Respiratory Effects on Fontan Circulation During Rest and Exercise Using Real-Time Cardiac Magnetic Resonance Imaging

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Background. **It is known that respiration modulates cavopulmonary flows, but little data compare mean flows under breath-holding and free-breathing conditions to isolate the respiratory effects and effects of exercise on the respiratory modulation.**

Methods. **Real-time phase-contrast magnetic resonance combined with a novel method to track respiration on the same image acquisition was used to investigate respiratory effects on Fontan caval and aortic flows under breath-holding, free-breathing, and exercise conditions. Respiratory phasicity indices that were based on beat-averaged flow were used to quantify the respiratory effect.**

Results. **Flow during inspiration was substantially higher than expiration under the free-breathing and exercise conditions for both inferior vena cava (inspiration/expiration: 1.6 ± 0.5 and 1.8 ± 0.5, respectively) and superior vena cava (inspiration/expiration: 1.9 ± 0.6 and 2.6 ± 2.0, respectively). Changes from rest to exercise in the respiratory phasicity index for these vessels further showed the impact of respiration. Total systemic venous flow showed no significant statistical difference between the breath-holding and free-breathing conditions. In addition, no substantial difference was found between the descending aorta and inferior vena cava mean flows under either resting or exercise conditions.**

Conclusions. **This study demonstrated that inferior vena cava and superior vena cava flow time variance is dominated by respiratory effects, which can be detected by the respiratory phasicity index. However, the minimal respiration influence on net flow validates the routine use of breath-holding techniques to measure mean flows in Fontan patients. Moreover, the mean flows in the inferior vena cava and descending aorta are interchangeable.**

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Completion of Fontan palliation in single ventricle patients usually culminates in the total cavopulmonary connection (TCPC) with either an extra cardiac (EC) or a lateral tunnel connection [1]. TCPC hemodynamics are affected in a complicated way by several factors, including anatomic and flow variables [2], vascular resistances and compliances [3], exercise, respiration, and peripheral muscular contractions [4]. Further, these complexities appear related to clinical outcomes [5].

Precise flow measurement in various physiologic states, especially respiration, is key for numerically assessing TCPC hemodynamics [6]. Current TCPC flow measurements are commonly acquired either during breath-holding (BH) or averaged during free-breathing (FB) (at the expense of image blurring) [7]. Despite the apparent effects of respiration and exercise, few studies have focused specifically on delineating these effects [8, 9]. Of the studies that do, some suggest that because of the high venous capacitance in the lower body, one primary effect of inspiration is to increase (as much as 80%) the flow rate and pulsatility of the inferior vena cava [9–14]. Hjortdal and colleagues [9] examined respiration effects and used an air-filled belt around the abdomen of patients to monitor their respiration, because their imaging method did not allow direct tracking of respiratory cycles. In addition, the literature lacks a comprehensive study, including a comparison of resting BH, resting FB, and exercise conditions, to isolate respiratory effects while keeping other factors constant.

With the advent of advanced real-time phase-contrast magnetic resonance (rtPCMR) imaging technologies and image processing techniques, a detailed analysis of respiration effects during rest and exercise is now feasible. In this study, we used rtPCMR to investigate respiration effects during resting FB, resting breath-hold, and supine exercise conditions. Respiratory patterns and vessel flow rates were simultaneously measured in real-time with the

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Abbreviations and Acronyms

AAo = ascending aorta
BH = breath-holding
BSA = body surface area
DAo = descending aorta
EC = extra cardiac
FB = free-breathing
HR = heart rate
IVC = inferior vena cava
PCMR = phase-contrast magnetic resonance
PI = pulsatility index
PI_{resp} = respiratory pulsatility index
Q_{expr} = mean flow rate during expiration
Q_{insp} = mean flow rate during inspiration
rtPCMR = real-time phase-contrast magnetic resonance
SVC = superior vena cava
VAT = ventilatory anaerobic threshold

use of a novel chest wall tracking method. The adequate flow metrics to accurately quantify respiration effects are also discussed.

