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Circ Cardiovasc Imaging. 2014;7:265-273; originally published online January 29, 2014;
doi: 10.1161/CIRCIMAGING.113.001243
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080

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Alexander Van De Bruaene, MD, PhD*; Andre La Gerche, MD, PhD*; Guido Claessen, MD; Pieter De Meester, MD; Sarah Devroe, MD; Hilde Gillijns, BSc; Jan Bogaert, MD, PhD; Piet Claus, PhD; Hein Heidbuchel, MD, PhD; Marc Gewillig, MD, PhD*; Werner Budts, MD, PhD*

Background—Patients with Fontan circulation have reduced exercise capacity. The absence of a presystemic pump may limit flow through the pulmonary circulation, restricting ventricular filling and cardiac output. We evaluated exercise hemodynamics and the effect of sildenafil on exercise hemodynamics in Fontan patients.

Methods and Results—Ten Fontan patients (6 men, 20±4 years) underwent cardiac magnetic resonance imaging at rest and during supine bicycle exercise before and after sildenafil. Systemic ventricular volumes were obtained at rest and during low- (34±15 W), moderate- (69±29 W), and high-intensity (97±36 W) exercise using an ungated, free-breathing cardiac magnetic resonance sequence and analyzed correcting for cardiac phase and respiratory translation. Radial and pulmonary artery pressures and cGMP were measured. Before sildenafil, cardiac index increased throughout exercise (4.0±0.9, 5.9±1.1, 7.0±1.6, 7.4±1.7 L/(min·m^2); P<0.0001) with 106±49% increase in heart rate. Stroke volume index (P=0.015) and end-diastolic volume index (P=0.001) decreased during exercise. End-systolic volume index remained unchanged (P=0.8). Total pulmonary resistance index (P=0.005) increased, whereas systemic vascular resistance index decreased during exercise (P<0.0001). Sildenafil increased cardiac index (P<0.0001) and stroke volume index (P=0.003), especially at high-intensity exercise (interaction P=0.004 and P=0.003, respectively). Systemic vascular resistance index was reduced (P<0.0001–interaction P=0.1), whereas total pulmonary resistance index was reduced at rest and reduced further during exercise (P=0.008–interaction P=0.029). cGMP remained unchanged before sildenafil (P=0.9), whereas it increased significantly after sildenafil (P=0.019).

Conclusions—In Fontan patients, sildenafil improved cardiac index during exercise with a decrease in total pulmonary resistance index and an increase in stroke volume index. This implies that pulmonary vasculature represents a physiological limitation, which can be attenuated by sildenafil, the clinical significance of which warrants further study. **(*Circ Cardiovasc Imaging*. 2014;7:265-273.)**

Key Words: cyclic GMP ■ exercise ■ Fontan procedure ■ pulmonary circulation ■ sildenafil

The Fontan circulation provides definite palliation for patients born with a single anatomic or functional ventricular chamber. However, exercise tolerance is significantly reduced in Fontan patients, even in those with apparently ideal anastomoses and ventricular function.[1,2] In these patients, the absence of a subpulmonary ventricle may limit pulmonary vascular flow and thus systemic ventricular filling. Furthermore, few data exist on the long-term consequences of a Fontan circulation on the pulmonary vascular bed because laminar flow (instead of pulsatile flow) may decrease the release of NO from the endothelium and increase pulmonary vascular resistance.[3] Thus, limitations in exercise-induced augmentation of pulmonary vascular flow could explain the cardiac limitation observed during exercise rather than the performance of the systemic ventricle and systemic circulation.[4] A reduced ventricular preload has been demonstrated during dobutamine stress echocardiography in Fontan patients, showing that cardiac index (CI) was dependent on presystemic determinants of preload rather than on ventricular contractility.[5,6] However, dobutamine may not be a perfect surrogate of the ventricular changes that occur with exercise because systemic venous preload is limited.

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Sildenafil targets the endothelial NO pathway by inhibiting phosphodiesterase-5, increasing cGMP, and inducing pulmonary vasodilation.[7] Giardini et al[8] demonstrated an improvement in peak oxygen consumption and CI after a single oral

Received July 9, 2013; accepted January 16, 2014.

From the Departments of Adult Congenital Cardiology (A.V.D.B., P.D.M., W.B.), Cardiovascular Medicine (A.L.G., G.C., H.H. H.G.), Anesthesiology (S.D.), Radiology (J.B.), and Pediatric Cardiology, University Hospitals Leuven, Leuven, Belgium (M.G.); St. Vincent's Hospital, Department of Medicine, University of Melbourne, Fitzroy, Australia (A.L.G.); and Medical Imaging Research Center, University of Leuven, Leuven, Belgium (P.C.).

*Drs Van De Bruaene and La Gerche contributed equally as first author. Drs Gewillig and Budts contributed equally as senior author.

The Data Supplement is available at http://circimaging.ahajournals.org/lookup/suppl/doi:10.1161/CIRCIMAGING.113.001243/-/DC1.

Correspondence to Alexander Van De Bruaene, MD, PhD, Congenital and Structural Cardiology, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium. E-mail alexvandebruaene@hotmail.com

dose of sildenafil in Fontan patients, although the underlying mechanism was not investigated. Extending this experience, Goldberg et al[9,10] demonstrated an improvement in ventilatory efficiency and ventricular performance after a 6-week period of sildenafil treatment.

We have recently validated a real-time, ungated cardiac magnetic resonance (CMR) imaging method, which enables accurate measurements of ventricular volumes obtained during intense exercise.[11]

Using this novel CMR methodology with simultaneous invasive vascular pressure recordings during exercise, we evaluated exercise hemodynamics and the effect of sildenafil on exercise hemodynamics in Fontan patients. We hypothesized that (1) the exercise capacity in patients with a Fontan circulation and seemingly normal anastomotic and ventricular function is limited attributable to an impaired augmentation in pulmonary vascular flow, and (2) sildenafil would improve pulmonary vascular flow and ventricular preload during exercise.[4,12]

Methods

Subjects

Ten patients with Fontan circulation who are routinely followed in the pediatric cardiology or adult congenital heart disease clinic of the University Hospitals Leuven were selected and included in the study. All patients were clinically stable. Two patients reported mild exercise intolerance consistent with a New York Heart Association class II, whereas the remaining patients were asymptomatic (New York Heart Association class I). None of the Fontan patients had significant atrioventricular valve regurgitation. Before a total cavopulmonary anastomosis was performed, 7 had bidirectional Glenn anastomoses and 2 had Blalock–Taussig shunts. In all patients, Fontan operations were performed by connecting the superior and inferior caval veins to the pulmonary arteries, excluding the right atrium using a GORE-TEX graft. Five patients had an intracardiac total cavopulmonary connection, and 5 had an extracardiac total cavopulmonary connection. None had neither residual fenestrations nor significant aorta-pulmonary collaterals on their last invasive evaluation. Eight patients had a systemic left ventricle, and 2 had a systemic right ventricle. The details of the individual patients are summarized in Table 1 in the Data Supplement.

