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Effects of Sildenafil on Ventricular and Vascular Function in Heart Failure With Preserved Ejection Fraction

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Abstract

Background—Early studies showed beneficial effects of phosphodiesterase 5 inhibitors (PDE5i) on cardiovascular function in heart failure (HF) patients, but the RELAX trial observed no improvement in exercise capacity with sildenafil treatment in subjects with HF and preserved ejection fraction (HFpEF).

Methods and Results—A subgroup of participants in the RELAX trial (n=48) underwent comprehensive noninvasive cardiovascular assessment before and after treatment with sildenafil or placebo in a prospective ancillary study. Left ventricular (LV) contractility was assessed by peak power index (PWR/EDV) and stroke work index (SW/EDV). Systemic arterial load was assessed by arterial elastance (Ea) and right ventricular afterload by pulmonary artery systolic pressure (PASP). Endothelial function was assessed by reactive hyperemia index (RHI) following upper arm cuff occlusion. Compared to placebo (n=25), sildenafil (n=23) decreased Ea (−0.29±0.28mmHg/ml vs +0.02±0.29, p=0.008) and tended to improve RHI (+0.30±0.45 vs −0.17±0.30, p=0.054). In contrast, LV contractility was reduced by 11–16% with sildenafil compared to placebo (ΔPWR/EDV −52±70 vs +0±40 mmHg/s, p=0.006; ΔSW/EDV +0.3±5.8 vs −6.0±5.1 mmHg, p=0.04). Sildenafil had no effect on PASP.

Conclusions—In subjects with HFpEF, sildenafil displayed opposing effects on ventricular and vascular function. We speculate that beneficial effects of PDE5i in the systemic vasculature and endothelium were insufficient to improve clinical status, or that the deleterious effects on left ventricular function offset any salutary vascular effects, contributing to the absence of benefit observed with sildenafil in subjects with HFpEF in the RELAX trial.

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Keywords

heart failure; diastolic heart failure; phosphodiesterase inhibitor heart failure; ventricular function; vascular function

Nearly half of people with heart failure (HF) have a preserved ejection fraction (HFpEF).[1] The pathophysiology of HFpEF is complex, caused by multiple impairments in ventricular diastolic, systolic, chronotropic, endothelial, vascular and peripheral functions.[2–8] Trials testing neurohormonal antagonists in HFpEF have produced neutral results to date, and novel HF therapies that target multiple ventricular-vascular domains may be more effective in this HF phenotype.[9]

Numerous lines of evidence point to abnormalities in nitric oxide-cyclic guanosine monophosphate (NO-cGMP) signaling as playing a key role in the pathophysiology of HFpEF.[2, 10, 11] Phosphodiesterase 5 inhibitors (PDE5i) enhance cGMP by decreasing its degradation. Studies in HF with reduced EF (HFrEF) have reported beneficial effects from PDE5i on ventricular structure, function and exercise capacity,[12–15] and a small, single center trial in HFpEF reported marked improvements in hemodynamics, ventricular function, and gas exchange with sildenafil therapy in HFpEF subjects with pulmonary hypertension and right ventricular dysfunction.[16]

The RELAX trial tested the hypothesis that the PDE5i sildenafil would improve exercise capacity and clinical status in people with HFpEF but observed no benefit compared to placebo.[17] In order to better understand the effects of sildenafil on cardiovascular function in people with HFpEF, we performed a prospective RELAX ancillary study comprehensively examining ventricular, vascular function and endothelial function at rest and during exercise in participants enrolled in the parent trial.

Methods

RELAX was a multicenter randomized (1:1) placebo-controlled trial testing the impact of chronic PDE5i with sildenafil on exercise capacity in patients with HFpEF.[17] The trial was conducted by the Heart Failure Clinical Research Network and funded by the National Heart, Lung, and Blood Institute. This prospective ancillary study was approved by the institutional review board and enrolled subjects participating in the parent study who provided separate written informed consent. Additional details on the rationale, study design and trial results for the RELAX trial have been published.[17, 18]

Study Participants

Consecutive HFpEF subjects participating at the Mayo Clinic site meeting the following criteria were enrolled: LVEF≥50%, peak oxygen consumption (peak VO_2) ≤60% predicted, and evidence for pulmonary venous hypertension (elevated pulmonary capillary wedge pressure or NT-proBNP≥400 pg/mL). Detailed inclusion and exclusion criteria have been

published.[17, 18] Subjects with irregular heart rhythm at enrollment were excluded from this ancillary study.

