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Effects of Phosphodiesterase Type 5 Inhibition on Systemic and Pulmonary Hemodynamics and Ventricular Function in Patients with Severe Symptomatic Aortic Stenosis

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Abstract

Background—Pressure overload due to aortic stenosis (AS) causes maladaptive ventricular and vascular remodeling that can lead to pulmonary hypertension, heart failure symptoms, and adverse outcomes. Retarding or reversing this maladaptive remodeling and its unfavorable hemodynamic consequences has potential to improve morbidity and mortality. Preclinical models of pressure overload have shown that phosphodiesterase type 5 (PDE5) inhibition is beneficial, however the use of PDE5 inhibitors in patients with AS is controversial because of concerns about vasodilation and hypotension.

Methods and Results—We evaluated the safety and hemodynamic response of 20 subjects with severe symptomatic AS (mean aortic valve area 0.7±0.2 cm^2, ejection fraction 60±14%) who received a single oral dose of sildenafil (40mg or 80mg). Compared to baseline, after 60 minutes sildenafil reduced systemic (−12%, p<0.001) and pulmonary (−29%, p=0.002) vascular resistance, mean pulmonary artery (−25%, p<0.001) and wedge (−17%, p<0.001) pressure, and increased systemic (+13%, p<0.001) and pulmonary (+45%, p<0.001) vascular compliance and stroke volume index (+8%, p=0.01). These changes were not dose dependent. Sildenafil caused a modest decrease in mean systemic arterial pressure (−11%, p<0.001), but was well-tolerated with no episodes of symptomatic hypotension.

Conclusions—This study shows for the first time that a single dose of a PDE5 inhibitor is safe and well-tolerated in patients with severe AS and is associated with acute improvements in pulmonary and systemic hemodynamics resulting in biventricular unloading. These findings support the need for longer-term studies to evaluate the role of PDE5 inhibition as adjunctive medical therapy in patients with AS.

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Keywords

aortic valve stenosis; heart failure; phosphodiesterase type 5 inhibitors; pulmonary hypertension; hemodynamics

Introduction

Calcific aortic stenosis (AS) is considered a "surgical disease." No medical therapy has been proven to delay/reverse the progression of disease, symptoms, or time to valve replacement.[1] Although attempts at medical therapy have focused on slowing progressive stenosis of the valve, prospective clinical trials with statin medications have yielded disappointing results with regard to this endpoint.[2,3] However, it bears emphasis that AS is more than simply a disease of the valve, insofar as the progressive remodeling of the left ventricle (LV) and vasculature (pulmonary and systemic) that occur secondary to pressure overload also contribute to significant morbidity and mortality in patients with AS.[4–6]

Maintenance of cardiac output in AS imposes a chronic increase in LV pressure that leads to ventricular remodeling (characterized by myocyte hypertrophy and myocardial fibrosis) and eventually diastolic and systolic dysfunction. This pressure overload caused by the valvular stenosis is often exacerbated by systemic hypertension, which causes an additional load on the LV.[4] Diastolic dysfunction of the hypertrophied ventricle causes elevated LV filling pressures, which are transmitted to the pulmonary vasculature, causing pulmonary venous congestion and associated heart failure symptoms.[7] Group II pulmonary hypertension (PH) develops in a majority of patients with AS, becoming severe in 15–20%.[8,9] Additionally, some patients with AS and PH develop a "reactive" or precapillary component to their PH, characterized by an elevated pulmonary vascular resistance (PVR).[7]

Patients treated with valve replacement have worse outcomes when there is associated hypertrophic LV remodeling, diastolic dysfunction, and pulmonary hypertension.[6,10–12] Although it would be ideal to treat all patients with AS in the "golden window" as they become symptomatic, the clinical reality is that often the AS is not recognized until after physiologic compensatory mechanisms have been exhausted and patients present with advanced symptoms, making them either inoperable or at increased risk for a poor surgical outcome.[13] Accordingly, retarding or reversing the maladaptive remodeling and its unfavorable hemodynamic consequences represents a significant unmet clinical need.[1]

Existing experimental and clinical studies raise the interesting possibility that phosphodiesterase type 5 (PDE5) inhibition may both favorably alter the abnormal hemodynamic profile and retard or reverse maladaptive remodeling in patients with AS. A preclinical model of pressure overload demonstrated that sildenafil both blunted the development of cardiac hypertrophy and fibrosis and reversed pre-established hypertrophic remodeling, while improving LV function.[14] Studies in patients with non-valvular left-sided heart failure have shown that PDE5 inhibition can unload the failing heart, improve pulmonary hemodynamics, and increase exercise capacity acutely.[15,16] Chronic PDE5 inhibition has led to improved diastolic and systolic function, decreased LV mass and PVR, and improvements in quality of life and functional capacity.[17–20]

However, there has been reluctance to use vasodilating medications such as PDE5 inhibitors in patients with AS due to concerns about precipitating hypotension. Although the UNLOAD study showed that an intravenous vasodilator (nitroprusside) is safe and well-tolerated in patients with severe AS, the intensive monitoring required and rapid tolerance of this approach limits its utility in routine clinical practice.[21] Accordingly, the objective of this

study was to assess the acute hemodynamic response to and safety and tolerability of orally administered sildenafil in patients with severe AS.

