forms is contraindicated (10) .It is well known that patients under nitrates treatment are those suffering from chronic congestive heart failure, chronic Chagas' disease or coronary artery disease. Nitric oxide is a well known vasodilator with effects over the whole vascular arterial system and it is published elsewhere (33-35) Recent data suggest that the coronary endothelium is important not only for the control of perfusion and vascular permeability, but also for the physiological modulation of the myocardial function and structure. In consequence, the endothelial dysfunction, a recognized component of

the pathophysiology of coronary disease and others cardiomyopathies such as Chagas' and diabetic cardioneuromyopathies, may influence ventricular function and dysfunction .(36-39) The production and release of nitric oxide by the endothelium as well as the prostacicline – two potent vasodilators – are reduced in these patients and the production and release of endothelin and angiotensin II, -two powerfull vasoconstrictors – are augmented.(40-42) The altered endothelial function stimulates vasoconstriction, migration and proliferation of smooth muscle cells, the increase of lipid deposits in the vascular wall, and coronary and microvascular thrombosis, which in term, may contribute to progression of ventricular dysfunction. (33,36,41,43) The release of endothelin is augmented in the failing heart and angiotensin II inhances the liberation of endothelin and the excesive degradation of nitric oxide. (41,44)

These observations suggest that there is an interaction between the failing myocardium and the endothelium that may potentiate the progression of vascular diseases and ventricular dysfunction , through the reduction of nitric oxide, a deletereous effect that could be stopped by sildenafil citrate administration.

Chronic chagas's cardioneuromyopathy – one of the most important causes of congestive heart failure and sudden death in the world, accordingly to the W.H.O. criteria – and diabetic cardioneuromyopathies are widespread with millons of patients affected by the diseases. (3- 8) Both pathologies shares in its pathogenesis two important mechanism: microvascular alterations on the myocardium and vascular tree , and dysfunction of the Sympathetic and Para-sympathetic Autonomic Nervous System, with different degrees of diminished myocardial perfussion leading to a hybernated heart, as well as erectil dysfunction because of the above mentioned autonomic nervous system disease - partial or total blockade of the neurotransmision and/ or partial denervation – and microvascular lesions.(3-8, 45)Patients suffering hypertensive and hypertrophic cardiomyopathies with or without chronic congestive heart failure, received drugs which in terms, lately affects the male erectil function (2)

The ideal drug for the treatment of the above mentioned diseases would be a drug able to induce a physiological vasodilatation without affecting the erectil function, and even more if the drug is able to induce an improvement of the physiological depressed erectil function that occurs with aging, taking into account that the older the patient, the most frequent are the cardiovascular alterations and the erectil dysfunction.

As sildenafil citrate is a potent donor of nitric oxide, it was the author idea, that it could benefit patients with known vascular alterations on its pathogenesis as those suffered by the studied patients

It was the author thought that the Pfizer Inc USA described cardiovascular adverse events as well as the death published elsewere around the world, were caused by an exagerated vasodilatation on the coronary circulation – in patients with a severe obstruction of one or more of the main coronary branches – caussing a shift of a great percentage of the coronary flow to the normal portion of the coronary tree, with a ""steal syndrome"", leading to a severe ischemia in the zone of the stolen coronary flow with concomitant severe arrhytmias, acute myocardial infarction, collapse and sudden death.

This is the reason why all patients with known coronary artery disease were excluded from the study and also the fact that lead to begin the study with patients suffering from chronic Chagas´cardioneuromyopathy because in these patients main branches are preserved in most cases (46).

Ventricular function evaluation is based today upon systolic function evaluation through ejection fraction and fraction shortening and diastolic function evaluation through the E/A ratio by echo-duplex evaluation of mitral and

tricuspid inflow to the left and right ventricles.

Systolic heart failure is a consequence of diminished ejection fraction and fraction shortening of the left ventricle among others factors, and diastolic heart failure walks together with a diminished compliance of the right and left ventricles , with an inverted or restrictive pattern of the E/A ratio of the tricuspid and mitral valves pulsed waves doppler evaluation. (13-15)

Sildenafil citrate 50 mgr, induced an improvement over the basal ECG findings, a signicant reduction of systolic and diastolic blood pressure, a normalization of the rhythm alterations as well as the repolarization changes and a significant improvement of the systolic and diastolic function of the studied patients.

None of the studied patients , after the administration of sildenafil citrate 50 mgr , suffer a worsening of the four investigated cardiovascular parameters.

It is important to emphasize that accordingly to the reported findings, sildenafil citrate seems not to be only highly selective on the peneal endothelial vascularization but it looks like it is able to have strong vasodilator effects in different parts of the vascular tree, specially where there is an alteration of the endovascular function. This statement arises from the fact that sildenafil citrate 50 mgr. was able to improve the heart rate and conduction disturbances in patients with sick sinus syndrome and severe bradyarrhythmia, while did not have any effect at all in those patients with basal normal heart rate, as well as for the fact that sildenafil citrate significantly improved the systolic function in patients with basal depresed function and had a very mild effect on those with basal normal systolic function.

In the same way, sildenafil citrate significantly improved the relaxation of both ventricles in those patients with basal altered function , with very little effect on those with normal function.

For all these observations it is possible that sildenafil citrate is able to have beneficial vasodilator effects where it is needed, be it the vascular arterial tree, the ventricular walls, the ofthalmic arteries or the peneal vascularization. The sildenafil citrate´strong effect over the miocardial contractility, points to a formal contraindication for patients suffering hypertrophic subaortic stenosis and must be excluded from being treated with sildenafil citrate.

The same accounts for patients with ophthalmic fundoscopic alterations such as microaneurism, retinal edema or hemorrage, because they could suffer transient or permanent lost of vision because of the effects mentioned above over the ophthalmic arteries.

CONCLUSIONS:

Based on the results of this study, it is feasible to propose the use of sildenafil citrate to treat patients with cardiovascular diseases such as Chagas's and diabetic cardioneuromyopathies, hypertensive and hypertrophic cardiomyopathies and chronic congestive heart failure, independent of the fact if they suffer or not of erectil dysfunction, with exclussion of severe obstructive coronary artery disease, hypertrophic subaortic stenosis and patients with funduscopic alterations that may be affected by a significant and acute increase of flow in the ofthalmic artery. The rifht ventricular diastolic changes observed with Sildenafil Citrate may be usefull in patients with abnormal right ventrcular compliance such as pulmonary stenosis or hypertension.

Conflict of Interest:all the investigation have been carried out by Dr Daniel Iosa MD PhD. without support of any kind from any person or company and are protected by law, with p. approved patent n p 98 01 05395 in favour of Dr Daniel Iosa.

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EDITORIAL NOTE: Due to the lengh of this article, tables graphics and other figures were restricted and may be asked to the author´s e-mail.

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