Study Protocol

At the first visit, prior to administration of study drug, a comprehensive resting echocardiogram was performed in the upright position to derive baseline measures of ventricular systolic, diastolic and vascular function. Arterial tonometry was performed to characterize central aortic waveforms. Endothelium-dependent vasodilation was assessed by digital tonometry. Brachial arterial blood pressure (BP) was determined by auscultation. Heart rate (HR) was determined by 12 lead electrocardiography continuously during the test. After resting assessments, subjects underwent maximal effort upright cycle exercise testing with gas exchange analysis. Echocardiographic measurements and BP assessment were repeated at low level exercise (20 Watts) and again at peak exercise. Subjects then repeated this protocol after 12 weeks of treatment with sildenafil 20 mg tid or placebo, and again after 24 weeks of sildenafil titrated to 60 mg tid or placebo. All outcome measures were analyzed offline by persons blinded to study drug allocation and time of study (baseline, 12 weeks, and 24 weeks).

Echocardiographic Assessment

All echocardiographic studies were recorded to optical disc and interpreted offline in a blinded fashion at the Mayo clinic core laboratory. Resting LV end systolic and end diastolic volumes (ESV, EDV), mass and EF were determined from biplane 2D echocardiography by trained cardiovascular sonographers according to current guidelines using the mean of ≥3 separate beats.[19] Stroke volume (SV) was determined from the LV outflow pulse wave Doppler spectrum.[20] Cardiac output (CO) was calculated as the product of SV and HR. Left ventricular contractility was assessed using load-independent indices as previously described: LV peak power index (PWR/EDV), determined as the product of peak LV systolic flow velocity and systolic BP divided by EDV, and LV stroke work index (SW/EDV), determined as the product of mean BP and SV divided by EDV.[2, 20–22] LV diastolic function was assessed by transmitral E and A flow velocities, mitral annular tissue velocity averaged from the medial and lateral annuli (E′), and the E/E′ ratio.[23] Pulmonary arterial systolic pressure (PASP) was estimated by the modified Bernoulli equation assuming a right atrial pressure of 10mmHg.[19]

Vascular assessment

Radial applanation tonometry (Millar Instruments) was performed at rest to derive central aortic BP waveforms (SphygmoCor device, Atcor Medical) as previously described.[24] Arterial stiffness and wave reflection were quantified by the augmentation index (cAIx), defined by the ratio of central augmented pressure to central pulse pressure (cPP). Effective arterial elastance (Ea) was calculated as 0.9*cSBP/SV, systemic vascular resistance (SVR) as cMBP*80/CO, and total arterial compliance (TAC) as SV/cPP.[2]

Endothelial function was assessed by reactive hyperemic (RH) change in digital blood flow in response to upper arm cuff occlusion (EndoPAT 2000, Itamar-Medical, Caesarea, Israel) as previously described.[2] Briefly, after 5 min of baseline recording, a BP cuff was inflated to

supra-systolic pressure in the test arm for 5 minutes. The cuff was then rapidly deflated with peripheral arterial tonometry (PAT) tracings recorded in the test and control arms. The RH index (RHI) was determined as the PAT ratio between 60 seconds and 120 seconds after occlusion in the test arm relative to the control arm, divided by the respective values for the 140 seconds prior to cuff inflation. Endothelial dysfunction was defined categorically by RHI<2.0.[2]

Exercise Protocol

Details of the RELAX cardiopulmonary exercise test (CPXT) protocol and HFN CPXT core laboratory (Massachusetts General Hospital, Boston, MA) methodologies have been reported.[18] Symptom-limited CPXT with simultaneous expired gas analysis was performed on an upright cycle ergometer during maximal effort exercise testing to derive peak oxygen consumption (peak VO_2) and respiratory exchange ratio (RER).

Statistical Analysis

Data are presented as mean±SD, median (25th–75th percentiles), and number (%). Baseline characteristics were compared using t test, Wilcoxon rank-sum test, or $\chi 2$ test. Baseline corrected parameters were compared in the sildenafil and placebo groups using a generalized linear model for changes at 12 weeks relative to baseline and 24 weeks relative to baseline. Analyses were performed using SAS version 9.2; $P<0.05$ (2-sided) was considered statistically significant.

Results

Of the 216 subjects enrolled in RELAX, 48 (22%) participated in this prospective ancillary study, 25 randomized to placebo and 23 to sildenafil. Similar to the parent trial, subjects were older-aged with high prevalence of comorbidities including hypertension, diabetes, obesity, and coronary disease (Table 1). Plasma NT-proBNP levels were similarly elevated in subjects randomized to placebo and sildenafil. There were no statistically significant baseline differences in age, sex, HF severity, comorbidities, exam findings, laboratories or medications.

