Title: Sildenafil Administration Improves Right Ventricular Function on 4D Flow MRI in Young Adults Born Premature

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Abstract

Background

Individuals born very or extremely premature have an elevated risk of heart failure by young adulthood. Prior studies demonstrate smaller ventricular chamber size, higher resting heart rates, diastolic dysfunction, and pulmonary hypertension. However, it remains unknown how hemodynamic manipulations may affect right ventricular function and coupling.

Methods

4D flow MRI was used to assess the effect of afterload reduction and heart rate reduction on cardiac hemodynamics and function. Young adults born premature were administered sildenafil (a pulmonary vasodilator) and metoprolol (a beta blocker) on separate days, and MRI with 4D flow completed before and after each drug administration. Endpoints include cardiac index (CI), direct flow fractions, and ventricular kinetic energy including E/A wave kinetic energy ratio.

Results

Sildenafil resulted in a 14% increase in CI ($P<0.01$), mediated through both an increase in heart rate and stroke volume. Although right ventricular (RV) ejection fraction improved only modestly, there was a significant 13% increase in RV direct flow fraction ($P=0.04$), consistent with improved hemodynamic flow. Metoprolol administration resulted in a 7% decrease in heart rate ($P=0.04$), an 11% decrease in CI ($P=0.03$), and an 18% reduction in time-averaged, normalized kinetic energy in both ventricles ($P<0.01$), despite improved RV diastolic function as measured by E/A wave kinetic energy ratio ($P=0.04$).

Conclusions

Despite improved RV diastolic function, metoprolol significantly depressed overall cardiac systolic function. Sildenafil, however, increased CI and improved RV function, as quantified by the direct flow fraction. The preterm heart appears dependent on heart rate, but sensitive to afterload manipulations.

Introduction

As advances in the treatment of extremely premature infants decrease mortality (36), the long-term ramifications of premature birth are coming to light. In addition to known pulmonary consequences of premature birth, including bronchopulmonary dysplasia (20, 30) and higher rates of asthma and chronic obstructive pulmonary disease (37), recent epidemiologic evidence suggests up to a 17-fold increased risk of heart failure in those born extremely premature (≤ 28 gestational weeks) (5).

Several imaging studies have investigated cardiac structural and functional differences in young adults born premature compared to term-born controls, finding smaller biventricular chambers and stroke volumes (2, 13, 19, 21–23, 26). Functionally, the right ventricle (RV) appears to be more affected throughout the lifespan. While some studies report preserved function, others note impairment in systolic and diastolic function from infancy through early adulthood (8, 26, 34). In a small catheter-based study, otherwise healthy young adults born very to extremely premature (≤ 32 gestational weeks) had an average mean pulmonary artery pressure (mPAP) of 19.7 mmHg (versus 14.0 mmHg in term-born), demonstrating pulmonary hypertension as defined by an mPAP above 20 mmHg in nearly half (12). Among these preterm-born individuals, many also had evidence of early decline in right ventricular-pulmonary vascular coupling (28). Considering that the impairments in right ventricular function are present despite only mild increases in pulmonary pressures, some have suggested that prematurity represents a unique insult to the transitioning RV that does not follow the classic paradigm of RV failure secondary to severe progressive pulmonary vascular disease (34). Thus, the preterm heart requires unique considerations with respect to potential pharmacologic intervention.

We have previously identified right ventricular diastolic dysfunction and pulmonary hypertension in young adults born preterm (12). While right ventricular diastolic dysfunction may be related to pulmonary hypertension (32), individuals born preterm frequently have higher resting heart rates which may also contribute to impaired filling time. Here, we sought to determine the effect of right ventricular afterload reduction and heart rate reduction on cardiac hemodynamics and function in a study using 4D flow MRI – a unique technique for comprehensive assessment of pulsatile, three-dimensional blood flow throughout the heart (7, 24). This study represents a novel use of 4D flow MRI to measure acute intraventricular hemodynamic effects of cardiac targeted therapeutics.