All patients (and parents when indicated) provided written informed consent for the study protocol, which was approved by the University Hospitals Leuven Institutional Review Board.

Study Protocol

Under local anesthesia and before exercise, a 14F or 18F central venous catheter (Braun Duofix, B. Braun, Melsunger, Germany) was inserted in the internal jugular vein and positioned near the upper cavopulmonary anastomosis. A 20-gauge arterial catheter (BD angiocath, BD medical) was placed in the radial artery. These catheters were connected to CMR-compatible pressure transducers and a hemodynamic monitor (Maglife Serenity, Shiller AG, Baar, Switzerland) in the CMR suite. The pressure transducer was attached to the control panel on the CMR machine, which approximated the level of the patients' anterior axillary line. This position ensured safe and secure management of the vascular lines during exercise and was the same for all patients and for all stages of exercise.

Patients then underwent exercise CMR at low, moderate, and high intensity. Low-intensity exercise was defined as a workload (in watts) perceived as easy (corresponding to a heart rate [HR] of 100–110 bpm). The programmed wattage was then increased to a level perceived as moderately intense (HR of 120–130 bpm) and then further increased to a level perceived as near-maximal intensity (HR of 140–150 bpm). If necessary, the wattage was reduced during the maximal exercise level so that the patient would manage to continue exercising. Each stage was maintained for ≈3 to 4 minutes—1 minute to obtain an exercise steady state, after which image acquisition was commenced.

Patients then took a single oral dose of sildenafil 50 mg and were allowed to rest for 30 to 60 minutes. Exercise CMR was repeated at low-, moderate-, and high-intensity workload using the same wattage as used during the baseline exercise CMR.

Exercise CMR

Ventricular volumes were measured during supine exercise using a real-time CMR methodology that we have previously described in detail and validated against invasive standards.[11] Subjects performed supine exercise within the CMR bore using a programmable ergometer. Images were acquired during free breathing at rest and low-, moderate-, and high-intensity exercise using a Philips Achieva 1.5T CMR with a 5-element phased-array coil (Philips Medical Systems, Best, The Netherlands). Images were acquired during free breathing using steady-state free precession cine imaging obtained in the short axis and horizontal long axis plane as described before.[11] A plethysmograph was placed on the upper abdomen providing data on the timing or respiration, and ECG data were obtained using a hemodynamic monitor (Maglife Serenity, Schiller, Baar, Switzerland). These physiological data were synchronized with the image acquisition using an in-house developed software program (RightVol—Right Volume Leuven, Leuven, Belgium), such that contouring could be performed at the same point in the respiratory cycle (see Figure 1 and Movie 1 in the Data Supplement).[11]

Volumes were indexed for body surface area. Stroke volume index (SVi) was measured as the difference between end-diastolic volume index (EDVi) and end-systolic volume index (ESVi). CI was calculated as the product of SVi and HR and ejection fraction (EF) as the ratio of SVi to EDVi. Total pulmonary resistance index (TPRi) was defined as the ratio of mean pulmonary artery pressure (PAP) to CI. Systemic vascular resistance index (SVRi) was calculated as follows: (mean arterial pressure−PAP)/CI.

Blood Samples

Arterial and mixed venous blood samples were collected at rest and peak exercise before and after sildenafil and analyzed for serum lactate, oxygen saturation, oxygen tension, and carbon dioxide tension. Blood samples were further analyzed for creatinine, hemoglobin, and N-terminal prohormone of brain natriuretic peptide. cGMP was determined at rest and at peak exercise before and after sildenafil. Measurements were done using a commercially available cGMP immunoassay (Amersham, Gent, Belgium).

Statistical Analysis

Data were analyzed using SPSS for Windows (version 19, SPSS, Chicago, IL). Descriptive data for continuous variables are presented as means±SD or as medians with ranges when appropriate. Descriptive data for discrete variables are presented as frequencies or percentages.

Mixed modeling statistical analysis in a random-effects model and the Bonferroni post hoc test for multiple comparisons were performed. A mixed model with a random component (intercept) for each patient and an unstructured 8-by-8 covariance matrix was used. Significance levels are reported after Bonferroni adjustment for multiple comparisons. The slope of the PAP–flow plot was evaluated as a linear approximation using linear regression analysis from pressure–flow plots for each patient and pooled per subgroup. A paired t test was used to evaluate the change in slope of the pressure–flow plot. A P value <0.05 was considered statistically significant.

Results

Subjects

All subjects completed the protocol as scheduled without adverse effects observed or reported. Median workload

at low, moderate, and high intensity was 35 (range, 10–55 W), 75 (range, 25–110 W), and 105 W (range, 35–145 W), respectively. Detailed patient and baseline characteristics are summarized in Supplement I in the Data Supplement and the Table.

Exercise Hemodynamics Before Sildenafil

As demonstrated in Figure 1, CI increased from rest to moderate intensity exercise but failed to increase further during high-intensity exercise ($P<0.0001$). The increase in CI was accompanied by a 106±49% increase in HR, but SVi decreased during high-intensity exercise ($P=0.015$). EDVi decreased during high-intensity exercise ($P=0.001$), whereas ESVi did not change during exercise ($P=0.8$), resulting in a net reduction in EF during exercise ($P=0.037$; Figure 2). As illustrated in Figure 3, mean PAP ($P<0.0001$) and mean arterial pressure ($P<0.0001$) increased during exercise. TPRi increased during high-intensity exercise ($P=0.005$), whereas SVRi decreased ($P<0.0001$).