Subjects displayed well-controlled BP, normal LV chamber size, LV diastolic dysfunction (low E′, elevated E/e′ and E/A ratios), increased arterial stiffness (median cAIx 24%) and normal PASP (median 29 mmHg, Table 2). Endothelium-dependent vasodilation was assessed in 33 subjects (19 randomized to placebo, 14 sildenafil) and endothelial dysfunction (ED, RHI<2.0) was observed in 58%. There were no statistically significant differences in baseline ventricular-vascular structure and function, endothelial function, arterial tonometry or exercise capacity between subjects randomized to sildenafil vs placebo (Table 2).

Exercise capacity was severely depressed in HFpEF subjects (median peak VO_2 12.6 ml/min/kg). There were similar increases in HR and BP at low level and peak exercise in subjects randomized to placebo and sildenafil at baseline (Table 2). As in prior studies,[2] subjects with HFpEF displayed blunted increases in EF during low level and peak exercise.

Subjects randomized to sildenafil tended to display less increase in EF during exercise at the baseline visit (Table 2).

Effects of Sildenafil on Resting Ventricular-Vascular Function

After 12 weeks treatment with study drug (20 mg tid), subjects randomized to sildenafil displayed greater reduction in resting central systolic BP (cSBP) and tended to display greater reductions in resting Ea and SVR compared to controls (Table 3). Low dose sildenafil had no statistically significant effect on resting LV systolic or diastolic function, cAIx, or PASP after 12 weeks as compared to placebo. As in the main RELAX trial, there was no significant effect of sildenafil on peak VO_2 compared to placebo after 12 or 24 weeks treatment (Table 3).

After 24 weeks of treatment with study drug titrated to 60 mg tid, subjects randomized to sildenafil displayed greater reductions in Ea and tended to show greater increases in RHI (Table 3, Figure). Improvements in Ea and RHI were not correlated with changes in peak VO_2 ($p>0.2$). There were no statistically significant differences in central BP, cAIx or SVR. Higher dose sildenafil treatment had no significant effect on LV EF, but resting LV stroke work index (SW/EDV) and peak power index (PWR/EDV) decreased by 11% and 16% respectively (Table 3, Figure). The change in LV peak power index correlated directly with the change in peak VO_2 compared to baseline, as patients with a larger decrease in contractility displayed greater decreases in peak VO_2 (Supplemental Figure). High dose sildenafil had no significant effect on PASP but increased early LV diastolic filling velocity (E) compared to controls (Table 3). Sildenafil had no significant effect on other measures of LV diastolic function at 12 or 24 weeks.

Effects of Sildenafil on Ventricular-Vascular Reserve Function

Subjects in this study were not selected based upon adequate echocardiographic images, and this fact, coupled with the technical limitations with 2D and Doppler imaging in the upright position during exercise, and the strict criteria for high quality of images/signals for quantitative analysis by the core laboratory, resulted in high rates of missingness for most variables during exercise. Thus assessment of reserve function was limited to measurement of changes in blood pressure and EF during low level and peak exercise. Adjusted to reserve responses observed in the baseline exercise test at study entry, there was greater enhancement in EF with exercise after 12 weeks in subjects randomized to sildenafil, coupled with a trend toward less increase in systolic BP (12 weeks, Table 4). After 24 weeks, there was less increase in systolic BP in subjects randomized to sildenafil at low level exercise, but no statistically significant difference in the change in EF with exercise (Table 4). Sildenafil tended to decrease peak exercise heart rate at both 12 and 24 weeks but this was not significant compared to placebo.

Discussion

This prospective study examined the effects of low dose (20 mg tid for 12 weeks) and high dose (60 mg tid from 12 to 24 weeks) sildenafil on cardiovascular function at rest and with submaximal and peak exercise in 48 subjects participating in the RELAX trial. Compared to

placebo, subjects randomized to sildenafil displayed greater systemic afterload reduction and tended to show improved endothelium-dependent vasodilation. While there was no change in resting EF, there were modest reductions in left ventricular contractility assessed using two load-independent measures of systolic function, and the degree of reduction in PWR/EDV was correlated with reductions in peak VO_2. There was no significant effect on PASP. Sildenafil tended to reduce the increase in BP during exercise, and this was coupled to slightly greater increases in EF with low dose but not high dose sildenafil. From these data we speculate that either the beneficial effects of sildenafil in the systemic vasculature and endothelium were insufficient to improve clinical status, or that the deleterious effects of sildenafil on left ventricular function offset any salutary vascular effects, contributing to the absence of benefit observed with sildenafil in subjects with HFpEF in the RELAX trial.[17]