Methods

Participants

Nine young adults participated in this study at our academic medical center from 2018-2020. The study was registered with the U.S. National Library of Medicine (identifier: NCT03696758). Subjects born very to extremely premature (gestational age ≤32 weeks, or birth weight <1500 g) were recruited from either the Newborn Lung Project, a cohort of infants born premature between 1988 and 1991 in Wisconsin and Iowa (31) and followed prospectively from birth, or from the local population after verification of preterm birth history from neonatal records. All participants were free of current cardiovascular or respiratory illness and were nonsmokers. The study had a crossover design with each participant undergoing two study visits (Figure 1). On the first visit, each subject was randomly assigned to receive either intravenous metoprolol tartrate (Lopressor; Novartis Pharmaceuticals Corporation; East Hanover, NJ, USA) or oral sildenafil citrate (Viagra; Pfizer; New York, NY, USA). Each subject received the other drug on the second

visit, so that all 9 subjects received both drugs. All participants provided written informed consent in accordance with the standards set by the Declaration of Helsinki. The protocol was approved by the Institutional Review Board at our institution.

Cardiovascular Magnetic Resonance Imaging Acquisition

Each subject underwent cardiac MRI on a 3.0 T MRI scanner (Signa Premier, GE Healthcare, Waukesha, WI) with a 30-channel phased-array flexible coil both before and after drug administration. The full MRI protocol is provided in the appendix. Scans analyzed in this work include breath-held, short-axis and long-axis cine balanced steady-state free precession (bSSFP; scan parameters in appendix) images and 4D flow cardiac MRI (acquired with radially undersampled flow sequence [PC VIPR(14)]. 4D flow sequence parameters include velocity encoding [VENC] = 150 cm/s; spatial resolution = 2.5 mm isotropic; retrospective cardiac gating for 20 cardiac phases). Metoprolol dosing was titrated (1-5 mg Q2 min) to achieve a resting heart rate of 55-65. For subjects with a resting heart rate already within range, a 10-15% reduction in heart rate was targeted. Sildenafil dose was 50 mg, with a one-hour delay before post-sildenafil scanning to allow for drug absorption. Systemic blood pressure was recorded during each scan with a blood pressure cuff.

Feature-tracking Strain Analysis

Three short-axis cine slices from the left and right ventricles (apex, mid and base) on short-axis cine bSSFP MR images were used to analyze peak circumferential (LV and RV) and radial (LV only) myocardial strain via feature tracking (18). The average value of the 3 slices was reported as global strain. Long-axis images were used to measure peak longitudinal strain in both ventricles. Strain analysis was performed using commercially available software (Segment, version 2.2 R6423 strain analysis module; *http://segment.heiberg.se*).

Cardiac 4D Flow Image Analysis

The LV and RV cavities were manually segmented at each time frame on short-axis bSSFP images using Segment (Medviso, http://segment.heiberg.se; v2.0 R5399)(35). The contours were used to compute the following metrics, which were normalized by body surface area (BSA) (27) to control for the influence of subject size: end diastolic volume index (EDVi), end systolic volume index (ESVi), stroke volume index (SVi), and cardiac index (CI). Time to peak filling rate (TTPFR) was calculated from the volume-time curves as the time from the MRI system's ECG trigger to the maximum slope of the diastolic volume-time curve. The short axis dataset, including the RV/LV segmentations, was then rigidly registered (using the ANTs software package (1)) to the 4D flow time-averaged magnitude image, and ventricular velocities were extracted for flow analysis using the method proposed by Gupta et al (15). KE was then computed at each time frame by summing the KE contributions for all voxels, as described in Carlsson et al (4). Five 4D flow parameters, normalized by EDV to control for the impact of heart size, were extracted from the KE-time curve per ventricle: average KE/EDV, peak systolic KE/EDV, peak E-wave KE/EDV, peak A-wave KE/EDV, and the ratio of E-wave KE to A-wave KE.

The distribution of different ventricular flow components was determined in all subjects using the method of Eriksson et al (9, 10). Blood pathlines were emitted from the blood volume of each ventricle and traced forwards and backwards in time from end diastole until end systole, thus including the entire cardiac cycle. Pathlines were computed by integrating the velocity field using a 4^{th} order Range-Kutta numerical integration through time. Pathline location was used to separate the pathlines into four different components of flow: Direct Flow (blood that enters the ventricle during diastole and leaves the ventricle during systole in the analyzed heartbeat),

Retained Inflow (blood that enters the ventricle during diastole but does not leave during systole in the analyzed heartbeat), Delayed Ejection Flow (blood that starts and resides inside the ventricle during diastole and leaves during systole), and Residual Volume (blood that resides within the ventricle for at least two cardiac cycles). Pathlines passing through the ventricle wall (either entering or leaving the ventricle through the mid-ventricle or apical regions) were excluded from analysis. The fraction of EDV containing pathlines from each compartment was computed in each ventricle for all subjects.

