Heart Rate Reserve in Fontan Patients: Chronotropic Incompetence or Hemodynamic Limitation?

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Background—Patients with a Fontan circulation achieve lower peak heart rates (HR) during exercise. Whether this impaired chronotropic response reflects pathology of the sinoatrial node or is a consequence of altered cardiac hemodynamics is uncertain. We evaluated the adequacy of HR acceleration throughout exercise relative to metabolic demand and cardiac output in patients with a Fontan circulation relative to healthy controls.

Methods and Results—Thirty subjects (20 healthy controls and 10 Fontan patients) underwent cardiac magnetic resonance imaging with simultaneous invasive pressure recording via a pulmonary and radial artery catheter during supine bicycle exercise to near maximal exertion. Adequacy of cardiac index, stroke volume, and HR reserve was assessed by determining the exercise-induced increase (Δ) in cardiac index, stroke volume, and HR relative to the increase in oxygen consumption (VO₂). HR reserve was lower in Fontan patients compared with controls (71±21 versus 92±15 bpm; P=0.001). In contrast, increases in HR relative to workload and VO₂ were higher than in controls. The change in cardiac index relative to the change in VO₂ (Δcardiac index/ΔVO₂) was similar between groups, but Fontan patients had increased ΔHR/ΔVO₂ and reduced Δ stroke volume/ΔVO₂ compared with controls. There was an early and marked reduction in stroke volume during exercise in Fontan patients corresponding with a plateau in cardiac output at a low peak HR.

Conclusions—In Fontan patients, the chronotropic response is appropriate relative to exercise intensity, implying normal sinoatrial function. However, premature reductions in ventricular filling and stroke volume cause an early plateau in cardiac output beyond which further increases in HR would be physiologically implausible. Thus, abnormal cardiac filling rather than sinoatrial node dysfunction explains the diminished HR reserve in Fontan patients. (J Am Heart Assoc. 2019;8:e012008. DOI: 10.1161/JAHA.119.012008.)

Key Words: cardiac magnetic resonance imaging • chronotropic incompetence • exercise physiology • Fontan procedure • heart rate

Chronotropic incompetence, broadly defined as the inability of the heart to increase its rate commensurate with increased activity or demand, is commonly observed in patients with a Fontan circulation and is associated with exercise limitation. The term “chronotropic incompetence” implies that the ability of the sinus node to respond appropriately to varying physical workload is impaired, suggesting that increasing heart rate (HR) reserve might improve exercise tolerance.1,2 This assumes, however, that cardiac filling and stroke volume are replete throughout exercise, which may not be valid in patients with a Fontan circulation, in whom flow through the pulmonary vasculature may be challenged during exercise because of a lack of a presystemic pump.3

Despite the reported association between exercise intolerance and chronotropic incompetence,4,5 the appropriateness of the HR response throughout exercise relative to exercise level has not been specifically studied in Fontan patients. This is clinically important because therapies that affect the chronotropic response to exercise are being...
Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Subjects

Twenty healthy subjects volunteered to participate after responding to local advertisements. All subjects were (1) healthy; (2) had no history of cardiovascular disease, symptoms, or risk factors; and (3) had a normal ECG and transthoracic echocardiogram.

The Fontan group consisted of 10 patients followed in the pediatric cardiology or adult congenital heart disease clinic. All patients were clinically stable, which was defined as (1) the absence of a history of atrial arrhythmias or sinus node dysfunction, (2) stable exercise capacity over time, and (3) long-term stable Fontan palliation. 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, a residual fenestration, or significant aortopulmonary collaterals on their last invasive evaluation; all had normal sinus rhythm. Five patients had an intracardiac total cavopulmonary connection, and 5 had an extracardiac total cavopulmonary connection. Eight patients had a systemic left ventricle, and 2 had a systemic right ventricle.

The study protocol conformed to the Declaration of Helsinki and was approved by the local ethics committee. All patients provided informed consent.