The pathophysiology of HFpEF is complex—related to global impairments in systolic and diastolic function in the left and right ventricles, abnormal vasodilation, pulmonary hypertension, endothelial dysfunction, chronotropic incompetence, and abnormalities in the skeletal muscle and periphery.[8] Clinical trials to date testing neurohormonal antagonists have been neutral in HFpEF, and novel therapies that target multiple components in the pathophysiology may be more effective.[9] Phosphodiesterase inhibitors such as sildenafil have been shown in other patient populations to improve pulmonary vascular resistance, right ventricular function, ventricular remodeling, endothelial function, quality of life, and exercise capacity, suggesting numerous reasons for patients with HFpEF to benefit from this class of medicine.[12–15, 18, 25]

In a single center study of 44 patients with HFpEF and severe pulmonary vascular disease, 12 months of treatment with sildenafil improved RV-PA coupling and reduced PA and biventricular filling pressures.[16] However, in the larger, multicenter RELAX trial, sildenafil use did not improve exercise capacity, plasma biomarkers or clinical status in patients with typical HFpEF as observed in the community.[17]

The current results may provide greater insight into the reasons for lack of benefit from sildenafil in HFpEF.[17] Modest systemic arterial vasodilation was observed, which was coupled with a trend toward improved endothelium-dependent vasodilation after 24 weeks treatment, similar to prior observations of PDE5i in HFrEF.[15, 25] Endothelial dysfunction has recently been proposed to play a major role in the pathophysiology of HFpEF, contributing to both ventricular and vascular dysfunction.[10] However, 42% of HFpEF participants in this ancillary study did not display digital endothelial dysfunction, suggesting that abnormal flow mediated dilation is not necessary to cause the disease. The prevalence of endothelial dysfunction in this cohort is similar to a prior study evaluating microvascular function in HFpEF,[2] but is higher than 2 other studies assessing large vessel flow mediated dilation.[26, 27] The discrepancy between these studies may relate to fundamental differences in the vascular beds studied and their assessment methods.[28] It may be that more chronic, sustained improvements in endothelial function are required to improve ventricular stiffness and remodeling, that different pharmacologic approaches to enhance cGMP signaling will be more effective, or that the degree of improvement in endothelial and vascular function achieved in RELAX was insufficient to improve aerobic capacity.

An alternative interpretation is that the deleterious effects on LV systolic function might have offset beneficial effects on the endothelium and vasculature. LV contractility, assessed by two load-independent measures, was modestly but significantly reduced with sildenafil. The mechanisms for this effect remain unclear, but previous studies have shown that enhanced NO-cGMP signaling can act as a negative inotrope.[20, 29, 30] Intracellular cGMP-PKG may serve as a "brake" to oppose cAMP-PKA mediated effects on calcium handling and myofilament interaction. This is achieved in the myocyte by activation of dual substrate PDEs that hydrolyze both cAMP and cGMP,[31] and through PKG, which directly counteracts multiple PKA effects that enhance contractile function.[29, 32] The change in LV peak power index was correlated with changes in exercise capacity, supporting the plausibility of a mechanistic relationship.

Sildenafil has been shown to reduce PA pressures in HF,[12, 13, 16] but in the current study there was no effect of sildenafil on resting PASP. This may relate in part to the absence of significant PH in the study population, as well as to the imprecision of echocardiography to estimate PA pressures. The presence of PH was not required for entry into RELAX, and it is possible that effects on ventricular-vascular function would have been different in a more diseased population with significant pulmonary vascular disease. Indeed, prior studies have shown that PDE5i may exert a positive inotropic effect in the right ventricle in groups with more severe PH.[33] One theoretical concern with pulmonary vasodilators in HFpEF is the development of left atrial hypertension with reduction in PA resistance.[34] There was greater increase in transmitral E velocity with high dose sildenafil, indicating an increase in the left atrium-LV pressure gradient, though the change in E/e′ did not differ between groups. If the magnitude of left atrial pressure elevation were matched to any reduction in PA resistance, there could be a neutral effect on PASP, but this hypothesis cannot be addressed with these noninvasive data.