Methods

Patients

We enrolled patients ≥18 years of age with severe calcific AS (aortic valve area [AVA] <1.0cm^2) undergoing right and left heart catheterization for clinical reasons. Exclusion criteria were nitrate use within 24 hours, systolic blood pressure (SBP) <110 mmHg, mean systemic arterial pressure (mSAP) <75 mmHg, severe mitral or aortic regurgitation, retinal or optic nerve problems, alpha antagonist medication use within 24 hours, recent (≤30 days) acute coronary syndrome, and oxygen saturation <90% on room air. Institutional review board approval was obtained and all patients signed informed consent prior to catheterization.

Clinical data

Clinical variables were obtained at the time of the cardiac catheterization from the medical record and through patient interview. Definitions for the clinical variables are in the data supplement.

Hemodynamic measurements

At each time point (baseline and 30 and 60 minutes after the administration of sildenafil), hemodynamic measurements were taken in triplicate (the average was reported) at end-expiration using a fluid-filled balloon tipped 7.5F Swan-Ganz catheter for right-sided pressures and a 4F pigtail catheter in the descending aorta for systemic pressures. Cardiac output was determined by the Fick method, using the Lafarge formula for estimating oxygen consumption. Standard hemodynamic variables were calculated using established formulas. Valvuloarterial impedance, a measure of global LV load, was also determined given its association with reduced LV function and survival in patients with AS.[22,23] Formulas are shown in the data supplement.

Study protocol

Medications with vasoactive or diuretic effects were withheld for 12–24 hours prior to the heart catheterization. No supplemental oxygen, sedatives, or pain medications (other than local anesthetics) were administered until after the pressures were measured 60 minutes after administration of sildenafil. After baseline right and left heart hemodynamic measurements were made, a single oral dose of sildenafil (40mg or 80mg) was given. Because of the possibility of a differential response to sildenafil based on ventricular function, each dose (40mg or 80mg) was distributed equally among those with reduced (EF <50%) or preserved (EF ≥50%) LV function. We anticipated that 30% of our subjects (n=6) would have a reduced EF and 70% (n=14) would have a preserved EF. For those with a reduced EF, the first 3 subjects received 40mg of sildenafil and the next 3 subjects were administered 80mg. For those with a preserved EF, the first 5 subjects received 40mg, the next 5 subjects received 80mg, and the doses were alternated for the remaining 4 subjects enrolled with a preserved EF. Repeat hemodynamic measurements were performed 30 and 60 minutes after sildenafil was administered. An echocardiogram was performed immediately prior to the catheterization and select images were repeated 50–60 minutes after administration of sildenafil.

Adverse Events

Any adverse events were recorded, including hypotension (defined as mSAP decrease by >20% and mSAP decrease to less than 65mmHg), symptomatic hypotension, syncope, arrhythmia (significant atrial or ventricular arrhythmias that were either new in onset or required intervention), or administration of a vasoconstrictor medication. Any side effects were also recorded. Patients were monitored for 3 hours after the drug was administered.

Echocardiographic data

Parasternal and apical views were used to acquire standard 2D and Doppler images on a GE Vivid 7 ultrasound system. The severity of AS was determined by measuring mean and peak gradients across the valve using the modified Bernoulli equation and by calculating aortic valve area (AVA) using the continuity equation. Measurements of LV chamber dimensions, relative wall thickness, LV mass, EF, systolic excursion velocity (LV S'), early diastolic mitral annular velocity (e'), and determination of valve regurgitation were made as recommended by the American Society of Echocardiography and described previously.[24–26] LV mass was indexed to body surface area (BSA). LV midwall shortening (MWS) was calculated using 2D linear measurements made at end-diastole and end-systole. MWS was corrected for afterload, measured as circumferential end-systolic stress.[27] Stress-corrected MWS (scMWS) was reported, reflecting the ratio of actual to predicted MWS for the actual circumferential end-systolic stress.[22] Standard 2D images were analyzed with GE EchoPac analysis software (versions 7.2 and 108.1.5; GE Vingmed Ultrasound A.S., Horten, Norway) to measure LV longitudinal strain, strain rate, rotation, and twist using the speckle tracking method as described previously.[26] Right ventricular (RV) function was assessed using systolic excursion velocity (RV S'), tricuspid annular plane systolic excursion (TAPSE), and RV Tei index per guideline recommendations.[28] Measurements of LV stiffness, viscoelasticity, and the load independent index of diastolic filling (LIIDF) were made using the Parameterized Diastolic Filling formalism as previously described and validated,[29–31] using transmitral Doppler E-waves recorded during different respiratory states (regular breathing and held expiration and inspiration). Echocardiographic measurements before and after sildenafil administration were made by the same echocardiographer, who was blinded to whether the images were obtained before or after drug administration.