Arterial oxygen tension (from 80.1±3.1 to 72.0±6.1 mm Hg; $P<0.0001$), arterial oxygen saturation (96.9±0.4%–94.3±1.2%; $P<0.0001$), and mixed venous oxygen saturation (68.5±6.1%–49.1±8.7%; $P=0.001$) decreased during exercise. The observed increase in serum lactate (1.3±0.3–4.4±1.3 mmol/L; $P<0.0001$) confirmed that patients exercised to an intensity exceeding their anaerobic threshold. The peripheral oxygen extraction increased during exercise from 5.5±1.2 to 9.6±1.9 mL/100 mL ($P=0.001$). cGMP did not change during exercise (33.2±8.9 to 33.6±8.5 pmol/mL; $P=0.9$; Figure 4).

Exercise Hemodynamics After Sildenafil

After sildenafil, CI increased from rest up until high-intensity exercise ($P<0.0001$). The increase in CI was accompanied by an 89±39% increase in HR, whereas SVi did not change during exercise ($P=0.2$). EDVi ($P=0.3$), ESVi ($P=0.5$), and EF ($P=0.3$) did not change during exercise. Unlike the pattern during exercise before sildenafil, TPRi did not increase but remained unchanged during exercise ($P=0.8$), whereas SVRi still decreased during exercise ($P<0.0001$; Figures 1–3 and 5).

Arterial oxygen tension (from 86.9±6.1 to 72.6±3.8 mm Hg; $P<0.0001$), arterial oxygen saturation (97.2±0.4%–94.3±1.2%; $P<0.0001$), and mixed venous oxygen saturation (75.1±4.8%–51.2±10.6%; $P<0.0001$) decreased, and serum lactate (2.2±0.7–5.0±1.9 mmol/L; $P=0.001$) was again observed to increase during exercise. The arteriovenous oxygen difference increased from 4.4±1.0 to 9.6±2.7 mL/100 mL ($P=0.001$). cGMP increased significantly during exercise (35.1±12.6–48.4±17.4 pmol/mL; $P=0.019$; Figure 5).

Table. Patient Baseline Characteristics

Variable	
Age, y	19.6±4.0
Age at TCPC, y	7.2±4.6
Male sex, n (%)	6 (60)
BMI, kg/m^2	22.0±2.0
Mean arterial pressure, mm Hg	81.2±7.2
Pulmonary artery pressure, mm Hg	9.2±3.2
End-diastolic volume index, mL/m^2	100±17
End-systolic volume index, mL/m^2	44±16
Stroke volume index, mL/m^2	57±10
Ejection fraction, %	57±10
Cardiac index, L/(min·m^2)	4.1±1.6

BMI indicates body mass index; and TCPC, total cavopulmonary connection.

Comparison of Exercise Hemodynamics Before and After Sildenafil

Resting CI increased after a single oral dose of sildenafil (4.1±0.9–4.8±1.0 L/[min·m^2]; $P=0.006$), and this effect became more pronounced during exercise (mean effect, +0.9±0.4 L/[min·m^2]; $P<0.0001$–interaction $P=0.004$). Sildenafil increased SVi during exercise, especially at high-intensity exercise (mean effect, +5±3 mL/m^2; $P=0.003$–interaction $P=0.003$). Sildenafil did not change EDVi at rest (100±17–98±16 mL/m^2; $P=0.066$) or during exercise (mean effect, −1±1 mL/m^2; $P=0.3$–interaction $P=0.089$). In contrast, sildenafil decreased ESVi at rest (44±16–39±11 mL/m^2; $P=0.032$), and this effect was maintained during exercise (mean effect, −6±3 mL/m^2; $P=0.002$–interaction $P=0.4$). Sildenafil increased EF during exercise (mean effect, +5±3%; $P=0.003$–interaction $P=0.1$).

SVRi decreased at rest (21.0±3.6–16.2±2.2 mm Hg·min·m^2/L; $P=0.001$), and this effect was maintained during exercise (mean effect, −3.0±0.8 mm Hg·min·m^2/L; $P<0.0001$–interaction $P=0.3$). TPRi also decreased at rest (2.5±1.5–1.9±1.1 mm Hg·min·m^2/L; $P=0.012$), but the effect became more pronounced during exercise (mean effect, −1.6±0.4 mm Hg·min·m^2/L; $P=0.008$–interaction $P=0.029$; Figures 1–4). The slope of the pressure-flow plot was significantly lower after administration of sildenafil (3.3±1.2 versus 2.2±0.7 mm Hg/L per min·m^2; $P=0.002$; Figure 6).

After sildenafil administration, arterial oxygen tension (mean effect, +3.2±3.2 mm Hg; $P=0.047$), mixed venous oxygen saturation (mean effect, +4.8±2.4%; $P=0.001$), and serum lactate (mean effect, +0.76±0.57 mmol/L; $P=0.015$) increased, whereas arterial oxygen saturation (mean effect, +0.16±0.47%; $P=0.475$) did not change. Arteriovenous oxygen difference decreased after administration of sildenafil (mean effect, −0.75±0.45 mL/100 mL; $P=0.005$–interaction $P=0.202$). cGMP did not change after administration of sildenafil (mean effect, +2.0±13.7 pmol/mL; $P=0.7$), but the change during exercise was significantly different (interaction $P=0.012$), with an increase in cGMP only evident after sildenafil (Figure 4).

Discussion

This study provides the first comprehensive description of changes in cardiac volumes and intravascular pressures during intense exercise in Fontan patients with seemingly good anastomotic and ventricular function. We hypothesized that the absence of a presystemic ventricle would attenuate normal increases in transpulmonary pressure gradients during exercise resulting in diminished augmentation of CI. Consistent with this, we demonstrated that the Fontan patients had impaired exercise capacity, an abnormal increase in TPRi, and a reduced augmentation of CI. In contrast, and more in keeping with normal biventricular physiology, SVRi fell during