Limitations

Ventricular-vascular function was assessed in this study using noninvasive techniques that have greater variability than invasive methods. Owing to the difficulties in obtaining diagnostic quality echocardiography at rest and particularly during exercise, there was missing data, especially at peak exercise, which increases the risk of Type 2 error. Myocardial strain imaging was not performed as part of this study. Right atrial pressure was not estimated based upon caval dimension or collapsibility in this study, but rather assumed to uniformly be equal to 10 mmHg. While the clinical characteristics in this ancillary study resemble those in the community, some markers of disease severity such as E/e′ ratio and PASP were numerically lower that median values in the parent RELAX trial, suggesting a less advanced stage of HFpEF, which may limit the generalizability of these findings to patients with more advanced HFpEF, especially patients with significant pulmonary vascular disease. Patients who were in atrial fibrillation were excluded and these results may not apply to that cohort. The aim of this study was to comprehensively assess ventricular, vascular and endothelial function, requiring a large number of comparisons. Statistical adjustments were not made for multiple comparisons in this study, because many of the ventricular-vascular parameters are correlated with one another, and correction techniques such as the Bonferroni method assume the observations are independent. Multivariable

analysis was not performed because of the missing data that varied between measured parameters of cardiac and vascular function, resulting in low power and higher risk of Type II error.

Conclusions

In patients with HFpEF, treatment with sildenafil was associated with systemic vasodilation, a trend toward improved endothelium-dependent vasodilation, and depressed resting left ventricular contractility, with no effect on estimated pulmonary artery pressure. We speculate that beneficial effects of PDE5i in the systemic vasculature and endothelium were insufficient to improve clinical status, or that the deleterious effects on left ventricular function offset any salutary vascular effects, contributing to the absence of benefit observed with sildenafil in subjects with HFpEF in the RELAX trial.

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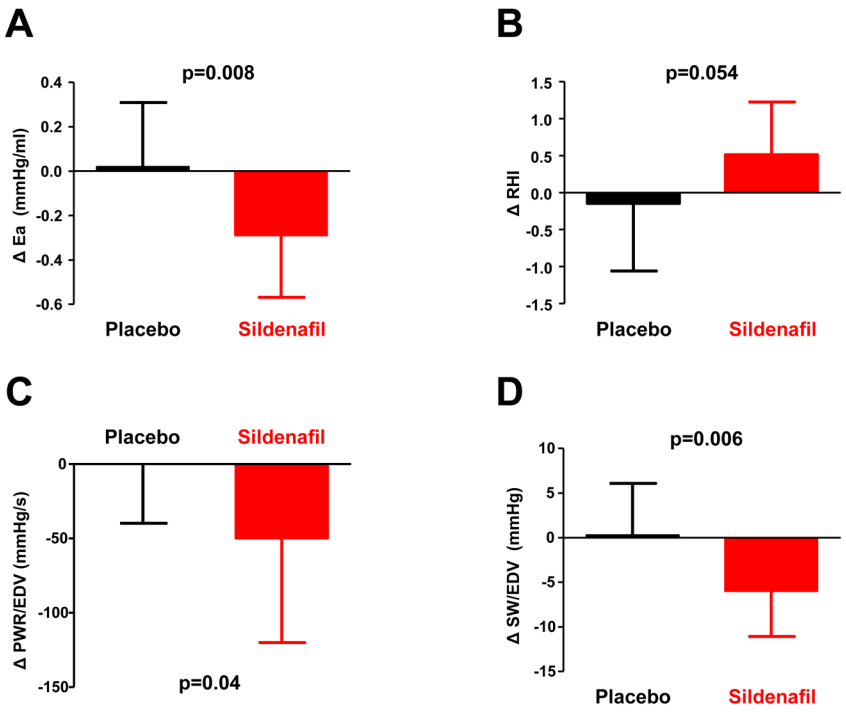

Figure.

[A] Effective arterial elastance (Ea) was reduced at rest after 24 weeks treatment in subjects randomized to sildenafil (red) compared to placebo. [B] 24 week changes in endothelial function, assessed as the reactive hyperemia index (RHI) in placebo and sildenafil. Left ventricular contractility, assessed as [C] peak power index (PWR/EDV) and [D] stroke work index (SW/EDV) was reduced after 24 weeks treatment with sildenafil (red) as compared to placebo (black).