Statistical Analysis

This study employed a paired sample technique where each subject participated in two experiments (one for each drug) and had two MRI scans for each experiment (pre and post drug administration), with each subject effectively serving as his or her own control. Paired sample Wilcoxon signed rank tests were used to test whether traditional CMR and 4D flow parameters changed significantly with each drug administration. Significance level was determined a priori at the 0.05 level and all tests were 2-tailed. No correction for multiple comparisons was performed. All data is presented as mean ± standard deviation, unless otherwise noted. All statistical analyses were performed in Excel (Microsoft Inc.; Redmond, Washington, USA; Version 16.35). The Matlab (MathWorks; Natick, MA; USA; Version 2019b) analysis scripts and 4D flow parameter data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Of the 9 subjects that participated in this study, 3 were males. Average gestational age and birth weight were 28.9 ± 2.7 weeks and 1120 ± 340 g, respectively. The subjects had a mean age

of 27.8 ± 3.7 years, a mean height of 163 ± 7 cm, and a mean weight of 75 ± 25 kg. The mean body surface area (BSA) and body mass index (BMI) of subjects was 1.83 ± 0.31 m^2 and 27.8 ± 7.9 kg/m^2, respectively.

Sildenafil

Sildenafil lowered systemic blood pressure from 113±17 / 63±8 mmHg to 105±13 / 61±11 mmHg (P=0.004 systolic; P=0.3 diastolic). Standard measures of cardiac morphometry and function on the sildenafil visit day (Table 1) revealed a 14% increase in cardiac index (P<0.01), mediated by a 9% increase in heart rate (P=0.02) and 6% increase in stroke volume index (P=0.07) after sildenafil administration. There was a nonsignificant increase in RV stroke volume to end systolic volume ratio, a noninvasive metric of RV-pulmonary vascular coupling. There were no significant changes in myocardial strain or ventricular kinetic energy after sildenafil administration (Table 1), although average KE in both ventricles trended higher (LV: P=0.25, RV: P=0.13). Flow compartment analysis of 4D flow MRI data (Table 2, Figure 2) revealed a significant shift towards direct flow in the RV, with a 13% increase in RV direct flow fraction (P=0.04) and a 17% decrease in RV residual volume fraction (P=0.03), consistent with improved hemodynamic flow within the RV.

Metoprolol

Metoprolol lowered systemic blood pressure from 115±13 / 69±11 mmHg to 107±11 / 63±10 mmHg (P=0.07 systolic; P=0.03 diastolic). Standard measures of cardiac morphometry and function on the Metoprolol visit day (Table 3) revealed an 11% decrease in cardiac index (P=0.03) mediated by a 7% decrease in heart rate (P=0.04) and 5% decrease in stroke volume (P=0.36) after Metoprolol administration. LV circumferential and longitudinal strain were reduced,

suggesting decreased LV contractility, while RV strain parameters were less impacted. Consistent with decreased contractility, ventricular kinetic energy was also reduced after metoprolol (Table 3). Time-averaged KE/EDV was reduced by 18% in both ventricles ($P<0.01$ for both ventricles). RV diastolic function, as measured by 4D flow MRI KE, improved with metoprolol: RV A-wave KE/EDV decreased by 29% ($P=0.01$) and the RV E/A KE ratio increased by 43% ($P=0.04$) after metoprolol administration. No significant changes in flow compartment distribution (Table 4) resulted from Metoprolol administration.

Discussion

Recent studies in young adults born premature have revealed reduced cardiac function (12, 13, 16, 19, 22, 23) as well as mild pulmonary hypertension (12) and early right ventricular-pulmonary vascular coupling impairments (28). In this study, we aimed to determine the effect of afterload reduction and heart rate reduction on cardiac hemodynamics and function using pharmacological MRI with 4D flow. We found that RV afterload reduction with sildenafil improved overall cardiac function and intraventricular flow hemodynamics. On the other hand, while heart rate reduction with metoprolol improved RV diastolic function, cardiac index, contractility, and ventricular kinetic energy were significantly reduced.