Patients and Methods

Patient Cohort

The patients involved in the present study were identified from our prospective enrolled Fontan database. Eleven consecutive single ventricle patients with TCPC anatomy (men/women = 7/4; age = 20.7 ± 2.9 years; body surface area [BSA] = 1.8 ± 0.2 m^2; lateral tunnel/EC = 10/1; left/right/mixed ventricular morphology = 3/6/2; hypoplastic left heart syndrome (n = 5; fenestration = 2), who completed rtPCMR at rest and at exercise were included. They all have normal bilateral diaphragm function and had at most mild ventricular dysfunction (ejection fraction = 42% to 73%). The inclusion criteria were (1) TCPC with no other sources of pulmonary blood flow and (2) the ability to undergo the metabolic exercise stress test with the use of a stationary cycle ergometer. Patients with pacemakers, other metal devices that produced detrimental imaging artifacts, and substantial differences in heart rate (HR) between individual vessel flow measurements were excluded. Any HR difference affected cardiac output which, in turn, affected the flow measurements. In this study, 4 patients were excluded because the HR difference between the acquisitions of their ascending aorta (AAo) and descending aorta (DAo) were greater than 20% of the Ao HR. Patients enrolled in this study had all previously completed a routine maximal metabolic exercise test with the use of a ramp cycle protocol. Ventilatory anaerobic threshold (VAT) was measured by the V-slope method, and BSA of all patients was calculated with the use of their measured weight and height. Informed consent was obtained from all patients, and all study protocols complied with the institutional review boards of the participating institutions.

Data Acquisition Protocol

A 1.5 T Avanto Whole Body system (Siemens Medical Solutions, Malvern, PA) was used in anatomic and PCMR imaging. The imaging protocol, which used parallel imaging, began with an anatomic survey with the use of static steady state free precession; these data were reformatted to acquire slice orientations and positions perpendicular to flow for rtPCMR acquisitions. The rtPCMR was an echoplanar sequence that used shared velocity encoding, the details of which have been described previously [15]. It used, in general, the following variables: repetition time of 9.5 milliseconds, echo time of 4.1 milliseconds, flip angle of 30 degrees, field of view of 320 to 400 mm, slice thickness of 8 to 10 mm, and bandwidth of 2,841 Hz/pixel. The acquisition protocol consisted of through-plane PCMR across the superior (SVC) and inferior (IVC) vena cava, AAo and DAo aorta for at least 10 seconds (20 frames per second, approximately). The IVC flow was acquired near the diaphragm but above the hepatic entrance to the IVC. The same imaging protocol was performed under the resting FB and BH conditions. Flows during the BH were acquired at the end of expiration, whereas FB flows include inspiration and expiration.

After the resting rtPCMR acquisition, the patients were slid partially out from the MI imaging (MRI) bore to perform lower leg exercise with the use of an MRI-compatible supine bicycle ergometer (Lode BV, Groningen, the Netherlands). This ergometer allows revolutions per minute-independent workload, ranging from 10 to 250 watts while the patient maintains his or her position by bracing with hand grips. The goal was to bring the patients from the resting conditions up to a steady work rate at their VAT as measured in their metabolic exercise test, which was a sustainable work rate for the completion of the PCMR data acquisition. HR was monitored continuously. Initially, the workload was set to 20 watts and was increased progressively at a rate of 20 watts per minute to obtain a HR corresponding to that of the HR at VAT on their prior metabolic exercise test. Exercise was then suspended, their feet quickly removed from the ergometer pedals, and they were automatically returned to the isocenter for imaging ($<$10 seconds). With the use of this method, rtPCMR measurements of the AAo, DAo, IVC, and SVC were acquired with repeated exercise performed in between for the patient to return to the target HR.

Image Processing and Data Analysis

A semiautomatic protocol for image processing, chest wall tracking, and flow segmentation was developed with the use of a freely available software, Segment (Medviso.com). First, time-varying velocity fields, from through-plane PCMR slices, were integrated spatially over vessel cross-sectional areas (eg, at DAo) to calculate the associated flow waveforms. Inspiration and expiration periods corresponding to each vessel's flow waveform were determined by tracking chest wall motion in each vessel's corresponding magnitude image and