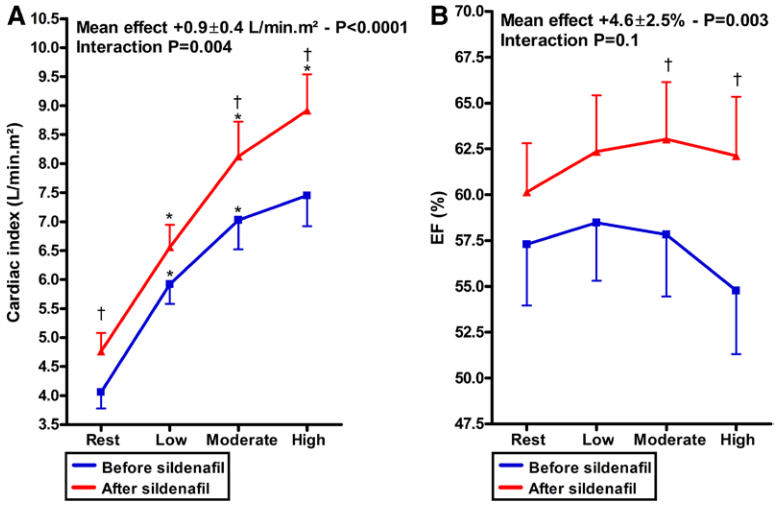

Figure 1. Comparison at rest and low-, moderate-, and high-intensity exercise before and after sildenafil. Cardiac index (**A**) and ejection fraction (EF; **B**). An asterisk indicates a significant change from the previous exercise intensity. A dagger indicates a significant difference before and after sildenafil. The *P* value at the upper left indicates the overall effect before and after sildenafil.

exercise. In further support of our hypothesis, we demonstrated that the abnormal increases in TPRi were attenuated with sildenafil and that this was associated with increases in CI, SVi, and EF during exercise. The means by which sildenafil affected this increase in CI was complex. Rather than increasing EDVi as a reflection of enhanced preload, sildenafil resulted in consistently lower SVRi and ESVi and an enhanced chronotropic response to exercise. Thus, we demonstrated that sildenafil improves exercise hemodynamics, but some ambiguity regarding the precise mechanism remains.

Since its original description,[13] the Fontan operation has known numerous modifications, but nowadays, a staged transition via a bidirectional Glenn shunt to a total cavopulmonary connection has become the procedure of choice.[14–16] The avoidance of ventricular overgrowth, dilatation and dysfunction, excessive unloading at the time of the Glenn shunt, and energy loss at the cavopulmonary anastomosis have resulted in a near-optimal Fontan circulation, and this has led to an improved patient prognosis.[17–20] Nevertheless, we are still faced with limitations inherent to the Fontan circulation, with patients presenting with severely reduced exercise capacity[1,2,20] and impaired long-term outcome.[20]

Determinants of Exercise Limitation in Fontan Patients

Despite only a few symptoms of exercise limitations reported by our study patients, exercise capacity was limited to a median workload at high-intensity exercise of 105 W (range, 35–145 W). As a means of investigating a cardiovascular cause of this exercise intolerance, CI can be limited by (1) impaired preload, (2) increased afterload, (3) decreased contractility, and (4) chronotropic incompetence.

At rest, our patients had a normal CI that was slightly higher than previously reported.[21–23] This confirms that exercise limitations in good Fontan patients are not predicted by abnormalities in resting measurements of cardiac function, including systolic ventricular function.[24]

Although CI nearly doubled during exercise in this study, peak CI was still lower than would be expected in healthy young individuals.[11] First, as measures reflecting preload, changes in EDVi and TPRi were evaluated. In a normal circulation, preload is determined by upstream factors such as venous return as well as right ventricular, pulmonary vascular, and atrial function. Even when there are increases in pulmonary vascular resistance, there is usually sufficient reserve for the systemic ventricle to be assured of adequate preload. After the Fontan operation, cardiac output becomes exquisitely dependent on there being minimal resistance through the pulmonary circulation given that central venous pressure provides only a limited means by which a transpulmonary pressure gradient can be maintained. Without a presystemic pump, the pulmonary circulation may be unable to augment flow sufficiently to maintain systemic ventricular filling when diastolic ventricular filling time shortens with increasing HR during exercise. Consistent with this premise, our results showed that TPRi increased and EDVi decreased during exercise. Normally, the pulmonary vascular bed is a low-resistance system that is able to further decrease pulmonary vascular resistance during exercise.[25] The observed increase in TPRi may be caused by a failure to recruit pulmonary blood vessels during exercise, loss of pulsatile blood flow with increased pulmonary impedance, and pulmonary endothelial dysfunction reducing the release of NO from the endothelium.[3,26] The latter was confirmed by a failure to increase cGMP during exercise, which is pathological in these young patients at this level of exercise.[27]

Second, as a measure reflecting both contractility of the systemic ventricle and systemic vascular afterload, changes in ESVi during exercise were evaluated. ESVi did not change during exercise, suggesting that ventricular contractility was insufficient to augment stroke volume against its arterial load.[28,29] The decrease in SVi occurred far earlier than would be expected in a normal biventricular circulation and is consistent with previous reports.[4–6,24,29] This fall in SVi may be a combination of impaired ventricular filling and reduced contractility relative to systemic afterload. These factors have a complex interdependence that cannot be easily separated using our methodology. Myocyte contractile force is determined by the extent of cross-bridge formation between actin and myosin, which, in turn, is greatly influenced by the stretch applied to the sarcomere. In the absence of significant stretch (ie, there is insufficient preload to the