Given that right ventricular failure typically develops in response to progressive rise in afterload, our initial consideration was a trial of acute afterload reduction using sildenafil. Sildenafil is a potent pulmonary vasodilator that may also have direct inotropic and/or lusitropic effects (11, 29). Thus, we hypothesized that sildenafil would reduce afterload and improve RV diastolic dysfunction in the preterm heart. Consistent with our hypothesis, afterload reduction with sildenafil resulted a significant increase in cardiac index, mediated through both heart rate

and stroke volume. LV and RV ejection fractions and RV-vascular coupling (SV/ESV) increased modestly, which may be physiologically significant even if not statistically significant in this small sample size.

In addition to afterload, diastolic dysfunction can also occur with impaired filling at higher heart rates. Several studies have demonstrated elevated resting heart rates in young adults born preterm (12, 23). In addition, preterm-born individuals have higher rates of autonomic dysfunction (16, 17, 25), for which first line treatment is often beta blockade. Thus, we hypothesized that heart rate reduction with metoprolol would improve RV filling time and therefore improve overall cardiac function. As expected, RV diastolic function as assessed by the RV E/A kinetic energy ratio did improve with metoprolol. However, global cardiac function declined due to reduced cardiac output overall and decreased LV contractility, suggesting that the preterm heart is dependent on both heart rate and baseline contractility.

We interpret these findings to mean that intrinsic morphologic differences as well as increased RV afterload (12) are stronger drivers of cardiac dysfunction in the preterm heart than decreased filling time. Further, the smaller biventricular cavity size signifies that the preterm heart is likely less able to augment stroke volume overall, and considerably more heart rate dependent at baseline.

This study indicates the feasibility of 4D flow MRI to identify the hemodynamic effects of targeted pharmacologic interventions in human subjects. To our knowledge, this study is the first to utilize 4D flow MRI to assess the acute intraventricular hemodynamic effects of cardiac targeted therapeutics in humans. An earlier study determined the RV direct flow fraction to be 44% (10), which compares well despite different imaging protocols to the pre-drug findings of

this study (40%/45% for sildenafil/metoprolol days). Our findings of an increased RV direct flow fraction with acute sildenafil use along with increased cardiac index corroborate the linkage between cardiac index augmentation and direct flow fraction increase uncovered in a porcine study using dobutamine stress (6). In that study, pigs increased cardiac output as well as LV direct flow fraction (from 43% to 53%) under dobutamine stimulation. We hypothesize that direct flow allows for higher cardiac output because it represents an efficient way of moving blood through the ventricle via its short route and fast transit (3, 33).

This study had several limitations. First, the sample size is small. While the numbers are small, we identified that hemodynamic effects of targeted pharmacologic interventions could be captured with 4D flow MRI. Second, this study sample was limited to preterm born subjects only, as required by our center's institutional review board, so we had to rely on previous studies comparing cardiac function between preterm- and term-born subjects to contextualize our findings. Finally, as none of the participants had overt heart failure, the role of therapeutic agents for heart failure treatment remains undetermined. Nonetheless, this study is valuable in that sheds light on the mechanisms of cardiac dysfunction in this population.

In summary, we used cardiac MRI including 4D flow to measure cardiac function before and after administration of metoprolol or sildenafil to investigate causes of cardiac dysfunction in young adults born premature. We found that the preterm heart appears dependent on heart rate, but sensitive to afterload manipulations with improved global function in response to sildenafil. Whether long-term sildenafil administration may improve ventricular-vascular interactions in more affected preterm-born individuals merits further study.

Appendix

MRI Protocol

1. 3-plane localizer
2. Cine SSFP imaging of cardiac function
    a. Axial Cine SSFP Stack
    b. Approximate 2-chamber slice
    c. Approximate 4-chamber slice
    d. Short-axis stack covering all of both ventricles*
        - *repetition time = 3.1 ms*
        - *echo time = 1.1 ms*
        - *field of view = 40x40 cm*
        - *acquired spatial resolution = 1.79x1.79 mm*
        - *reconstructed spatial resolution = 1.56x1.56 mm*
        - *slice thickness = 8 mm*
        - *reconstructed cardiac phases = 20*
    e. Long-axis slices (2-, 3-, and 4-chamber views)
    f. Left ventricular outflow tract view
    g. Right ventricular outflow tract view
3. 2D phase contrast cine planes
    a. Ascending aorta view
    b. Main pulmonary artery view
4. **4D Flow MRI w/PC VIPR***
    - *repetition time = 6.2 ms*
    - *echo time [TE] = 2.0 ms*
    - *imaging volume = 32x32x32 cm*
    - *retrospective ECG gating with spatial frequency dependent temporal interpolation*
    - *retrospective abdominal bellows respiratory gating efficiency = 50%*
    - *spatial-wavelet transform compressed sensing L1-norm penalty [λ] = 0.01*
    - *scan time = 9.2 minutes.*
5. Strain-encoded MRI
    a. Long axis views
    b. Short axis views (3 slices)
6. T1 mapping short-axis view (3 slices)
7. <u>Drug administration</u>
    a. Wait for uptake (until target heart rate achieved for metoprolol or 1 hour for sildenafil)
8. Cine SSFP imaging of cardiac function
    a. Short-axis stack covering all of both ventricles (same parameters as pre-med scan) *
    b. Long-axis slices (2-, 3-, and 4-chamber views)
9. 2D phase contrast cine planes
    a. Ascending aorta view
    b. Main pulmonary artery view
10. **4D Flow MRI w/PC VIPR (same parameters as pre-med scan) ***
11. Strain-encoded MRI
    a. Long axis views
    b. Short axis views (3 slices)