Table 1

Baseline Characteristics

	Placebo (n=25)	Sildenafil (n=23)	p
Clinical Characteristics			
Age (years)	71 (65, 77)	69 (62, 72)	0.2
Female (%)	56	61	0.7
Body Mass Index (kg/m^2)	31.2 (28.4, 33.3)	29.9 (27.4, 38.4)	0.97
NYHA class II/III (%)	44/56	43/57	0.97
Hypertension (%)	84	74	0.4
Diabetes (%)	32	39	0.6
Obese (%)	64	48	0.3
Coronary artery disease (%)	32	35	0.8
Atrial fibrillation/flutter history (%)	24	30	0.6
Exam			
Jugular venous pressure (%)			0.4
< 8 cm	48	61	
8–12 cm	28	26	
13–16 cm	20	4	
> 16 cm	4	9	
Peripheral Edema (%)			0.2
None	40	57	
Trace	44	35	
Moderate	16	9	
Severe	0	0	
Laboratories			
Hemoglobin (gm/dL)	13.3 (12.3, 13.7)	13.1 (12.4, 14.4)	0.4
Creatinine (mg/dL)	1.0 (0.9, 1.1)	1.0 (0.8, 1.3)	0.7
NT-proBNP (pg/mL)	435 (132,618)	353 (76,788)	0.5
Medications			
ACEI/ARB (%)	72	61	0.4
Beta Blocker (%)	80	74	0.6
Diuretic (%)	68	65	0.8

Table 2

Baseline Cardiovascular Structure and Function

	Placebo (n=25)	Sildenafil (n=23)	p
Heart rate (bpm)	61 (56, 75)	62 (58, 75)	0.8
SBP (mmHg)	122 (108, 128)	118 (110, 128)	0.8
DBP (mmHg)	64 (62, 70)	70 (62, 74)	0.15
LV structure and function			
EDV (ml, n=23/21)	126 (113, 137)	114 (101, 128)	0.18
LV mass (gm, n=22/18)	167 (153, 225)	167 (123, 207)	0.4
E velocity (cm/s, n=25/22)	70 (60, 100)	70 (60, 90)	0.6
DT (ms, n=24/22)	215 (202, 251)	221 (190, 251)	0.8
E/A ratio (n=23/20)	1.0 (0.8, 2.1)	1.1 (0.8, 1.3)	0.7
E′ (cm/s)	6.5 (5.5, 7.0)	6.0 (5.0, 6.5)	0.2
E/e′ ratio (n=25/22)	11.7 (9.3, 15.0)	12.5 (9.3, 20.0)	0.6
EF (%, n=24/23)	60 (55, 60)	60 (55, 60)	0.6
PWR/EDV (mmHg/sec, n=23/21)	327 (277, 365)	359 (319, 380)	0.19
SW/EDV (mmHg, n=23/21)	50.7 (46.5, 55.2)	54.2 (47.3, 56.8)	0.3
Vascular Function			
Ea (mmHg/ml, n=24/21)	1.5 (1.2, 1.7)	1.7 (1.6, 1.9)	0.07
RHI (n=19/14)	1.9 (1.6, 2.3)	1.9 (1.5, 2.1)	0.6
ED (%)	53	64	0.5
SVR (DSC, n=24/21)	1417 (1245, 1700)	1688 (1385, 1828)	0.11
TAC (ml/mmHg, n=22/20)	1.69 (1.40, 2.43)	1.71 (1.33, 1.99)	0.7
cSBP (mmHg, n=23/22)	110 (100, 121)	109 (99, 118)	0.7
cAIx (%, n=23/22)	24 (17, 29)	24.5 (17, 29)	0.98
PASP (mmHg, n=19/11)	30 (28, 43.4)	28 (26.2, 41)	0.3
Exercise Capacity			
Peak VO_2 (ml/min/kg)	12.6 (11.1, 14.3)	11.6 (10.1, 15.7)	0.97
Peak RER	1.07 (10.4, 1.11)	1.09 (1.03, 1.17)	0.4
Exercise Hemodynamics and Reserve			
ΔHR, low (bpm)	13 (9, 18)	16 (9, 18)	0.8
ΔHR, peak (bpm)	47 (34, 53)	52 (34, 70)	0.13
ΔSBP, low (mmHg)	10 (2, 16)	14 (6, 18)	0.4
ΔSBP, peak (mmHg)	38 (28, 56)	34 (22, 58)	0.5
ΔDBP, low (mmHg)	2 (0, 4)	0 (−2, 4)	0.4
ΔDBP, peak (mmHg)	2 (−6, 8)	6 (−2, 10)	0.2
ΔEF, low (%, n=23/23)	5 (0, 5)	0 (0, 5)	0.06
ΔEF, peak (%, n=21/21)	10 (5, 10)	5 (5, 10)	0.19

Column 1 parentheses indicate number of placebo/sildenafil subjects with available data for each parameter; if no numbers are presented there was no data missing. P values are not adjusted for multiple comparisons.