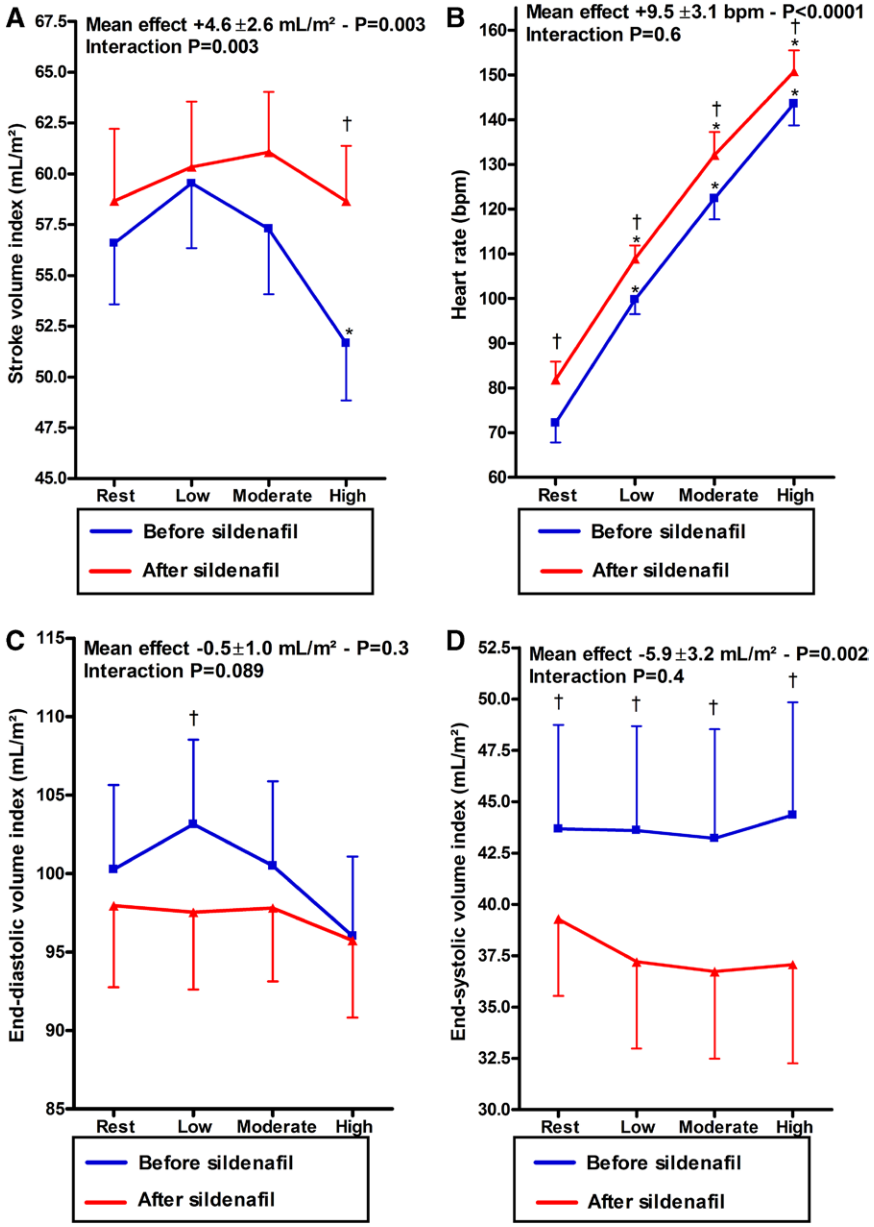

Figure 2. Comparison at rest and low-, moderate-, and high-intensity workload before and after sildenafil. Stroke volume index (**A**), heart rate (**B**), end-diastolic volume index (**C**), and end-systolic volume index (**D**). An asterisk indicates a significant change from the previous exercise intensity. A dagger indicates a significant difference before and after sildenafil. The *P* value at the upper left indicates the overall effect before and after sildenafil.

ventricle), contractile force is reduced, and the influence of afterload is more profound.[30]

Third, as a further measure reflecting afterload of the systemic ventricle, SVRi was evaluated. SVRi decreased during exercise as expected, suggesting that increased afterload may not be the dominant reason for exercise limitation in these patients. Finally, changes in HR during exercise were evaluated. During exercise, HRs increased progressively but were far lower (147±15 bpm) than would be expected at maximal exertion in a normal biventricular circulation. It is difficult to evaluate the extent to which chronotropic incompetence limits cardiac output augmentation. However, our finding that SVi started to decrease at low levels of exercise suggests that impairment of ventricular filling precedes failures in HR augmentation. This suggests that chronotropic incompetence may be a secondary phenomenon that prevents precipitous decreases in cardiac output resulting from inadequate filling during progressively shorter diastolic times. This concept is supported by Paridon et al,[31] who observed that pacing beyond maximal HRs did not improve aerobic capacity in Fontan patients.

Effect of Sildenafil on Exercise Hemodynamics

A low pulmonary vascular resistance is of utmost importance for early success rate[17,32] and late outcome after the Fontan operation.[33] Fontan patients residing at moderate altitude present with worse prognosis, presumably related to an increase in pulmonary vascular resistance.[34] Khambadkone et al[3] showed that pulmonary vascular resistance was elevated late after the Fontan operation and may fall in response to inhaled NO. Giardini et al[8] showed an improvement in peak oxygen consumption after a single oral dose of sildenafil, whereas Goldberg et al[9,10] observed an improvement in ventilatory efficiency and ventricular performance after a 6-week period of sildenafil therapy. Rhodes et al[35] noted a similar beneficial effect of inhaled iloprost on exercise capacity. The hemodynamic mechanisms for the improvement remained unclear.

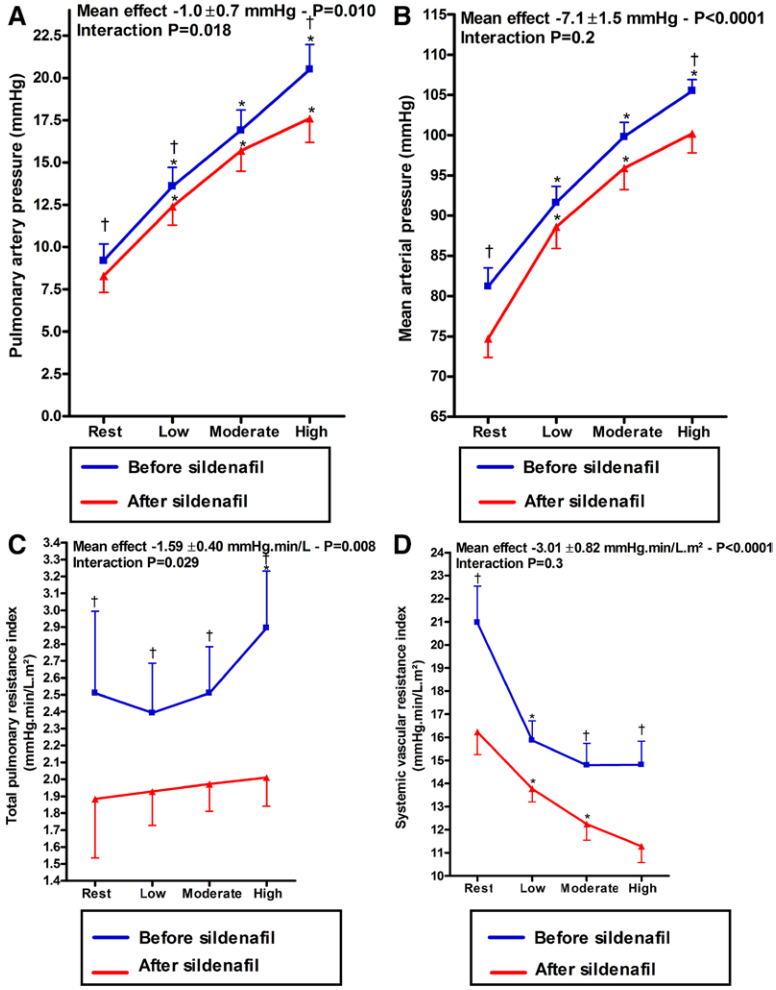

Figure 3. Comparison at rest and low-, moderate-, and high-intensity workload before and after sildenafil. Cardiac index (**A**), ejection fraction (**B**), pulmonary artery pressure (**C**), mean arterial pressure (**D**), total pulmonary resistance index (**E**), and systemic vascular resistance index (**F**). An asterisk indicates a significant change from the previous exercise intensity. A dagger indicates a significant difference before and after sildenafil. The *P* value at the upper left indicates the overall effect before and after sildenafil.