Statistical analysis

This was a single center, open label study in which a single oral dose of sildenafil (40mg or 80mg) was administered at the time of right and left heart catheterization. The primary end-point of the study was the change in mean pulmonary artery pressure (mPAP) from baseline to 60 minutes after sildenafil administration. All data are reported as mean±SD except where indicated. Hemodynamic and ventricular function changes from baseline to 60 minutes were evaluated using the Wilcoxon signed-ranks test. Group comparisons were conducted using the Mann-Whitney U-test or Fisher's exact test as appropriate. Spearman correlations were used to examine the linear relationships between continuous variables. All tests of statistical significance were evaluated at a 2-sided significance level of 0.05. All statistical analyses were performed using SAS for Windows version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Patients

Baseline characteristics of patients enrolled in the study (n=20) are shown in Table 1. The average age of the patients was 86 years, 50% were female, AVA was 0.65±0.2cm^2, and the EF was 60±14%. Ninety percent of the patients were NYHA functional class III or IV and 65% had coronary disease. The clinical characteristics for those with baseline mPAP <35 vs.

≥35 mmHg were similar except that systolic blood pressure was greater in those with mPAP ≥35 mmHg (Table 1). The clinical characteristics for those who received the 40mg vs. 80mg dose of sildenafil were similar (Supplemental Table 1).

Effects of sildenafil on LV load and systemic hemodynamics

Hemodynamic responses to sildenafil at both 30 and 60 minutes are shown in Table 2. Pulmonary capillary wedge pressure (PCWP) decreased 17% (24±7 to 19±8 mmHg, p<0.001) 60 minutes after sildenafil compared to baseline. The magnitude of the decrease was not dependent on dose or baseline hemodynamic characteristics (Supplemental Fig. 1). Systemic vascular resistance (SVR) decreased 12% (27±8 to 22±6 Wood units, p<0.001), systemic arterial compliance (SAC) increased 13% (0.57±0.20 to 0.66±0.21 ml/mmHg, p<0.001), and valvuloarterial impedance (VAI) decreased 11% (7.8±2.0 to 6.7±1.7 mmHg/ml/m^2, p<0.001) after sildenafil (Table 2). mSAP decreased 11% (108±15 to 94±16 mmHg, p<0.001); however, there was no significant correlation between baseline characteristics and percent change in mSAP (Supplemental Table 2).

Despite the decrease in PCWP, sildenafil administration was associated with a 8% increase in stroke volume index (29±6 to 31±6 mL, p=0.01) (Table 2 and Fig. 1a). Figures 1b–1e show that the increase in stroke volume following treatment with sildenafil correlated with a decrease in systemic (r_s=−0.79, p<0.001 [1b]) and pulmonary (r_s=−0.51, p=0.02 [1c]) vascular resistance, as well as an increase in systemic (r_s=0.69, p<0.001 [1d]) and pulmonary (r_s=0.63, p=0.003 [1e]) arterial compliance, but did not correlate with changes in systolic myocardial function measured by scMWS (r_s=0.31, p=0.21 [1f]).

Effects of sildenafil on pulmonary vascular hemodynamics

In the whole cohort, the mPAP decreased 25% from 37±11 (baseline) to 27±9 mmHg (60 minutes after sildenafil) (p<0.001) (Table 2). As shown in Figure 2a, all but 1 subject had a reduction in mPAP with sildenafil at 60 minutes compared to baseline. Among the 17 subjects with PH (mPAP ≥25) on baseline measurements, 14 (82%) improved by at least one category of severity of PH after sildenafil and 3 subjects improved by ≥2 categories (Fig. 2b). Figure 2c shows that there was a significant decrease in mPAP irrespective of dose administered or baseline pulmonary vascular hemodynamics. There was also a decrease in PVR by 29% (3.5±2.8 to 2.2±1.1 Wood units, p=0.002) and an increase in pulmonary arterial compliance (PAC) by 45% (2.1±1.1 to 2.8±1.2 mL/mmHg, p<0.001) (Table 2). The decrease in PVR was limited to those with an elevated baseline PVR (Fig. 3b), whereas the increase in PAC was observed regardless of baseline hemodynamic characteristics (Supplemental Fig. 2).

We also assessed whether there was a difference in the response to sildenafil among those with “passive” PH, defined as mPAP ≥25, PVR <3 (n=10), and those with “reactive” PH, defined as mPAP ≥25, PVR ≥3 (n=7). These 2 groups of patients had similar improvements in mPAP and PAC after sildenafil, but there were differences in the relative effects on PCWP and PVR (Fig. 3).

Sildenafil showed relative selectivity for the pulmonary circulation with greater changes observed in pulmonary arterial pressure and compliance as well as pulmonary vascular resistance than the corresponding measures in the systemic circulation (Table 2). There were no differences in the percent changes of the pulmonary vascular hemodynamic variables based on the dose of sildenafil administered, but there was a trend toward a greater decrease in VAI and increase in SAC and SVI with 80mg of sildenafil (Supplemental Table 3).