Exercise Cardiac Magnetic Resonance Protocol

Before exercise, a 7F pulmonary artery catheter was inserted in the internal jugular vein and guided under fluoroscopy or pressure curve monitoring to the proximal right main pulmonary artery. A 20-gauge arterial catheter was placed in the radial artery. In the cardiac magnetic resonance (CMR) suite, these catheters were attached to CMR-compatible pressure transducers that were connected to a PowerLab recording system (AD Instruments, Oxford, United Kingdom).

Patients then underwent CMR at rest, and at low, moderate, and peak exercise using an electronically controlled supine CMR ergometer (Lode, Groningen, The Netherlands). Exercise intensities were determined by prior measurement of maximum exercise power using cardiopulmonary exercise testing, as determined previously. Peak exercise power corresponded to the maximal exercise intensity that could be sustained for ~120 seconds of data acquisition in the CMR bore. Pulmonary and systemic arterial pressures were continuously recorded throughout exercise and analyzed off-line using LabChart v6.1.1 (AD Instruments). Using an in-house developed software program (RightVol, Leuven, Belgium), end-diastolic and end-systolic volumes (EDVi, ESVi) of the systemic ventricle (left ventricle in controls) were calculated by a summation of disks and indexed for body-surface area. From these measurements, stroke volume (SVi), cardiac index (CI), and ejection fraction were inferred.

At rest and at peak exercise, arterial and central venous blood samples were collected and analyzed for oxygen saturation (SaO2, ScvO2), oxygen tension (PaO2, PcvO2), and carbon dioxide tension (PaCO2, PcvCO2) using an automated blood gas analyzer (ABL 700, Radiometer; Copenhagen, Denmark). Arteriovenous O2 content difference C(a-cv)O2
was measured directly as the difference between arterial and central venous oxygen content. Oxygen consumption ($\text{VO}_2$) was calculated according to the Fick principle from CMR-derived cardiac output, arterial and central venous oxygen saturations, and hemoglobin.

HR reserve (HRR) was defined as the difference between peak exercise and resting HR. Age-predicted maximal HR was defined as 220 – age. Adjusted HRR was determined as HRR divided by the difference between age-predicted maximal HR and resting HR. Furthermore, similar to the approach by Wilkoff and Miller, adequacy of cardiac output, stroke volume, and HRR was assessed by determining the exercise-induced increase in CI, SVi, and HR relative to the increase in VO2 (in mL/min per kg).

**Statistical Analysis**

Data were analyzed using IBM SPSS statistics 22 software. Gaussian distribution of all continuous variables was tested using a Kolmogorov–Smirnov test. Descriptive data for continuous variables are presented as means±SD or as medians (25th and 75th percentile) when appropriate. Categorical data were reported as numbers (percentage) and compared using the Fisher exact test. Comparisons between groups were performed using unpaired 2-sample $t$ tests or the Mann–Whitney test, as appropriate. The impact of exercise on biventricular regression analysis. Differences in HR-workload slope coefficients of the relationships between HR and absolute workload (in watts) were derived from serial measurements of HR and exercise power during incremental exercise using linear regression analysis. Differences in HR-workload slope coefficients between groups were compared using independent samples $t$ test. The relationship between cardiac filling (SVi) and HR was estimated using a quadratic regression analysis. Differences in curves for each group (control versus Fontan patients) were compared using the extra sum-of-squares $F$ test. Tests were 2-sided and a $P<0.05$ was considered significant.

**Results**

**Clinical Characteristics**

The clinical characteristics and resting hemodynamic data are depicted in Table 1. Fontan patients were younger than the controls (20±4 versus 35±11 years; $P<0.001$). None of the subjects were receiving pulmonary vasodilator therapy and none was treated with bradycardic drugs. Fontan patients had a slightly higher resting HR than controls. Systemic ventricular volumes, ejection fraction (Figure 1), as well as CI were similar between both groups.