*Boldface text indicates these data were included in the scope of this work.

Disclosures

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Tables

Table 1. Cardiac MRI on Sildenafil Day

	Pre	Post	Change	P-Value
Cardiac Structure and Function				
HR (bpm)	64 ± 7	70 ± 11	5.5 ± 4.5	**0.02**
SVi (mL/m^2)	43.1 ± 8.1	45.7 ± 9.2	2.5 ± 3.7	0.07
CI (L/min/m^2)	2.8 ± 0.7	3.2 ± 0.9	0.4 ± 0.3	**<0.01**
LV EDVi (mL/m^2)	71.2 ± 8.8	72.2 ± 8	1 ± 4	0.91
LV ESVi (mL/m2)	28.1 ± 5.4	26.6 ± 5.7	-1.5 ± 5.3	0.36
LV EF (%)	60% ± 7%	63% ± 8%	3% ± 6%	0.25
LV SV/ESV	1.60 ± 0.50	1.84 ± 0.78	0.25 ± 0.53	0.25
RV EDVi (mL/m^2)	76.2 ± 9.1	74.6 ± 11.3	-1.7 ± 7.6	0.57
RV ESVi (mL/m2)	35.8 ± 8.5	33.3 ± 7.3	-2.6 ± 4.9	0.13
RV EF (%)	53% ± 7%	55% ± 10%	2% ± 5%	0.43
RV SV/ESV	1.19 ± 0.37	1.33 ± 0.63	0.14 ± 0.34	0.30
Myocardial Strain (%)				
LV Radial	22.9 ± 7.5	24.3 ± 7.7	1.3 ± 2.6	0.20
LV Circumferential	-19.5 ± 3.5	-19.8 ± 3.4	-0.3 ± 1.6	0.65
LV Longitudinal	-15.8 ± 2.3	-15.9 ± 2.3	-0.1 ± 0.8	0.91
RV Circumferential	-9.6 ± 1.6	-10.4 ± 2.1	-0.8 ± 2.4	0.43
RV Longitudinal	-17.1 ± 2.9	-16.6 ± 3.8	0.5 ± 1.7	0.50
Kinetic Energy Normalized by EDV (μJ/mL)				
LV Average	11.1 ± 2.8	12.3 ± 4	1.2 ± 2.3	0.25
LV Peak Systolic	21.5 ± 7.2	24.5 ± 8.5	3 ± 4.1	0.05
LV E-Wave	44.1 ± 11	42.3 ± 16.1	-1.8 ± 14.7	0.65
LV A-Wave	6.6 ± 4.2	8.1 ± 4.6	1.5 ± 3.9	0.36
LV E/A Ratio	8.3 ± 3.3	6.8 ± 4.3	-1.4 ± 2.7	0.25
RV Average	15.8 ± 3.7	17.9 ± 6.2	2.1 ± 3.9	0.13
RV Peak Systolic	55.1 ± 17.6	65.8 ± 29.5	10.8 ± 25.3	0.25
RV E-Wave	21.5 ± 9	21.9 ± 8.1	0.4 ± 4.8	0.65
RV A-Wave	6.5 ± 4.5	8.5 ± 6.2	2.1 ± 5.3	0.43
RV E/A Ratio	5.7 ± 6.7	3.8 ± 3.5	-1.9 ± 3.9	0.25

Data are expressed as mean ± SD. *p-values by paired-sample Wilcoxon signed rank tests. Abbreviations: HR, heart rate; CO, cardiac output; CI, cardiac index; EDVi, end diastolic volume index; ESVi, end systolic volume index; SVi, stroke volume index; EF, ejection fraction; PFR, peak filling rate; EDV, end diastolic volume.