Responders vs. non-responders to sildenafil

The response to sildenafil in the pulmonary circulation (mPAP, PCWP, and PAC) was consistently, albeit not uniformly, favorable (Table 2, Figs. 2 and 3, and Supplemental Figs. 1 and 2); very few subjects had no/poor response to sildenafil in these pulmonary hemodynamic indices. The decrease in PVR after sildenafil was mostly confined to those with an abnormally elevated baseline PVR (PVR ≥3) (Fig. 3). In those patients (n=7), the reduction in PVR was uniform with a minimum decrease of 35%. Although the effects of sildenafil on the systemic circulation were also favorable, there were more subjects who had either no response or a blunted response in the systemic hemodynamic indices. There was a median decrease in SVR after sildenafil of 12%, but 2 subjects had an increase in SVR (<3%) and 6 subjects had a decrease of <10%. Likewise, although there was a median increase in SAC of 13%, 1 subject had a decrease in SAC (6%) and 7 subjects had an increase of <10%. Of the 18 subjects with VAI measured before and after sildenafil, there was a median decrease in VAI of 11%, but 2 subjects had an increase in VAI (<4%) and 7 subjects had a decrease of <10%. Although there was a median increase in SVI of 8%, 6 subjects did not have any increase after sildenafil.

Effects of sildenafil on left and right ventricular function

Echocardiographic measures of left and right ventricular function before and 60 minutes after the administration of sildenafil are shown in Table 3. No acute changes were observed in LV diastolic function and there were no changes in radial or longitudinal measures of systolic function or LV twist. There was a trend toward improved global RV function as measured by the RV Tei index (p=0.06), but no change in RV systolic function.

Adverse events and side effects

Three subjects met the pre-specified criteria for adverse events. Two subjects experienced hypotension as defined by the study protocol, however these episodes were transient, were not associated with symptoms, and did not require any intervention. One subject had a supraventricular arrhythmia during the angiographic portion of the catheterization when the left main coronary artery was engaged with a catheter. After the catheter was removed, the arrhythmia ceased and no intervention or hemodynamic instability occurred. One other subject experienced a hypertensive emergency associated with pulmonary edema requiring noninvasive ventilation after receiving the angiographic contrast load. This patient tolerated the 60 minute period of hemodynamic monitoring after receiving sildenafil without difficulty. The only side effects from sildenafil reported were transient shortness of breath (1 subject) and rhinorrhea (2 subjects).

Discussion

This single center hemodynamic study shows for the first time that a single dose of a PDE5 inhibitor is safe and well-tolerated in patients with severe symptomatic AS and acutely improves hemodynamics in the pulmonary and systemic circulations. Sildenafil unloaded the LV as it decreased afterload and preload and increased stroke volume without a change in heart rate. This unloading was associated with a modest decrease in systemic blood pressure. There were also significant, favorable changes in the pulmonary vasculature from sildenafil including a 25% decrease in pulmonary artery pressures, 29% decrease in pulmonary vascular resistance, and 45% increase in pulmonary artery compliance. Taken together, these findings suggest that PDE5 inhibition is safe in patients with symptomatic AS and raise the possibility that PDE5 inhibitors may be useful as adjunctive medical therapy in AS to stabilize patients with advanced heart failure symptoms by improving abnormal hemodynamics.

Sildenafil ameliorates abnormal hemodynamics in AS by unloading the heart and favorable effects in the pulmonary vasculature

Sildenafil unloads the heart

It has long been recognized that patients with AS develop concentric hypertrophy secondary to pressure overload. The stenotic valve presents a relatively fixed orifice and is usually the dominant cause of the pressure overload state. This has led to the still widely held notion that the afterload in AS is a "fixed afterload," which has led to the classic teaching that vasodilators are relatively contraindicated in AS.[32] More recent studies, however, have suggested that increased vascular afterload adds to the LV afterload in patients with AS and may contribute to adverse patient outcomes.[23,33] The UNLOAD study challenged prevailing dogma and showed that in critically ill patients with severe AS, severe LV dysfunction (EF ~20%) and decompensated heart failure, an intravenous vasodilator (nitroprusside) was well tolerated and associated with unloading of the LV: decreased SVR, decreased PCWP, and increased stroke volume accompanied by a modest decrease in systemic pressure.[21] Here we confirm these earlier findings and extend them by showing similar acute unloading effects during cardiac catheterization in patients with severe symptomatic AS using an oral medication that has vasodilating properties. The observation that stroke volume increased despite a decrease in PCWP can be explained by a decrease in afterload and/or an increase in contractility. Given that there was no change in LV systolic myocardial function after sildenafil (Fig.1f), the most likely explanation for our findings is that sildenafil led to peripheral unloading of the LV (Figs.1b,1d). Importantly, these data suggest that afterload is not necessarily "fixed" in patients with symptomatic AS and that reducing vascular afterload may improve hemodynamics in these patients. Sildenafil was also associated with significant unloading of the RV. Because RV dysfunction has been shown to be a predictor of poor outcome in high-risk valve surgery,[34] the unloading of the RV with sildenafil may have beneficial consequences. Although not measured directly, the reduction in preload and afterload with sildenafil (with no change in heart rate or contractility) might be expected to reduce myocardial oxygen demand and allow the heart to function in a more optimal energetic state, potentially mitigating adverse cardiac remodeling over time.

