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Exercise Induced Systemic Venous Hypertension in the Fontan Circulation

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Abstract

Increasingly end-organ injury is being demonstrated late after institution of the Fontan circulation, particularly liver fibrosis and cirrhosis. The exact mechanisms for these late phenomena remain largely elusive. Hypothesizing that exercise induces precipitous systemic venous hypertension and insufficient cardiac output for the exercise demand, i.e. a possible mechanism for end-organ injury, we sought to demonstrate the dynamic exercise responses in systemic venous (SVP) and concurrent end organ perfusion. Ten stable Fontan patients and 9 control subjects underwent incremental cycle ergometry based cardiopulmonary exercise testing. SVP was monitored in the right upper limb and regional tissue oxygen saturation was monitored in the brain and kidney using Near Infrared Spectroscopy. SVP rose profoundly in concert with workload in the Fontan group, described by the regression equation 15.97+0.073 Watts per mm Hg. In contrast SVP did not change in healthy controls. Regional renal ($p<0.01$) and cerebral tissue saturations ($p<0.001$) were significantly lower and fell more rapidly in Fontan patients. We conclude that in a stable group of adult patients with Fontan circulation high intensity exercise was associated with systemic venous hypertension and reduced systemic oxygen delivery. This physiologic substrate has the potential to contribute to end-organ injury.

Introduction

The Fontan operation has transformed outcomes for children born with single ventricle physiology. [1] This circulation separates pulmonary and systemic venous return, minimizes systemic desaturation, and volume offloads the single systemic ventricle at the cost of placing two arteriolar capillary resistor beds in series (arterial and pulmonary capillary) downstream from single ventricular action. This presents the single ventricle with an enormous total afterload. The venous bed is subject to obligatory hypertension. [2] Gravitational hydrostasis contributes to diminished venous conductance [2] [3] as does the terminal location of the pulmonary vascular bed in the venous circulation. Intermittent or sustained venous hypertension and diminished cardiac output may contribute to liver damage in Fontan patients. [4,5] There is also growing evidence that hepatic fibrosis can be induced by liver stiffness and cyclical uniaxial strain pressure strain. [6,7] Very few data exist however describing the characteristics of venous pressure responses to exercise in Fontan patients. In this investigation we sought to demonstrate (a) exercise induced changes in SVP and (b) regional renal and cerebral oxygenation during exercise, to examine pathophysiological changes in end-organ oxygen delivery that may contribute to liver and or other organ injury.

Methods

The South Central NRES Committee granted ethical approval and Southampton University Hospitals NHS Trust (RHM CAR0437) gave local Trust Research and Development approval. Ten consecutive stable Fontan patients were recruited using the Southampton Congenital Cardiac Database. Patients were excluded if they had uncontrolled arrhythmias or heart failure, were being evaluated for surgical or catheter based intervention, or had associated known systemic venous thrombosis. All patients had prior cardiac catheterization on clinical grounds and pathway obstruction was excluded. Nine healthy age and sex matched control participants were recruited.

Ventilation and gas exchange, and arterial saturation earlobe pulse oximetry were prospectively measured during rest and exercise using a metabolic cart (Geratherm Respiratory GmbH with Blue Cherry software, Love Medical Ltd, Manchester, UK). The equipment was

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calibrated and operated to the standards specified in the ATS/ACCP (2003) guidelines. Participants initially sat at rest on an electromagnetically braked cycle ergometer (Ergoline 2000) for 3 minutes (baseline phase), followed by 3 minutes of unloaded cycling, and then performed a ramp-incremental to intolerance (exercise phase). Exercise duration was targeted to range from 8 to 12 minutes and power output incrementation individualized accordingly. Power output for Fontan patients was increased at 10-15 W/min depending on the patient's reported and assessed physical ability. The ramp-incremental was 30 W/min for controls. In all participants a cadence of 60 rpm was maintained throughout. At volitional intolerance the power output was immediately reduced to zero and cardiopulmonary variables were monitored for at least 5 minutes (recovery phase).

NIRS (near infra-red spectroscopy) was measured using an Adult Equanox Advance™ Sensor (Model 8004CA, Nonin, Plymouth, USA) connected to a conversion box (7600 PA Oximeter, Nonin, Plymouth, USA). NIRS was used to measure regional cerebral (StO_2-C; left frontal lobe) and renal (StO_2-R; left lumbar region, directly over the left kidney, confirmed by ultrasound) tissue oxygen saturation every minute during the rest, exercise, and recovery phases.