In agreement with these studies suggesting an acute hemodynamic benefit, our data demonstrated an overall increase in CI, which was more pronounced during high-intensity exercise after sildenafil administration.[3,8–10] This postsildenafil increase in CI may be attributed to a relative increase in HR, an unchanged EDVi, and a decrease in both TPRi and ESVi when compared with the presildenafil setting. TPRi was observed to be lower throughout exercise in the postsildenafil setting, but the most significant difference was observed during high-intensity exercise where TPRi remained unchanged, in contrast to the increase observed during exercise before sildenafil. This improvement of TPRi was related to an increase in cGMP, suggesting improved endothelial function during exercise with sildenafil.

Contrary to expectations following an improvement in TPRi, we observed that EDVi did not increase after sildenafil administration. This may be explained, at least in part, by the fact that the HR was consistently greater postsildenafil. When compared with baseline, sildenafil enhanced the ventricular filling rate as evidenced by the greater increase from ESVi to EDVi (ie, greater filling volume) within a shorter diastolic period.

The reduction in ESVi likely reflects the reduction in SVR that was observed postsildenafil. Several studies have reported an increased SVR with abnormal ventriculoarterial coupling in Fontan patients and that the reduction in SVR during exercise is less than in the normal subject.[6,36–38] However, afterload reduction using enalapril has failed to improve exercise hemodynamics and has even showed a tendency to worsen exercise performance in Fontan patients.[39] It is difficult to determine whether the abnormal vascular characteristics are a primary phenomenon associated with the Fontan circulation or that the increased peripheral tone is established as a means to maintaining blood pressure when cardiac output augmentation is reduced.[4,40]

The complex interactions between contractility and load cannot be adequately appraised using cardiac volumes alone. It has been demonstrated that the ventricle with insufficient preload has reduced contractile force and is, therefore, more greatly affected by changes in afterload.[30] Presumably, a combination of afterload reduction and a decrease in TPRi is responsible for improved cardiac output in these patients, with the decrease in TPRi being most apparent during high-intensity exercise.

The indirect measures of cardiac function were of interest. Lactate levels increased as would be expected during maximal exercise, but the postsildenafil levels were consistently higher compared with the baseline setting. This may partly be explained by incomplete lactate clearance during the 30-minute recovery between exercise bouts, consistent with

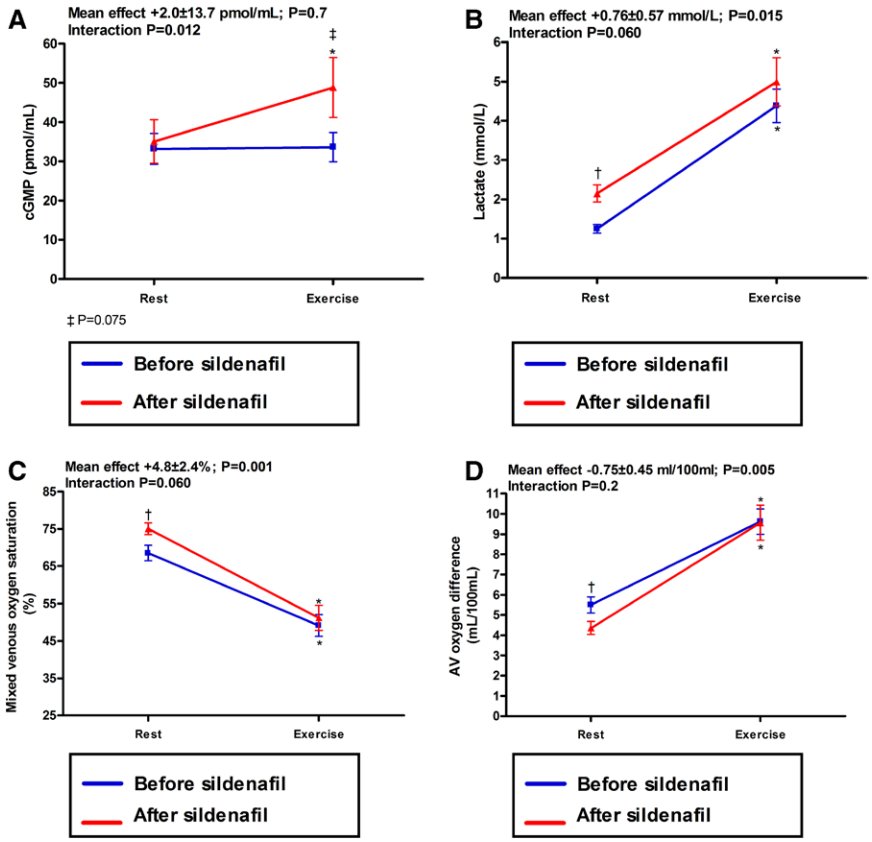

Figure 4. The change in (**A**) cGMP, (**B**) lactate, (**C**) mixed venous oxygen saturation, and (**D**) arteriovenous (AV) oxygen difference from rest to peak exercise before and after sildenafil. An asterisk indicates a significant change from the previous exercise intensity. A dagger indicates a significant difference before and after sildenafil. The *P* value at the upper left indicates the overall effect before and after sildenafil.

previous experience.[41] However, given that CI was greater with sildenafil, we would have expected a lesser increase in lactate (better oxygen supply resulting in less lactate production). This inconsistency may reflect the potential errors in equating muscle metabolism with plasma lactate levels. Lactate may be caused by hypoperfusion of any tissue, and it is possible that phosphodiesterase 5 inhibition interferes with normal vascular autoregulation in which blood flow is prioritized to tissues of highest metabolic requirements. Intriguingly, we found that the resting arteriovenous oxygen difference decreased after sildenafil despite increases in CI. This may suggest that selective PDE5 vasodilation results in less blood flow to the working muscles. If confirmed in further studies, this may be an important confounder in the interpretation of cardiopulmonary tests involving PDE5 antagonists.