Although sildenafil led to favorable unloading of the heart, we did not observe any acute changes in diastolic or systolic function from one dose of drug consistent with prior studies.[15] However, it is important to note that PDE5 is expressed in the hypertrophied LV and RV and chronic PDE5 inhibition can improve diastolic and systolic function.[18,19,35] The mechanisms for improved load-independent diastolic and systolic function may require greater tissue penetration and/or alterations in signaling pathways and myocardial structure that take longer than 60 minutes.

Sildenafil improves pulmonary vascular hemodynamics

PH is common in patients with severe AS (affecting 50–65%) and is usually characterized as pulmonary venous hypertension, driven by the elevated filling pressures in the left side of the heart causing a "passive" increase in pulmonary artery pressures.[6,7] In a significant minority, however, there also appears to be a "reactive" response in the pulmonary vasculature characterized by increased vascular resistance.[7] PH delineates a group of patients at increased risk and no medical therapy particularly targets this pathophysiology in patients with AS.[6] In this regard, our results demonstrating a significant improvement in pulmonary vascular hemodynamics with sildenafil may have important implications. There was a consistent ~25% decrease in pulmonary artery pressures in patients with severe AS, which did not depend upon subjects having an elevated baseline mPAP or PVR. Sildenafil also decreased PVR by 52% in those with PVR ≥3, likely due to improved cGMP release across the pulmonary vascular bed with sildenafil.[36] Additionally, the 45% increase in PAC

with sildenafil may improve patient outcomes as PAC is an independent predictor of mortality in patients with pulmonary arterial hypertension.[37]

Clinical Implications

Reversing the decompensated hemodynamic state

Advanced heart failure symptoms are associated with increased operative risk in patients with AS.[13] These patients are often characterized by pulmonary venous congestion, PH, afterload mismatch, and a low output state. In some cases, the PH is so severe and the PVR so elevated that patients are considered inoperable, particularly if they are deemed to have "irreversible" PH as determined by a vasodilator study. Others will not get an operation due to the severity of co-morbidities or patient refusal.[38]

The need for medical therapy to reverse this abnormal and deleterious hemodynamic state to decrease operative risk or to relieve symptoms in those not undergoing surgical correction represents a significant unmet clinical need.[1] Diuretics are sometimes avoided because of concerns that patients with AS are "preload dependent." If diuretics are used, they have little ability to address the breadth of hemodynamic abnormalities (because it's not just a "volume overload problem") and can precipitate renal dysfunction in elderly patients with limited renal reserve. Nitroprusside improves hemodynamics acutely, but it is an intravenous medication that requires intensive monitoring in an ICU and leads to rapid tolerance and toxicity.[21]

Our results suggest that PDE5 inhibition has the potential to address this unmet clinical need in ambulatory patients, insofar as sildenafil unloads both the LV and RV and is associated with a significant decrease in pulmonary vascular load. Unlike other vasodilators that dilate only systemic or pulmonary vascular circulations, our results suggest that the reduction in both systemic and pulmonary vascular resistance with PDE5 inhibition may offer a particular advantage for treating patients with decompensated AS. As such, it is interesting to considering whether the administration of a PDE5 inhibitor to patients with AS in a decompensated clinical and hemodynamic state may reverse abnormal hemodynamics, reduce patient symptoms, and/or reduce operative risk by allowing for stabilization of the patient. It is important to remember, however, that in patients with coronary disease or heart failure the combination of nitrates and PDE5 inhibitors is contraindicated.

Retarding or reversing maladaptive remodeling

Even when valve replacement is performed, outcomes are worse in patients with pre-operative evidence of maladaptive remodeling in the LV and pulmonary vasculature.[6,10–12] Reverse remodeling can occur after the valve replacement relieves the pressure overload on the heart, but this reversal is often incomplete, which is associated with less symptomatic improvement and decreased survival.[6,39–41] Although speculative, experimental pressure overload studies[14] and emerging clinical studies with PDE5 inhibition in non-AS heart failure populations[17–20] raise the interesting possibility that longer-term treatment with PDE5 inhibitors prior to aortic valve surgery may lead to favorable remodeling of the ventricle and pulmonary vasculature and potentially improve long-term surgical outcomes. While other vasodilators may also unload the LV, PDE5 inhibitors also directly affect myocardial biology in a way that improves cardiac remodeling.[14] Whether such a strategy could also delay the onset of symptoms related to AS is of significant interest. The present study provides an initial report of the safety of PDE5 inhibition in patients with AS and should encourage longer-term studies to investigate these possibilities.