**HR Reserve**

As depicted in Table 2, augmentation of HR from rest to peak exercise was lower in Fontan compared with controls as expressed by impaired HRR (71±21 versus 92±15 bpm; $P<0.001$) and adjusted HRR (56±14 versus 76±11; $P<0.001$). Peak exercise HR was lower in Fontan patients than in controls (144±15 versus 155±13 bpm; 72±8 versus 84±8% of predicted; both $P<0.05$), whereas peak lactate levels were similar (4.4±1.3 versus 4.2±1.3 mmol/L), confirming exercise to a similarly intense level beyond ventilatory threshold. In contrast, for any given value of exercise power or oxygen consumption, HR was actually higher in the Fontan group than in controls (Figure 2A). Similarly, $\Delta HR/\Delta VO_2$ ($\Delta HR$ 6.0±3.2 versus 3.7±2.5/mL/kg oxygen consumption; $P=0.007$).

| Table 1. Baseline Characteristics |
|----------------------------------|
| Healthy Controls | Fontan Patients | $P$ Value |
| **Clinical** |
| Age, y | 35±11 | 20±4 | $<0.0001$ |
| BSA, m² | 1.96±0.09 | 1.68±0.14 | $<0.0001$ |
| BMI, kg/m² | 23.9±3.3 | 22.0±2.0 | 0.118 |
| Male sex, n (%) | 19 (95) | 6 (60) | 0.031 |
| **Resting systemic ventricular volumes and hemodynamics** |
| Heart rate, bpm | 62±10 | 72±14 | 0.030 |
| EDVi, mL/m² | 107±17 | 100±17 | 0.336 |
| ESVi, mL/m² | 43±9 | 44±16 | 0.967 |
| SVi, mL/m² | 63±12 | 57±10 | 0.134 |
| Ejection fraction, % | 59.4±5.7 | 57.3±10.5 | 0.482 |
| CI, L/min per m² | 3.9±0.7 | 4.1±0.9 | 0.546 |
| mPAP, mm Hg | 13±3 | 9±3 | 0.007 |
| msAP, mm Hg | 93±9 | 81±7 | 0.001 |
| tPVR, dynes s/cm⁵ | 140±44 | 119±69 | 0.306 |
| tSVR, dynes s/cm⁵ | 1017±226 | 1003±234 | 0.875 |
| SatO₂, % | 98.2±1.0 | 97.2±0.5 | 0.011 |
| ScvO₂, % | 73.5±7.8 | 75.1±4.8 | 0.581 |

BMI indicates body mass index; BSA, body surface area; CI, cardiac index; EDVi, end-diastolic volume index; ESVi, end-systolic volume index; mPAP, mean pulmonary artery pressure; msAP, mean systemic arterial pressure; ScvO₂, central venous oxygen saturation; SatO₂, arterial oxygen saturation; SVi, stroke volume index; tPVR, total pulmonary vascular resistance; tSVR, total systemic vascular resistance.
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observed when HR was expressed as a percentage of lower peak HR (Figure 2B), whereas the opposite was observed when HR was expressed as a percentage of maximal exercise power (Figure 2C).

Exercise Hemodynamics

Changes in cardiac volumes and pressures are depicted in Table 3. In both controls and Fontan patients, there was a decrease in systemic ventricular EDVi during exercise. However, in controls EDVi was maintained through moderate-intensity exercise and fell modestly at peak intensity (P=0.001; Figure 3). In Fontan patients, EDVi fell quite markedly from low- to moderate-intensity exercise and then fell further at peak exercise (P=0.035). Systemic ventricular ESVi decreased progressively from rest to peak exercise in controls, whereas in Fontan patients ESVi did not change (P=0.001 for interaction). As a result, whereas controls had an increase in SVi during exercise, SVi decreased during exercise in the Fontan patients (P<0.001 for interaction; Figure 3). Figure 4 depicts the individual changes in CI, HR, and SVi from rest to peak exercise. Figure 5 compares the SVi response to exercise in the 5 youngest controls versus the 5 oldest Fontan patients (age 24±4 versus 22±4 years; P=0.612). The differences in the SVi pattern during exercise in these age-matched groups were similar to those observed in the total study population.