Table 2. Intraventricular Flow Compartments on Sildenafil Day

	Pre	Post	Change	P-Value*
LV Direct Flow	49% ± 8%	51% ± 9%	2% ± 6%	0.25
LV Retained Inflow	17% ± 2%	18% ± 4%	1% ± 4%	0.73
LV Delayed Ejection Flow	19% ± 5%	18% ± 4%	-2% ± 3%	0.16
LV Residual Volume	15% ± 6%	13% ± 5%	-1% ± 5%	1.00
RV Direct Flow	40% ± 9%	45% ± 10%	5% ± 7%	**0.04**
RV Retained Inflow	20% ± 3%	22% ± 4%	2% ± 5%	0.43
RV Delayed Ejection Flow	22% ± 5%	18% ± 4%	-4% ± 3%	**<0.01**
RV Residual Volume	18% ± 6%	15% ± 5%	-3% ± 4%	**0.03**

Data are expressed as mean ± SD. *p-values by paired-sample Wilcoxon signed rank tests.

Table 3. Cardiac MRI on Metoprolol Day

	Pre	Post	Change	P-Value
Cardiac Structure and Function				
HR (bpm)	65 ± 8	60 ± 7	-4.3 ± 5	**0.04**
SVi (mL/m^2)	43.7 ± 7.1	41.4 ± 5.6	-2.3 ± 5.3	0.36
CI (L/min/m^2)	2.8 ± 0.5	2.5 ± 0.3	-0.3 ± 0.3	**0.03**
LV EDVi (mL/m^2)	72.5 ± 10.1	72.1 ± 9.7	-0.4 ± 3.2	0.65
LV ESVi (mL/m2)	28.8 ± 6	30.6 ± 8.2	1.9 ± 4.8	0.36
LV EF (%)	60% ± 6%	58% ± 8%	-2% ± 6%	0.30
LV SV/ESV	1.57 ± 0.41	1.46 ± 0.53	-0.11 ± 0.37	0.36
RV EDVi (mL/m^2)	75.2 ± 9.8	74.4 ± 9.4	-0.8 ± 6	0.82
RV ESVi (mL/m2)	33.7 ± 7.5	36.6 ± 9.3	3 ± 4.9	0.10
RV EF (%)	55% ± 8%	51% ± 8%	-4% ± 6%	0.10
RV SV/ESV	1.32 ± 0.53	1.11 ± 0.38	-0.21 ± 0.28	0.13
Myocardial Strain				
LV Radial	22.1 ± 6	21.3 ± 5.9	-0.8 ± 2.6	0.57
LV Circumferential	-19.5 ± 2.6	-18.5 ± 2.8	1 ± 1.1	**0.03**
LV Longitudinal	-15.8 ± 1.9	-14.9 ± 2	0.9 ± 1.1	0.05
RV Circumferential	-10.1 ± 2.1	-9.4 ± 2	0.7 ± 1.6	0.36
RV Longitudinal	-16.6 ± 2.8	-15.8 ± 2.1	0.7 ± 2.3	0.65
Kinetic Energy Normalized by EDV (μJ/mL)				
LV Average	11.6 ± 5	9.5 ± 3.7	-2.1 ± 1.8	**<0.01**
LV Peak Systolic	22.8 ± 9.9	18.8 ± 9.7	-4.1 ± 3.7	**0.02**
LV E-Wave	41.3 ± 16.2	35.8 ± 17.2	-5.5 ± 5.7	**0.03**
LV A-Wave	7.6 ± 6	5.9 ± 3.4	-1.7 ± 4.9	0.30
LV E/A Ratio	7.7 ± 4.6	7.5 ± 3.9	-0.2 ± 3.5	0.65
RV Average	15.5 ± 2.6	12.7 ± 2.5	-2.8 ± 2.1	**<0.01**
RV Peak Systolic	60.1 ± 17.7	47.6 ± 13.5	-12.5 ± 16.1	0.05
RV E-Wave	23.9 ± 12.5	22.3 ± 11.2	-1.5 ± 3.5	0.16
RV A-Wave	6.2 ± 3.3	4.4 ± 2.2	-1.8 ± 1.7	**0.01**
RV E/A Ratio	5.5 ± 5	7.9 ± 9.8	2.4 ± 5.2	**0.04**

Data are expressed as mean ± SD. *p-values by paired-sample Wilcoxon signed rank tests. Abbreviations: HR, heart rate; CO, cardiac output; CI, cardiac index; EDVi, end diastolic volume index; ESVi, end systolic volume index; SVi, stroke volume index; EF, ejection fraction; PFR, peak filling rate; EDV, end diastolic volume.