Limitations

First, the comprehensive procedures undertaken in this study limited the sample size. However, the established accuracy of exercise CMR measures enabled us to evaluate meaningful hemodynamic differences with this modest-sized cohort. Second, Shafer et al[42] recently commented on the importance of the muscle and ventilatory pump during exercise. Our methodology did not enable us to separate the effects of these processes on venous return and transpulmonary blood flow. However, our CMR protocol corrects for respiratory phase translation so that all contours were delineated during the same phase of respiration, thus avoiding the potential for confounding and inaccuracy resulting from comparing cardiac volumes under different states of filling.[11] Third, pulmonary blood flow was not measured directly but estimated to be similar to systemic cardiac

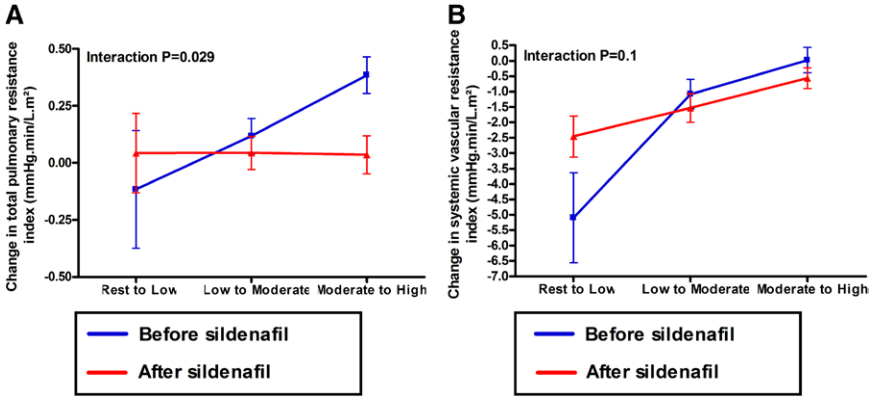

Figure 5. Change in (**A**) total pulmonary resistance index and (**B**) systemic vascular resistance index before and after sildenafil. The *P* value at the upper left indicates the interaction before and after sildenafil.

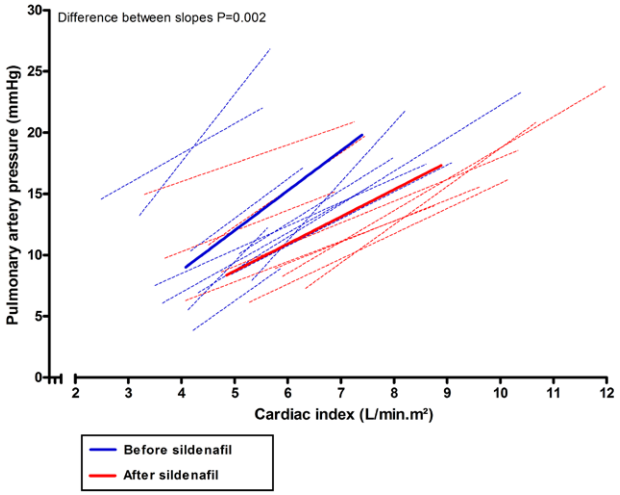

Figure 6. The pressure-flow plot before and after sildenafil. The blue line indicates no sildenafil; and the red line, sildenafil.

output. Although Fontan patients may present with systemic-to-pulmonary collateral flow and fenestrations, none of the patients had a patent fenestration at the time of the study. It is difficult to exclude systemic collaterals, although the consistent fall in oxygen tension would suggest that such shunting must be minimal. Fourth, observed PAPs were lower than might have been expected for a Fontan cohort. This likely reflected the wellness of the enrolled cohort but also attributable to the fact that the most stable fixation point for the pressure transducers was at the level of the anterior axillary line. Thus, although the pressure measures may have been systematically underestimated, this will have had no bearing on the change in vascular pressures. Fifth, analyses of the CMR data were not blinded, introducing a potential source of bias. Finally, exercise was performed in a supine position, which is a current limitation of exercise CMR imaging. The resultant facilitation of venous return may be expected to compensate somewhat for the lack of a prepulmonary pump. Thus, it may be hypothesized that the changes may have been greater had it been possible to perform these experiments in an upright position.

Conclusions

In patients with good Fontan physiology, pulmonary vascular resistance appears to be a critical determinant of circulatory output. Sildenafil effected a reduction in TPRi and improved CI at rest and during exercise. This implies that pulmonary vasodilation is a potential physiological target for improving exercise hemodynamics, the clinical significance of which warrants further study.

Acknowledgments

First and foremost, we thank all patients for participating in the study. We also thank Stefan Ghysels, Guido Putzeys, and Chris Byloos for their help in performing the exercise magnetic resonance imaging studies and Astrid Vloemans and Sonia Rens for their help with the logistics.

Sources of Funding

We thank the Rotary Club of Tienen, Sporta monVentoux, and Eddy Merckx research grant for donating toward the cost of the CMR-compatible ergometer. A. Van De Bruaene received a research grant from Fonds voor Wetenschappelijk Onderzoek Vlaanderen. A. La Gerche was supported by a grant from the National Health and Medical Research Council of Australia.

Disclosures

None.

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CLINICAL PERSPECTIVE

Although Fontan patients often present with decreased exercise capacity, the determinants of exercise intolerance remain poorly understood. We hypothesized that the absence of a presystemic ventricle would attenuate normal increases in transpulmonary pressure gradients during exercise, resulting in diminished augmentation of cardiac index. Consistent with this, we demonstrated that Fontan patients had impaired exercise capacity, an abnormal increase in pulmonary vascular resistance, and a reduced augmentation of cardiac index. In contrast, and more in keeping with normal biventricular physiology, systemic vascular resistance fell during exercise. In further support of our hypothesis, we demonstrated that the abnormal increases in pulmonary vascular resistance were attenuated with sildenafil and that this was associated with increases in cardiac index, stroke volume, and ejection fraction during exercise. However, the means by which sildenafil affected this increase in cardiac index was complex. Rather than increasing end-diastolic volume as a reflection of enhanced preload, sildenafil resulted in consistently lower systemic vascular resistance, end-systolic volume, and an enhanced chronotropic response to exercise. Unfortunately, the complex interactions between contractility and load cannot be adequately appraised using cardiac volumes alone. Presumably, a combination of afterload reduction and a decrease in pulmonary vascular resistance is responsible for improved cardiac output in these patients, with the decrease in pulmonary vascular resistance being most apparent during high-intensity exercise. Thus, we demonstrated that sildenafil improves exercise hemodynamics in Fontan patients with seemingly good anastomotic and ventricular function, the clinical significance of which warrants further study.