Limitations

This was an acute hemodynamic study, assessing the effects of one dose of sildenafil while other vasoactive medications were held and subjects were supine during a cardiac catheterization. Because anti-hypertensive medications were held and patients with lower blood pressure were excluded, the average blood pressure was quite elevated when sildenafil was administered. As such, these data cannot be directly applied to patients with aortic stenosis and lower blood pressure. However, in a stratified analysis of those with higher vs. lower baseline blood pressure, there were no differences in the hemodynamic effects of sildenafil (Supplemental Table 4). We did not obtain post-sildenafil electrocardiograms or troponin values on our subjects, so we cannot rule out that the drop in diastolic blood pressure associated with sildenafil could have precipitated myocardial ischemia by decreasing the transmyocardial pressure gradient. However, the concomitant drop in PCWP suggests that the effect of sildenafil on coronary blood flow may have been neutral. Herrmann et al. evaluated coronary blood flow in stenosed and normal coronary vessels and found that sildenafil administration was associated with an improvement in coronary flow reserve and no change in the velocity of coronary blood flow.[42] The UNLOAD study did not identify any ischemic changes on electrocardiography in patients with severe AS receiving nitroprusside despite a modest decrease in systemic blood pressure.[21] Additionally, despite the fact that many of our subjects had significant coronary disease, none of them complained of chest discomfort after receiving sildenafil. This study was an important first step and demonstrated safety acutely, but further studies are needed with chronic PDE5 inhibition to determine tolerability when subjects are ambulating and taking other vasoactive medications.

Conclusion

This study shows for the first time that a single oral dose of a PDE5 inhibitor is safe and well-tolerated in patients with severe AS and provides favorable acute hemodynamic effects in the pulmonary and systemic circulations. Treatment with sildenafil decreased both LV preload and afterload, and increased stroke volume, without adverse consequences. Sildenafil also significantly improved pulmonary artery pressure, pulmonary vascular resistance, and pulmonary arterial compliance, and thus unloaded the RV as well. As such, these results raise the intriguing possibility that PDE5 inhibition may be useful as adjunctive medical therapy in patients with symptomatic AS. Perhaps, the administration of a PDE5 inhibitor to patients with AS in a decompensated clinical and hemodynamic state may improve abnormal hemodynamics, reduce patient symptoms, and/or reduce operative risk by allowing for stabilization of the patient. To evaluate these potential clinical benefits, longer-term studies are needed to assess the safety and efficacy of chronic PDE5 inhibition in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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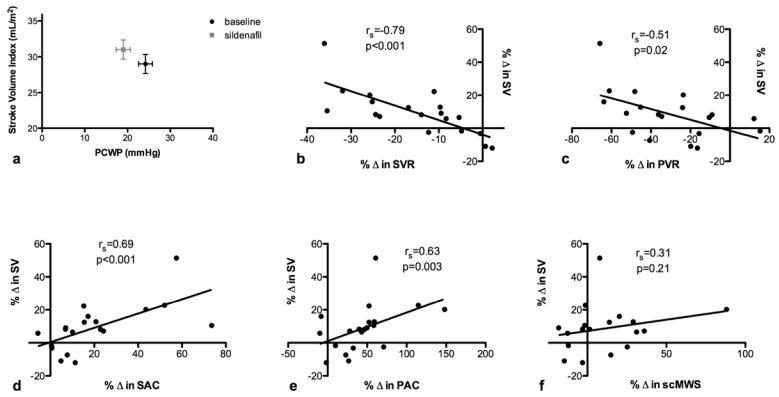

Figure 1. Unloading of the left ventricle after sildenafil

A decrease in pulmonary capillary wedge pressure (PCWP) was associated with an increase in stroke volume index (mean±SEM) (a). The increase in stroke volume (SV) after sildenafil correlated with a decrease in systemic and pulmonary vascular afterload (b–e), but not with an increase in systolic myocardial function (f). Abbreviations same as Table 2; scMWS, stress-corrected midwall shortening.