Figure 6 depicts quadratic regression analysis of the mean values for SVi and cardiac output versus the average values of HR. A significantly different pattern of SVi augmentation is observed with a peak stroke volume occurring at a HR of ≈140 bpm in control subjects as compared with 95 bpm in Fontan patients. For the purpose of this regression analysis, the pattern of SVi and cardiac output in the higher HR ranges is assumed to follow the quadratic trend.

Discussion

Our study demonstrates that the determinants of cardiac output at rest and during exercise are very different in healthy controls and Fontan patients. In normal individuals, cardiac output augmentation is achieved by an increase in HR and stroke volume, which in turn is determined by increased contractility and nonlimited preload. On the contrary, in Fontan patients, the exercise-induced increase in cardiac output is primarily achieved by increases in HR. We show that the increase in HR relative to workload or metabolic demand is robust or even enhanced in Fontan patients but then ceases to increase further at a lower peak exercise value. This corresponds to a point at which stroke volume is falling abruptly and cardiac output is starting to plateau, which suggests that further increases in HR would not be physiologically possible. In other words, this suggests that the chronotropic constraint in Fontan patients is more likely a secondary phenomenon caused by inadequate systemic ventricular filling, inappropriate ventricular contraction, and impaired cardiac output augmentation rather than true “chronotropic incompetence.”

HR during exercise is determined by the sinus node function, the local effect of autonomic innervation, circulating catecholamines, and increased ventricular preload. Previous studies have used the term “chronotropic incompetence” when peak exercise HR failed to reach a lower arbitrary percentage (either 85%, 80%, or, less commonly, 70%) of the age-predicted maximal HR. However, chronotropic “incompetence” implies that the ability of the sinus node to respond appropriately to varying physical workload is impaired. Therefore, Wilkoff and Miller utilized the expired gas analysis

Table 2. Heart Rate Reserve

|                          | Healthy Controls (n=20) | Fontan Patients (n=10) | P Value |
|--------------------------|-------------------------|------------------------|---------|
| Resting HR, bpm          | 62±10                   | 72±14                  | 0.030   |
| Peak HR, bpm             | 155±13                  | 144±15                 | 0.047   |
| HRR, bpm                 | 71±21                   | 92±15                  | 0.001   |
| Adjusted HRR, bpm        | 56±14                   | 76±11                  | <0.001  |
| ΔCI/ΔVO₂                | 0.26±0.09               | 0.26±0.10              | 0.925   |
| ΔHR/ΔVO₂               | 6.0±3.2                 | 3.7±2.5                | 0.054   |
| ΔHR/ΔW                 | 0.83±0.35               | 0.51±0.09              | 0.018   |

ΔCI indicates change in cardiac index from rest to peak exercise; HR, heart rate; ΔHRR, change in heart rate from rest to peak exercise; HRR, heart rate reserve; ΔVO₂, change in oxygen consumption (in mL/min per kg) from rest to peak exercise; ΔW, change in exercise power (workload) from rest to peak exercise.

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technique to calculate the metabolic–chronotropic relationship from the ratio of the HRR to the metabolic reserve during submaximal exercise. This physiological concept enables evaluation of whether a single HR value at any point during the exercise protocol is consistent with normal chronotropic function. Using this approach, previous investigators demonstrated that patients with sick sinus syndrome were unable to accelerate their HR to the level of normal subjects at a comparable exercise-induced VO₂ value. In Fontan patients, it has been shown that the sinus node may be dysfunctional, either congenital or by damage caused by multiple surgeries (direct damage or indirectly by damaging the arterial supply or innervation). In this study, however, we demonstrate that in a selected cohort of well-functioning Fontan patients, HR was actually higher at any given value of VO₂ than in healthy subjects, indicating that the capacity to increase HR during exercise was intact in these patients.