Table 3

Sildenafil Effects on Resting Cardiovascular Function

	Placebo (n=25)	Sildenafil (n=23)	p
Changes at 12 weeks			
Δ HR (bpm)	0 ± 10	−2 ± 9	0.5
Δ EDV (ml, n=22/18)	3 ± 20	4 ± 20	0.9
Changes at 24 weeks			
Δ HR (bpm)	−1 ± 10	−2 ± 10	0.6
Δ EDV (ml, n=21/18)	3 ± 19	12 ± 23	0.2
Changes in vascular function, 12 weeks			
Δ cSBP (mmHg, n=21/20)	7 ± 17	−9 ± 20	0.005
Δ cAIx (%, n=21/20)	1 ± 7	−1 ± 10	0.4
Δ Ea (mmHg/ml, n=23/18)	0.08 ± 0.45	−0.14 ± 0.25	0.17
Δ SVR (dyne/s*cm^5, n=23/18)	73 ± 457	−131 ± 300	0.2
Δ TAC (ml/mmHg, n=19/15)	0.01 ± 0.70	0.30 ± 0.60	0.3
Δ RHI (n=16/12)	0.05 ± 0.60	0.20 ± 0.51	0.5
Δ PASP (mmHg, n=16/8)	−1 ± 8	0 ± 4	0.8
Changes in vascular function, 24 weeks			
Δ cSBP (mmHg, n=16/17)	2 ± 16	1 ± 29	0.9
Δ cAIx (%, n=16/17)	−1 ± 5	1 ± 11	0.6
Δ Ea (mmHg/ml, n=22/18)	0.02 ± 0.29	−0.29 ± 0.28	0.008
Δ SVR (dyne/s*cm^5, n=22/18)	−27 ± 370	−169 ± 375	0.4
Δ TAC (ml/mmHg, n=15/15)	0.04 ± 0.73	0.25 ± 0.61	0.7
Δ RHI (n=15/14)	−0.17 ± 0.61	0.30 ± 0.45	0.054
Δ PASP (mmHg, n=15/10)	0 ± 6	3 ± 7	0.5
Changes in LV systolic function, 12 weeks			
Δ EF (%, n=24/22)	−1 ± 7	1 ± 4	0.08
Δ SW/EDV (mmHg, n=22/18)	0.6 ± 8.1	−2.8 ± 4.5	0.2
Δ PWR/EDV (mmHg/s, n=22/18)	37 ± 80	18 ± 50	0.8
Changes in LV systolic function, 24 weeks			
Δ EF (%, n=23/21)	0 ± 5	0 ± 4	0.95
Δ SW/EDV (mmHg, n=21/18)	0.3 ± 5.8	−6.0 ± 5.1	0.006
Δ PWR/EDV (mmHg/s, n=21/18)	0 ± 40	−52 ± 70	0.04
Changes in LV diastolic function, 12 weeks			
Δ E velocity (cm/s, n=24/20)	1.7 ± 19	8.5 ± 18	0.3
Δ DT (ms, n=22/19)	−4 ± 48	2 ± 38	0.7
Δ E/A ratio (n=21/19)	−0.0 ± 0.5	0.2 ± 0.7	0.3
Δ E′ (cm/s, n=24/19)	0.1 ± 1.0	0.2 ± 1.0	0.9
Δ E/E′ (n=23/19)	−0.0 ± 3.8	1.2 ± 3.8	0.3
Changes in LV diastolic function, 24 weeks			
Δ E velocity (cm/s, n=23/20)	−0.4 ± 19	12.5 ± 19	0.02
Δ DT (ms, n=22/18)	−4 ± 39	−8 ± 39	0.8

	Placebo (n=25)	Sildenafil (n=23)	p
Δ E/A ratio (20/18)	−0.0 ± 0.6	0.4 ± 0.8	0.07
Δ E′ (cm/s, n=23/20)	−0.2 ± 0.0	0.4 ± 0.0	0.2
Δ E/E′ (n=22/20)	0.9 ± 4.9	1.9 ± 5.2	0.6
Changes in Exercise Capacity, 12 weeks			
Δ Peak VO2 (ml/min/kg)	−0.4 ± 1.5	−0.7 ± 3.0	0.7
Δ RER	0.01 ± 0.08	0.02 ± 0.11	0.8
Changes in Exercise Capacity, 24 weeks			
Δ Peak VO2 (ml/min/kg, n=24/23)	−0.8 ± 1.7	−0.6 ± 2.7	0.8
Δ RER (n=23/23)	0.01 ± 0.11	0.01 ± 0.11	0.5

Column 1 parentheses indicate number of placebo/sildenafil subjects with available data for each parameter; if no numbers are presented there was no data missing. P values are not adjusted for multiple comparisons.