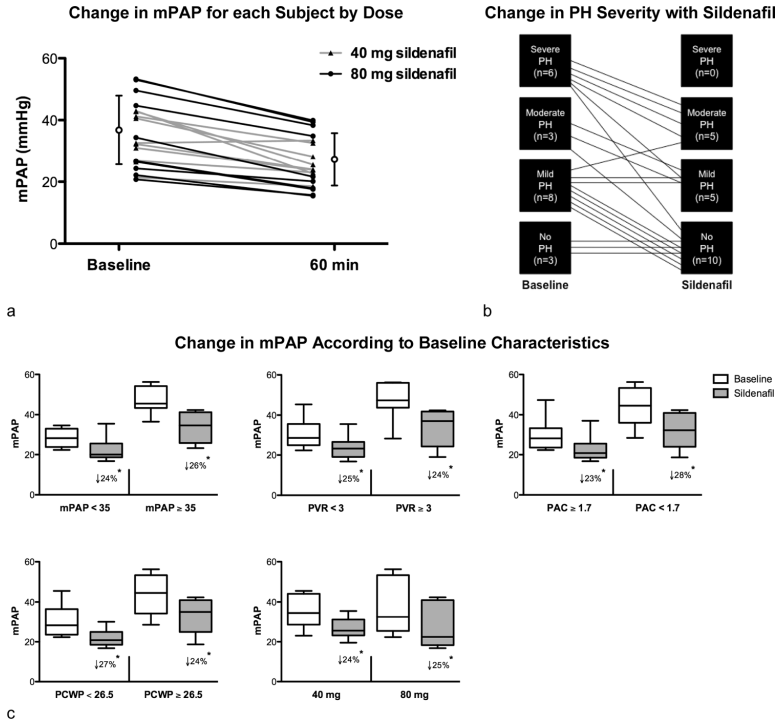

Figure 2. Change in mean pulmonary artery pressure after sildenafil

The change in mPAP from baseline to 60 minutes is shown for each patient by dose; error bars (SD) (a). The change from baseline to 60 minutes in the category of severity of pulmonary hypertension (PH) is shown for each subject; no PH (mPAP <25), mild PH (25–34), moderate PH (35–44), severe PH (≥45) (b). Change in mPAP with sildenafil from baseline to 60 minutes according to dose or baseline hemodynamics with median % change reported; the cut-points for the PAC and PCWP groups were determined by the median value for the whole cohort (c). *Based on Wilcoxon signed-ranks test of the percent change from baseline to 60 minutes; indicates significance at $p<0.05$. Abbreviations as in Table 2.

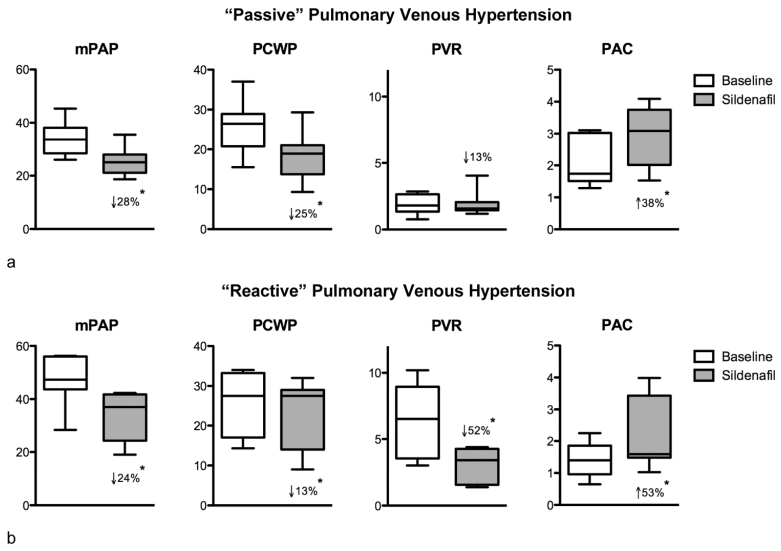

Figure 3.

Effect of sildenafil on passive (mPAP ≥25 and PVR <3) (a) and reactive (mPAP ≥25 and PVR ≥3) (b) pulmonary venous hypertension. Median % change reported. *Based on Wilcoxon signed-ranks test of the percent change from baseline to 60 minutes; indicates significance at $p<0.05$. Abbreviations as in Table 2.

Table 1

Clinical Characteristics

	Whole cohort (n=20)	mPAP <35 (n=11)	mPAP ≥35 (n=9)
Age (years)	86±10	85±10	86±10
Female gender	50	45	56
Body surface area (m^2)	1.9±0.3	1.8±0.3	1.9±0.3
Systolic blood pressure (mmHg) †	153±21	145±20	163±17 *
Diastolic blood pressure (mmHg) †	72±9	69±7	75±11
Prior myocardial infarction	10	9	11
Coronary artery disease	65	55	78
Hypertension	95	91	100
Atrial arrhythmia	25	9	44
Diabetes mellitus	45	27	67
Obstructive lung disease	35	22	50
NYHA functional class			
II	10	18	0
III	65	73	56
IV	25	9	44
Glomerular filtration rate (mL/min/1.73m^2) ‡	57±22	64±24	50±17
B-type natriuretic peptide (pg/mL)	741±813	454±312	1092±1094
ACE-inhibitors or ARBs	30	27	33
ß-blockers	75	73	78
Calcium channel blockers	15	18	11
Diuretics	80	73	89
Statins	60	73	44
Prior use of a PDE5 inhibitor	10	18	0
Aortic valve area (cm^2)	0.7±0.2	0.6±0.2	0.7±0.2
Ejection fraction (EF) (%)	60±14	65±13	53±13
Reduced EF (<50%)	30	18	44
LV mass index (g/m^2)	155±22	152±17	160±29
Relative wall thickness	0.6±0.2	0.7±0.2	0.6±0.1
Aortic regurgitation severity			
0	30	27	33
1	50	55	44
2	20	18	22
Mitral regurgitation severity			
0	15	27	0
1	50	55	44
2	35	18	56

All values are mean ± SD or % unless otherwise specified.