A 16-18 Gauge cannula was inserted in a large left antecubital vein prior to the exercise test. The cannula was connected to a venous pressure manometer via a transducer set. The transducer was individually flushed, de-aired, calibrated and "zeroed" to atmospheric pressure at the level of the right atrium. To ensure measurement reliability, the pressure trace was evaluated during a Valsalva maneuver, with proximal occlusion of the axillary vein and while raising and lowering the arm. At all times during exercise the transducer was kept at the mid-right atrial level and care was taken to ensure the arm was kept relaxed and extended. A baseline SVP reading was obtained at rest, and the pressure was monitored continuously, and recorded every minute, until a return to baseline following exercise. Recordings were only used when a phasic waveform was demonstrable. Peripheral upper limb venous pressure in Fontan patients reflects pulmonary artery pressure, and are concordant with central venous pressures. [8]

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Statistical analysis was performed with R version 2.4.122 and MedCalc 10.1.2.0 (MedCalc Software, Mariakerke, Belgium). For all analyses, a probability value <0.05 was used as the criterion for statistical significance. All values are presented as mean ± standard deviation (SD) or median for non-normally distributed variables. Categorical variables are presented as frequencies and percentages. Exercise gas exchange and ventilatory variables were analyzed and presented at the following defined points: resting, unloaded cycling, 20, 40, 50, 60, 80, 100, and 120 W. Comparison between Fontan patients and control subjects were performed using an unpaired student's t-test. Changes in physiologic variables with exercise were assessed by random mixed-effects models using the R nlme package. Association between physiologic variables during exercise and laboratory serology, were assessed using non-parametric correlation (Spearman's Rho).

Results

There were 8 male and 2 female Fontan subjects (n=10), with a mean age of 26.4 years, range 19 – 31 years. Their underlying anatomic diagnoses included:

1. *Double inlet left ventricle* (n=2) with D-transposition of the great arteries and aortic coarctation, with extra-cardiac Fontan connections
2. *Pulmonary atresia* (n=1) with intact septum and a lateral tunnel Fontan
3. *Tricuspid atresia* (n=7) with normally related great vessels. Of these 4 had previously had extra cardiac revision of an atrio-pulmonary Fontan, 1 had a primary lateral tunnel, and the other had an unrevised atrio-pulmonary Fontan connection and 1 had a homograft connection between the RA and a diminutive RV. Nine age and gender matched controls ranged from 22-25 yrs (p=0.25 for age).

Fontan patients had significantly lower peak power output (119±36 vs. 267±73 W, p=0.022), estimated lactate threshold (LT: 0.95±0.30 vs. 1.59±0.48 L/min, p=0.003), peak oxygen uptake (21±8 vs. 35±8 ml/kg/min, p=0.001), and had a greater ventilatory equivalent for CO_2 at LT (V_E/VCO_2: 34.9±1.7 vs. 23.4±2.7, p<0.001) compared with control subjects.

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SVP was significantly greater in Fontan patients at rest (14±4 vs. 6±2 mm Hg, p<0.0001), during unloaded exercise (16±4 vs. 7±3 mm Hg, p=0.0001), and at peak exercise (25±6 vs. 9±3 mm Hg, p<0.0001). SVP increased abruptly at exercise onset in both Fontan and control participants, but unlike the control, SVP continued to increase progressively during exercise in Fontan. The rate of the exercise-induced SVP increase was significantly greater in Fontan than control (0.087±0.045 vs. 0.006±0.011 mm Hg/W, p=0.0001) (Figure 1, 2).

Resting StO_2-C (76±4 vs. 66±7 %, p=0.001) and StO_2-R (79 ±9 vs. 65±9 %, p=0.001) were lower in Fontan patients than controls (Figure 3): both declined during exercise more rapidly in Fontans than controls (peak StO_2-C 74±6 vs. 55±6 %; peak StO_2-R 70±6 vs. 48±10 %). This significantly lower S_tO_2 values in Fontans were sustained into the recovery period (p<0.02). StO_2-C fell significantly from mid to peak exercise in Fontan patients, but not in controls. While resting arterial saturation (by pulse oximetry) was greater in controls than Fontan (99±1 vs. 93±6 %, p=0.01), exercise induced arterial desaturation was not significant in Fontan (-3±5 %, p=0.26) or controls (-1±1 %, p=0.09), and was not different between groups (p=0.15). Three Fontan patients had resting desaturation due to veno-venous collateralization.

Discussion

The main findings of this study are that (a) there is a clear relationship between exercise power output and SVP augmentation in stable adult patients with a Fontan circulation, and (b) high intensity exercise in Fontan patients is associated with co-existent and intensified renal and cerebral deoxygenation. We believe these observations present a plausible premise for the development and perpetuation of end organ dysfunction such as hepatic fibrosis during the natural history of the Fontan circulation.