Table 4

Effects of Sildenafil on Exercise Reserve Responses

	Placebo (N=25)	Sildenafil (N=23)	P value*	P-value**
12 Weeks				
Baseline SBP, low (mmHg, n=25/22)	131 ± 18	138 ± 18		
Week 12 SBP, low (mmHg, n=25/22)	133 ± 16	129 ± 23		
ΔSBP, low	2 ± 21	−9 ± 16	0.15	0.3
Baseline SBP, peak (mmHg, n=25/23)	163 ± 23	169 ± 24		
Week 12 SBP, peak (mmHg, n=25/23)	166 ± 24	165 ± 24		
ΔSBP, peak	3 ± 19	−3 ± 16	0.3	0.4
Baseline DBP, low (mmHg, n=25/22)	72 ± 9	75 ± 13		
Week 12 DBP, low (mmHg, n=25/22)	72 ± 8	72 ± 10		
ΔDBP, low	−0.2 ± 9	−3 ± 13	0.6	0.7
Baseline DBP, peak (mmHg, n=25/23)	71 ± 13	77 ± 15		
Week 12 DBP, peak (mmHg, n=25/23)	73 ± 14	74 ± 12		
ΔDBP, peak	2 ± 13	−3 ± 12	0.4	0.4
Baseline HR, low (mmHg, n=25/23)	80 ± 12	83 ± 16		
Week 12 HR, low (mmHg, n=25/23)	79 ± 11	79 ± 17		
ΔHR, low	−1 ± 9	−4 ± 9	0.3	0.4
Baseline HR, peak (mmHg, n=25/23)	110 ± 19	119 ± 25		
Week 12 HR, peak (mmHg, n=25/23)	109 ± 18	108 ± 19		
ΔHR, peak	−1 ± 13	−11 ± 19	0.11	0.08
Baseline EF, low (mmHg, n=22/20)	62 ± 6	61 ± 6		
Week 12 EF, low (mmHg, n=22/20)	61 ± 6	63 ± 5		
ΔEF, low	−1 ± 6	2 ± 4	0.054	0.09
Baseline EF, peak (mmHg, n=19/18)	68 ± 6	66 ± 6		
Week 12 EF, peak (mmHg, n=19/18)	64 ± 7	68 ± 6		

	Placebo (N=25)	Sildenafil (N=23)	P value*	P-value**
ΔEF, peak	−3 ± 6	2 ± 4	0.008	0.01
24 Weeks				
Baseline SBP, low (mmHg, n=24/23)	130 ± 18	140 ± 19		
Week 24 SBP, low (mmHg, n=24/23)	133 ± 16	130 ± 28		
ΔSBP, low	3 ± 16	−9 ± 19	0.047	0.07
Baseline SBP, peak (mmHg, n=24/23)	163 ± 24	169 ± 24		
Week 24 SBP, peak (mmHg, n=24/23)	162 ± 25	163 ± 30		
ΔSBP, peak	−0.2 ± 19	−5 ± 22	0.5	0.5
Baseline DBP, low (mmHg, n=24/23)	72 ± 9	75 ± 13		
Week 24 DBP, low (mmHg, n=24/23)	71 ± 11	70 ± 9		
ΔDBP, low	−1 ± 10	−5 ± 13	0.5	0.4
Baseline DBP, peak (mmHg, n=24/23)	70 ± 12	77 ± 15		
Week 24 DBP, peak (mmHg, n=24/23)	71 ± 15	72 ± 13		
ΔDBP, peak	1 ± 12	−6 ± 12	0.2	0.2
Baseline HR, low (mmHg, n=24/23)	80 ± 12	83 ± 16		
Week 24 HR, low (mmHg, n=24/23)	79 ± 10	77 ± 14		
ΔHR, low	−1 ± 9	−6 ± 10	0.07	0.09
Baseline HR, peak (mmHg, n=24/23)	109 ± 19	119 ± 25		
Week 24 HR, peak (mmHg, n=24/23)	110 ± 19	107 ± 24		
ΔHR, peak	1 ± 13	−12 ± 19	0.02	0.01
Baseline EF, low (mmHg, n=25/22)	62 ± 5	61 ± 6		
Week 24 EF, low (mmHg, n=25/22)	62 ± 6	62 ± 6		
ΔEF, low	−0.2 ± 6	0.3 ± 5	0.99	0.93
Baseline EF, peak (mmHg, n=20/18)	68 ± 6	66 ± 6		
Week 24 EF, peak (mmHg, n=20/18)	66 ± 6	66 ± 6		
ΔEF, peak	−1 ± 6	1 ± 6	0.5	0.6

*P-values adjusted for baseline

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** P-values adjusted for age and baseline

Column 1 parentheses indicate number of placebo/sildenafil subjects with available data for each parameter.