Aortic and mitral regurgitation were graded: 0 (none), 1 (mild), 2 (moderate), 3 (moderately severe), 4 (severe).

[*] $p<0.05$, comparing those with mPAP <35 vs. mPAP ≥35.

[†] Obtained in the holding area outside the cardiac catheterization procedure room (cuff pressure).

[‡] Estimated by the Modification of Diet in Renal Disease Study method.

Table 2

Hemodynamic Effects of Sildenafil in Patients with Severe Aortic Stenosis (n=20)

	Baseline	30 min	60 min	% Δ0–60min*	p-value†
Heart rate	73±12	72±11	71±13	−2 (−9,4)	0.14
mPAP (mmHg)	37±11	29±9	27±9	−25 (−32,−21)	<0.001
PASP (mmHg)	55±16	42±13	41±13	−23 (−33,−19)	<0.001
PADP (mmHg)	24±9	19±7	18±7	−23 (−35,−19)	<0.001
PVR (Wood units)	3.5±2.8	1.9±1.6	2.2±1.1	−29 (−49,−13)	0.002
TPG (mmHg)	13±8	8±4	8±3	−27 (−47,−16)	0.004
PAC (ml/mmHg)	2.1±1.1	2.4±1.5	2.8±1.2	+45 (25,59)	<0.001
RA (mmHg)	10±5	9±5	8±5	−13 (−26,0)	0.01
PCWP (mmHg)	24±7	21±8	19±8	−17 (−35,−13)	<0.001
mSAP (mmHg)	108±15	94±16	94±16	−11 (−20,−5)	<0.001
SBP (mmHg)	171±23	151±22	153±24	−9 (−17,−4)	<0.001
DBP (mmHg)	69±14	60±14	59±14	−13 (−19,−7)	<0.001
SVR (Wood units)	27±8	22±6	22±6	−12 (−25,−5)	<0.001
SAC (ml/mmHg)	0.57±0.20	0.61±0.30	0.66±0.21	+13 (6,24)	<0.001
VAI (mmHg/ml/m^2)	7.8±2.0		6.7±1.7	−11 (−19,−5)	<0.001
SVI (ml/m^2)	29±6	29±12	31±6	+8 (−2,14)	0.01
CI (ml/min/m^2)	2.1±0.4	2.1±0.8	2.2±0.3	+4 (−4,12)	0.15
PVR / SVR	0.13±0.09	0.10±0.06	0.10±0.04	−16 (−42,3)	0.04
mPAP / MAP	0.35±0.11	0.31±0.09	0.29±0.09	−14 (−20,−9)	<0.001
PAC / SAC	3.7±1.2	4.3±1.5	4.4±1.5	+25 (3,32)	0.001

Abbreviations: mPAP, mean pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient; PAC, pulmonary arterial compliance; RA, right atrium; PCWP, pulmonary capillary wedge pressure; mSAP, mean systemic arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; SVR, systemic vascular resistance; SAC, systemic arterial compliance; VAI, valvuloarterial impedance; SVI, stroke volume index; CI, cardiac index. Data expressed as mean±SD.

*Percent values represent the median percent change (25^{th},75^{th} percentiles) between baseline and 60 minute measurements.

†Based on Wilcoxon signed-ranks test of the percent change from baseline to 60 minutes.

Table 3

Effects of Sildenafil on Left and Right Ventricular Function

	Baseline	60 minutes	p-value*
Aortic Stenosis Measurements			
AVA (cm^2)	0.65±0.2	0.70±0.2	0.04
Mean gradient (mmHg)	47±14	47±13	0.67
Peak gradient (mmHg)	77±22	76±19	0.87
LV Systolic Function			
Ejection fraction (%)	60±14	63±15	0.095
LV S' (cm/s)	4.9±1.2	4.9±1.13	0.24
scMWS (%)	49±10	53±11	0.15
Longitudinal strain (%)	−13.5±4.3	−13.8±3.9	0.72
Longitudinal strain rate (1/s)	−0.9±0.2	−1.0±0.3	0.21
LV twist (°)	17.5±4.6	20.8±8.8	0.12
LV Diastolic Function			
e' (cm/s)	4.8±1.5	4.8±1.4	0.53
E/e'	27±11	27±16	0.82
LIIDF	1.02±0.07	1.03±0.08	0.93
Stiffness ($1/s^2$)	291±110	285±126	0.39
Viscoelasticity (1/s)	49±22	49±24	0.80
RV Function			
RV S' (cm/s)	10.7±3.0	10.7±2.8	0.89
TAPSE (cm)	1.9±0.7	1.9±0.6	0.91
Tei index	0.4±0.1	0.3±0.1	0.057

Abbreviations: AVA, aortic valve area; S', systolic excursion velocity; scMWS, stress-corrected midwall shortening; LV, left ventricle; e', early diastolic mitral annular velocity (average of lateral and septal); LIIDF, load independent index of diastolic filling; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion. Data expressed as mean±SD.

* Based on Wilcoxon signed-ranks test.