We demonstrated significant exercise induced systemic venous hypertension in adults with a Fontan circulation. The SVP rise during exercise was similar to the increment observed in central

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venous and pulmonary arterial pressures by others. [9-11] Peak power output was lower in Fontan patients than controls, and this was associated with a steep rise in SVP during exercise. In the two Fontan patients with greatest peak power output, the baseline and increase in SVP response was the least impaired and similar to controls (Figure 1). During maximal exercise in normal individuals, cardiac output may increase 4- to 5-fold [12,13] with a concomitant decrease in pulmonary vascular resistance, accommodating the augmented flow. Pulmonary artery pressures still rise however because the fall in PVR is insufficient. The transpulmonary pressure gradient therefore rises, typically from a mean of ~12 to ~26 mm Hg. Despite these changes in pulmonary artery pressures, however, SVP does not increase when there is a functioning sub-pulmonic pump, as confirmed in our control subjects. In Fontan circulations, passive blood flow through the pulmonary vasculature depends on the gradient generated between central venous pressure and ventricular end-diastolic pressures, as well as resistance across the pulmonary vascular bed. Exercise induced elevation in ventricular EDP and/or PVR de facto will increase SVP.

Our data support the notion that there is considerable individual variation in the composite resistance to blood flow across the pulmonary vascular bed, constituted by the combination of proximal conduit vessel compliance, pulmonary vascular tone, and exercise induced systemic ventricle end-diastolic pressures. The observation that an abrupt and marked SVP increase is associated with poorer exercise tolerance suggests that despite this precipitous rise in venous pressure, systemic ventricular pre-load may still be inadequate. In this study we did not assess left ventricular compliance, pulmonary vascular resistance, or cardiac output. A prior study showed diastolic dysfunction was present in 57% of Fontan patients assessed and was associated with a reduced peak VO_2 and peak power, and none showed the expected decrease in PVR on exercise. [9]

NIRS derived StO_2 has been used as a marker of the adequacy of end-organ O_2 delivery relative to demand. [14] We demonstrated profound changes in StO_2-C and StO_2-R in Fontan patients at rest and during exercise. By contrast, control subjects showed only a mild decline in StO_2-R, and no decline in StO_2-C. In Fontan, StO_2-R likely reflects diminished renal perfusion as is expected as blood

flow is redistributed to the exercising muscle. This effect was however more profound and occurred earlier in exercise in the Fontan patients than controls. StO_2-C declined in the later phase of exercise in Fontan patients. Frontal lobe desaturation is common in high-intensity exercise associated with ventilatory compensation for a metabolic acidosis and reduced P_aCO_2, and is implicated in exercise limitation in athletes and patients. [15] Although, the magnitude of the exercise-induced cerebral desaturation is mild, the absolute StO_2-C is low throughout rest and exercise and therefore cannot be ruled out as a limiting factor for exercise. We hypothesize that the decline in StO_2-C in this cohort probably reflects an inadequately augmented cardiac output relative to the demands of the exercising muscle. This phenomenon of constrained cerebral blood-flow provides an interesting additional potential mechanism for exercise restraint. [14] Resting cerebral oxygen saturation (StO_2-C) values below 30% have been associated with biochemical and histologic evidence of injury in many animal models, and time-dependency has also been demonstrated. [16]

Direct pressure transmission to the liver parenchyma at rest and during exercise has the ability to activate mechanical matrix transduction and stellate cell activation leading to fibromyoblast transformation and deposition of fibrosis. [6] [7] Chronic congestive cardiac failure for example has long been recognized to cause fibrosis bridging between central veins (reversed lobulation), associated centrilobular hepatocyte loss, reticulin condensation, thickening of central veins and perivenous fibrous spur formation. [17,18]

These effects are likely to be amplified in the presence of tissue ischemia, which has been implicated in the development of liver fibrosis via hypoxia-inducible factor-1α signaling. [19,20,21] We demonstrated markedly lower StO_2-R in Fontan patients throughout rest and exercise compared with controls, with a striking acceleration in StO_2-R decline approaching peak exercise. The superimposed effects of this hypoxic environment together with increased mechanical tension provide the ideal conditions to promote the hepatic fibrosis observed in multiple clinical observational studies.