The question then arises as to why HRR is reduced in these patients with Fontan physiology. Although the increase in HR relative to metabolic load is increased relative to controls, the HR augmentation in Fontan patients stops abruptly at a low peak value. This lower peak exercise HR might constitute a “brake” in Fontan patients that serves to prevent the precipitous falls in stroke volume and cardiac output that would be expected if further increases in HR were possible. The extrapolated relationships between cardiac output and HR in Figure 6 provide a hypothetical illustration of this principle and depict a premature inflection point beyond which continued increases in exercise would not be considered possible because of a falling cardiac output.

This attenuated increase in cardiac output can be explained by the lower stroke volume in Fontan patients relative to controls, and this is further exacerbated by quite profound reductions in stroke volume that occur at only mild-to-moderate exercise intensities. The cause of these early and profound reductions in stroke volume during exercise may be explained by abnormalities in cardiac filling, reductions in systolic contractility, or both. Stroke volume represents the...
Table 3. Exercise Hemodynamics

|                  | Healthy Controls (n=20) | Fontan Patients (n=10) | P Value |
|------------------|-------------------------|------------------------|---------|
| Heart rate, bpm  | 155±13                  | 144±15                 | 0.047   |
| EDVI, mL/m²      | 104±18                  | 96±16                  | 0.237   |
| ESVI, mL/m²      | 32±9                    | 44±17                  | 0.013   |
| SVi, mL/m²       | 72±12                   | 52±9                   | <0.001  |
| Ejection fraction, % | 69.7±5.4              | 54.8±10.9              | 0.002   |
| CI, L/min per m² | 11.0±2.0                | 7.4±1.7                | <0.001  |
| mPAP, mm Hg      | 27±7                    | 21±5                   | 0.022   |
| mSAP, mm Hg      | 121±13                  | 106±5                  | <0.001  |
| tPVR, dynes-s/cm³ | 104±43                  | 137±45                 | 0.068   |
| tSVR, dynes-s/cm³ | 467±126                | 710±164                | <0.001  |
| SatO₂, %         | 97.0±2.7                | 94.3±1.2               | 0.005   |
| SatcvO₂, %       | 41.0±10.7               | 49.1±8.7               | 0.056   |

CI indicates cardiac index; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; mPAP, mean pulmonary artery pressure; mSAP, mean systemic arterial pressure; SatO₂, arterial oxygen saturation; SatcvO₂, central venous oxygen saturation; SVi, stroke volume index; tPVR, total pulmonary vascular resistance; tSVR, total systemic vascular resistance.

The small sample size was an expected limitation of this study, given the constraints of recruiting healthy subjects for an

Clinical Implications

The novel and important clinical implication of this study is that a lower HRR in Fontan patients is not a primary electrical phenomenon and that any increases in HR during exercise would be expected to reduce exercise performance. Just as for other conditions associated with systemic ventricular inflow restriction (Mustard,16 Senning,17 and mitral stenosis), a HR inappropriate for cardiac output is dangerous and may result in hypotension and death. The term “chronotropic limitation” may be more appropriate to describe the reduced HRR rather than chronotropic incompetence, which has previously been associated with impairment of the sinoatrial pacemaker apparatus. The suggestion that reduced HRR, in certain patient populations, may be the consequence of impaired exercise hemodynamics rather than constituting a primary electrical phenomenon is clinically relevant because therapies that affect the chronotropic response to exercise, such as β-blockers and ivabradine, are being actively investigated as a novel therapeutic target in Fontan patients.18 Our data would support the hypothesis that medications resulting in relative bradycardia during exercise may improve exercise capacity because of enhanced diastolic filling, whereas chronotropic medications or pacing would be expected to have negative effects.