Table 4. Intraventricular Flow Compartments on Metoprolol Day

	Pre	Post	Change	P-Value*
LV Direct Flow	51% ± 9%	47% ± 13%	-4% ± 9%	0.36
LV Retained Inflow	18% ± 5%	20% ± 5%	2% ± 6%	0.73
LV Delayed Ejection Flow	18% ± 5%	16% ± 5%	-1% ± 5%	0.50
LV Residual Volume	13% ± 5%	17% ± 8%	3% ± 5%	0.16
RV Direct Flow	45% ± 8%	39% ± 9%	-6% ± 9%	0.10
RV Retained Inflow	19% ± 5%	24% ± 6%	4% ± 7%	0.10
RV Delayed Ejection Flow	20% ± 3%	19% ± 3%	-1% ± 3%	0.50
RV Residual Volume	16% ± 7%	19% ± 7%	3% ± 5%	0.13

Data are expressed as mean ± SD. *p-values by paired-sample Wilcoxon signed rank tests.

Figures

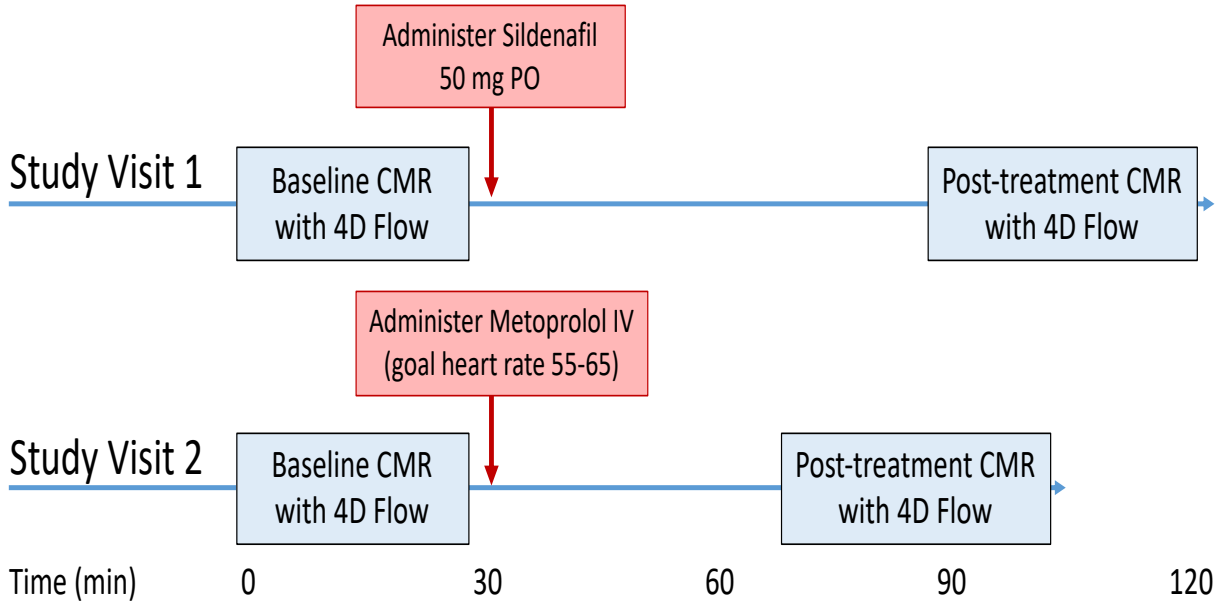

Figure 1: Overall study design. On the first visit, each subject was randomly assigned to receive either intravenous metoprolol tartrate or oral sildenafil citrate. Each subject received the other drug on the second visit, so that all 9 subjects received both drugs. On each visit, the subject received 2 cardiac MRI scans: one baseline and one after drug administration.