Study Limitations

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This study has several limitations. The sample size was small. However, the observed results were concordant with other studies documenting elevation in right atrial and pulmonary arterial pressures during exercise. While muscle tone during exercise may have confounded SVP measurements, we attempted to minimize the influence of this by measuring SVP in the upper limb (rather than lower limb), and by ensuring that the upper limb was in an extended relaxed position throughout the exercise test. We were limited by the absence of more invasive techniques to assess the exact cause of the observed venous hypertension. Interpretation of NIRS results in the presence of venous hypertension and distension needs careful consideration as preferential venous pooling may contribute to the tissue deoxygenation. Similarly, exercise induced arterial hypoxemia could contribute to renal or cerebral tissue deoxygenation, and this was slightly, although not significantly, greater in Fontans.

Acknowledgements

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Figure legends

Figure 1. Individual systemic venous pressure (SVP) responses during exercise in Fontan patients and controls. In Fontan the SVP change (in mm Hg) relative to power output is described by: 15.97+0.073*Watts. In Control the SVP change (in mm Hg) relative to power output is described by: 7.52+0.005*Watts ($p < 0.0001$).
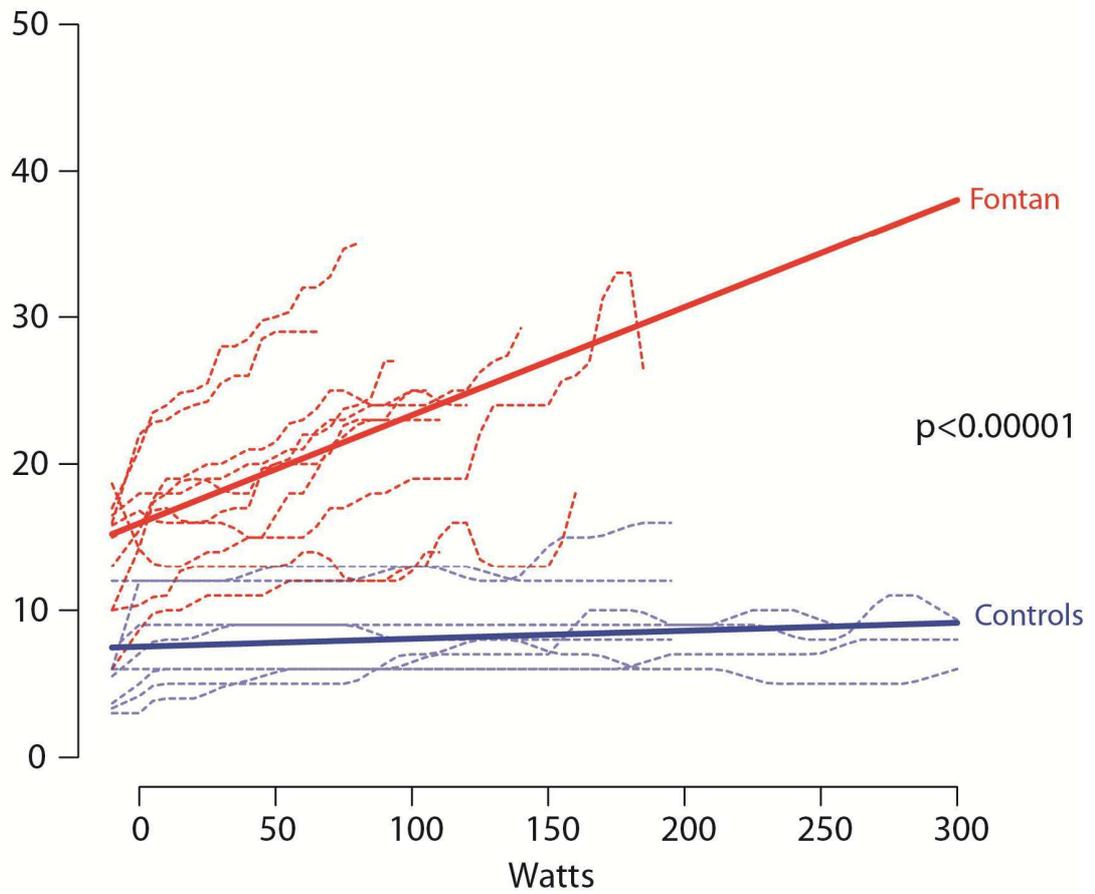

Figure 2: The relationship between peak ramp-incremental power output and SVP rate of increase for Fontan patients and controls.

Figure 3: NIRS (Near Infrared Spectroscopy) derived renal (-R) and cerebral (-C) tissue saturation (StO_2) in Fontan patients and controls from rest to peak exercise and recovery.
* $p < 0.02$ Fontan vs. Control at the same power or time point. # $p < 0.001$ Fontan vs. Control at peak. The numbers in the Fontan group indicate the number of participants included in the mean. R on the x-axis indicates rest.

Systemic venous pressure
SVP (mmHg)

Fontan

p<0.00001

Controls

Watts