Limitations

The small sample size was an expected limitation of this study, given the constraints of recruiting healthy subjects for an
invasive study protocol and the low community prevalence of patients with a Fontan circulation. Because of its low prevalence, the Fontan population was relatively mixed including both patients with intracardiac and extracardiac conduits as well as different ventricular geometry. However, the dominant feature of all patients was Fontan physiology. Moreover, previous studies did not reveal any association between ventricular geometry and exercise capacity or outcome. The Fontan patients were significantly younger, more likely to be female, and had lower body surface area, but this is unlikely to explain the observed differences in HRR. Rather, the younger age would be expected to diminish the observed differences. Furthermore, the overall cardiovascular response to exercise has been shown to be similar in men and women.

VO₂ was calculated by the direct Fick method as the product of cardiac output derived by CMR and C(a-cv)O₂ measured by blood gas collection rather than direct measurement of expiratory gases because of incompatibilities between the cardiopulmonary testing equipment and the CMR environment. Central venous gases rather than true mixed venous gases were obtained because of the complex geometry of the Fontan circulation (e.g., tubing offset and connection angles). The development of CMR-compatible ergospirometry systems may enable simultaneous evaluation of cardiac volumes and expiratory gases, thereby avoiding the need for invasive blood gas measurements in future studies. It should be pointed out that the exercise CMR protocol consisted of supine cycling exercise. It is well known that changes in HR and hemodynamics depend on body position (supine versus upright) because of the difference in venous return. During supine posture, passive left ventricular filling is enhanced by the effects of gravity. Therefore, the observed reduction in EDVi and SVi during

Figure 3. Changes in systemic ventricular volume and output during exercise. Changes in end-diastolic volume, end-systolic volume, stroke volume, and CI from rest to peak exercise in controls and Fontan patients. Data are presented as means and SEM at each time point. CI indicates cardiac index; ex. intensity, exercise intensity.
exercise may be even more apparent during exercise in the upright position. Although sinus node dysfunction is a known complication after Fontan operations, this study specifically focused on well-functioning Fontan patients without established sinus node dysfunction. The slope of HR versus workload or VO$_2$ is affected by the individuals’ exercise capacity, which may partly explain the attenuated slope of HR to VO$_2$ ($\Delta$HR/$\Delta$VO$_2$) in the control subjects. Nevertheless, $\Delta$HR/$\Delta$VO$_2$ in the Fontan population was 2 times higher than that observed in a prior study in patients with sick sinus syndrome, thereby arguing against overt sinoatrial dysfunction in our cohort of well-functioning Fontan patients.

Because of the small, but potentially serious, potential for adverse events in performing pulmonary capillary wedge pressure measurements during exercise, no wedge pressure measurements were obtained as part of the exercise protocol. Thus, we cannot directly validate our assertion that reduced left atrial pressures were the prequel to impaired ventricular filling and reduced left ventricular EDVi during exercise. We did not find an association between HRR and pulmonary artery pressures. However, the latter do not only depend on left-sided filling pressures but also on the characteristics of the pulmonary circulation (resistance and compliance) and flow. Finally, peak HRs in the CMR bore were slightly lower.

**Figure 4.** Individual changes in cardiac hemodynamics during exercise. Changes in cardiac index, heart rate, and stroke volume from rest to peak exercise are depicted in controls (left panels) and Fontan patients (right panels).
than true peak values in all groups because peak exercise power needed to be sustained for \( \approx 120 \) seconds of data acquisition during supine cycling.

**Conclusion**

At any given exercise intensity, chronotropic responsiveness is preserved, and even increased, in Fontan patients, indicating normal sinoatrial function. However, exercise capacity and maximum HR are attenuated, likely as a consequence of reduced systemic ventricular filling, falling stroke volume, and a premature plateau in cardiac output. Thus, it would appear that the diminished HRR observed in Fontan patients is a secondary phenomenon rather than an incompetence of the sinoatrial pacemaker apparatus.

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Disclosures

None.

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