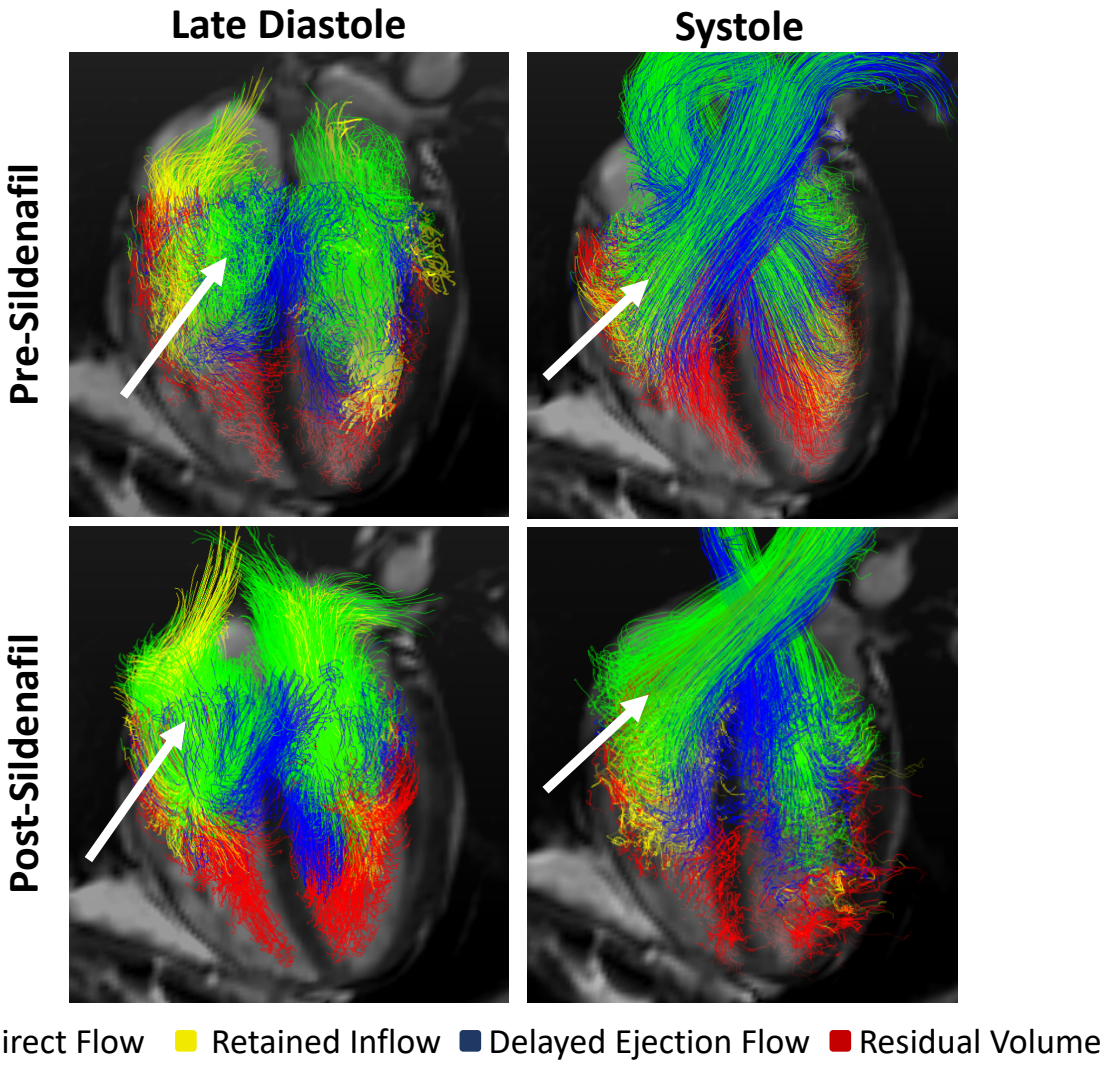

Figure 2: Visualization of flow compartments in a representative example before (top row) and after (bottom row) sildenafil administration. The fraction of right ventricular pathlines in the direct flow compartment (green pathlines) increases after sildenafil administration (white arrows). Green=Direct Flow: Blood that enters the ventricle during diastole and leaves during systole of the same heartbeat. Yellow=Retained Inflow: Blood that enters the ventricle during diastole but does not leave during systole. Blue=Delayed Ejection Flow: Blood that starts inside the ventricle during diastole and leaves during systole. Red=Residual Volume: Blood that resides within the ventricle for at least two cardiac cycles.