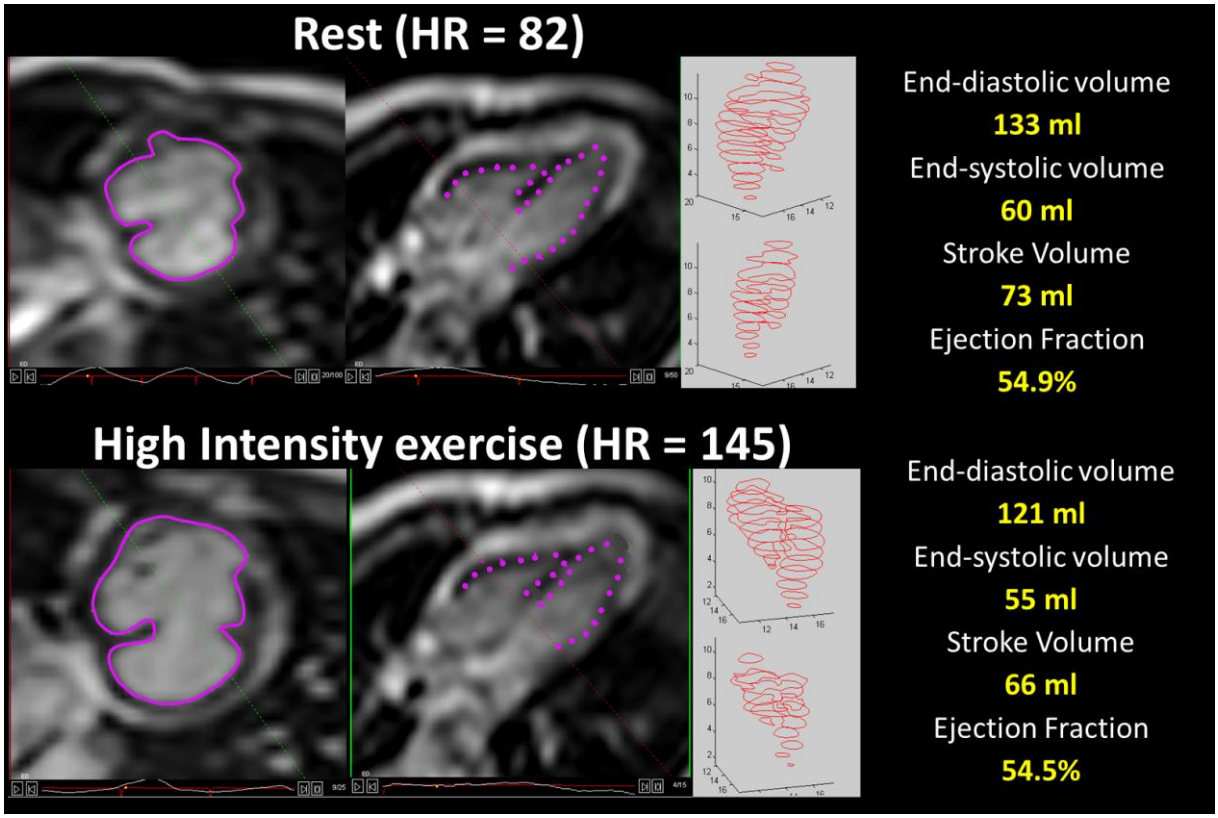
SUPPLEMENTAL MATERIAL

Supplement 1: Fontan patient detailed characteristics.

Patient number	Gender	Age at Fontan (years)	Age at analysis (years)	Time since Fontan (years)	Anatomy	Previous procedures
1	F	7.8	29.0	21.2	Dextrocardia, pulmonic atresia, TGA, VSDs	BT shunt left and right
2	M	3.9	16.1	12.2	DILV, L-TGA, VSD, ASD II, Coarct, subaortic stenosis, PS	PA banding, coarctectomy, Damus-Kaye-Stansel, bidirectional Glenn
3	M	5.8	18.7	12.9	Dextrocardia, DILV, VSD, pulmonic atresia, ODB	BT shunt left and right, bidirectional Glenn
4	F	4.7	19.0	14.3	HLHS, AVSD, subaortic stenosis, Coarct	Coarctectomy, Damus-Kaye-Stansel, bidirectional Glenn
5	M	12.8	21.5	8.7	Tricuspid atresia, VSD	BT shunt left, Fontan CPAP
6	M	10.0	15.7	5.7	DORV, D-TGA, multiple VSDs, PS	Rashkind, BT shunt left and right, bidirectional Glenn, atrial septectomy
7	F	3.8	19.9	16.1	DILV, L-TGA, VSD	PA banding, bidirectional Glenn
8	F	16.6	18.7	2.1	DILV, D-TGA, VSD, ASD II, PS	bidirectional Glenn, PA banding
9	M	2.7	15.4	12.7	Tricuspid atresia, VSD, PS	Rashkind, BT shunt left, septectomy IAS, hemi-Fontan
10	M	4.1	22.4	18.3	DILV, L-TGA, VSD, PS	balloon dilatation PA

F: female – M: male -TGA: transposition of the great arteries – VSD: ventricular septal defect – BT: Blalock-Taussig – TCPC: total cavopulmonary connection – DILV: double inlet left ventricle – ASD: atrial septal defect – PA: pulmonary artery – PS: pulmonic stenosis - HLHS: hypoplastic left heart syndrome – AVSD: atrioventricular septal defect – DORV: double outlet right ventricle – IAS: interatrial septum – ODB: open ductus Botalli

Supplement 2: Cardiac magnetic resonance (CMR) Images were acquired during free-breathing in the SAX and HLA plane at rest and during exercise. A plethysmograph, placed on the upper abdomen, provided data on the timing of respiration and ECG data was obtained using a hemodynamic monitor. These data was synchronized with the image acquisition using an in-house developed software program (RightVol - Right Volume Leuven, Leuven, Belgium) such that contouring could be performed at the same point in the respiratory cycle in the short-axis and referenced against the long-axis view.



Supplement 3: Example of real-time ungated CMR imaging at rest and during maximal exercise in a Fontan patient.