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RESEARCH ARTICLE | *Translational Physiology*

Ventilatory and sensory responses to incremental exercise in adults with a Fontan circulation

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Guenette JA, Ramsook AH, Dhillon SS, Puyat JH, Riahi M, Opotowsky AR, Grewal J. Ventilatory and sensory responses to incremental exercise in adults with a Fontan circulation. *Am J Physiol Heart Circ Physiol* 316: H335–H344, 2019. First published November 2, 2018; doi:10.1152/ajpheart.00322.2018.—Many adults with single-ventricle congenital heart disease who have undergone a Fontan procedure have abnormal pulmonary function resembling restrictive lung disease. Whether this contributes to ventilatory limitations and increased dyspnea has not been comprehensively studied. We recruited 17 Fontan participants and 17 healthy age- and sex-matched sedentary controls. All participants underwent complete pulmonary function testing followed by a symptom-limited incremental cardiopulmonary cycle exercise test with detailed assessments of dyspnea and operating lung volumes. Fontan participants and controls were well matched for age, sex, body mass index, height, and self-reported physical activity levels (all $P > 0.05$), although Fontan participants had markedly reduced cardiorespiratory fitness and peak work rates ($P < 0.001$). Fontan participants had lower values for most pulmonary function measurements relative to controls with 65% of Fontan participants showing evidence of a restrictive ventilatory defect. Relative to controls, Fontan participants had significantly higher breathing frequency, end-inspiratory lung volume (% total lung capacity), ventilatory inefficiency (high ventilatory equivalent for CO_2), and dyspnea intensity ratings at standardized absolute submaximal work rates. There were no between-group differences in qualitative descriptors of dyspnea. The restrictive ventilatory defect in Fontan participants likely contributes to their increased breathing frequency and end-inspiratory lung volume during exercise. This abnormal ventilatory response coupled with greater ventilatory inefficiency may explain the increased dyspnea intensity ratings in those with a Fontan circulation. Interventions that enhance the ventilatory response to exercise in Fontan patients may help optimize exercise rehabilitation interventions, resulting in improved exercise tolerance and exertional symptoms.

NEW & NOTEWORTHY This is the first study to comprehensively characterize both ventilatory and sensory responses to exercise in adults that have undergone the Fontan procedure. The majority of Fontan participants had a restrictive ventilatory defect. Compared with well-matched controls, Fontan participants had increased breathing frequency, end-inspiratory lung volume, and ventilatory inefficiency. These abnormal ventilatory responses likely form the mechanistic basis for the increased dyspnea intensity ratings observed in our Fontan participants during exercise.

cardiopulmonary exercise testing; congenital heart disease; dyspnea; restrictive lung disease; ventilatory limitation

INTRODUCTION

Single ventricle physiology encompasses a spectrum of malformations in which both pulmonary venous and systemic venous (superior and inferior vena cava) blood flow are directed back into a functional single ventricle via the atria (27). The basic premise of the Fontan operation is to separate the pulmonary and systemic venous circulations by directing systemic venous blood to the pulmonary artery without an interposed ventricle, leaving the single ventricle to serve the systemic circulation. However, a univentricular Fontan circulation does not replicate a normal biventricular circulation. As a result, exercise capacity is reduced to ~60% of normative values during midadolescence and continues to fall at a rate of ~2.6% per year until the mid-20s (18).

The reduced exercise capacity in those with a Fontan circulation is thought to be driven, in large part, by an inability to adequately increase cardiac output attributable to a reduction in ventricular preload (17). Thus, it is well understood that these individuals experience a "cardiac limitation" to exercise. However, emerging evidence suggests that other noncardiac factors may also contribute to reduced exercise capacity in this population. For example, pulmonary function abnormalities have been documented in Fontan patients, including symmetric reductions in forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) (16). FVC correlates with exercise capacity (19) and is an independent predictor of survival in adults with congenital heart disease (2). Whether these abnormalities in resting pulmonary function result in ventilatory limitations and increased levels of exertional dyspnea has not been systematically evaluated.

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The majority of studies that have examined ventilatory limitations in Fontan patients have focused on gross measures of ventilatory reserve [i.e., the ratio between maximal exercise minute ventilation ($\dot{V}_E$) and maximum voluntary ventilation (MVV)] (40, 45). Values exceeding 85% are generally considered evidence of a "ventilatory limitation" (3). This widely used method is simple to interpret but has a number of drawbacks. First, $\dot{V}_E$/MVV provides little insight into the factors that contribute to ventilatory constraints during exercise (25). Second, a voluntary measure of ventilatory capacity performed under resting conditions (i.e., MVV) bears little resemblance to the breathing patterns, operating lung volumes, and respiratory muscle recruitment patterns adopted during the hyperpnea of exercise (28). Finally, objective evidence of ventilatory limitations can be demonstrated even in the setting of a normal $\dot{V}_E$/MVV (10, 24, 25). Accordingly, more detailed assessments of breathing pattern responses, operating lung volumes, and expiratory flow limitation have the potential to advance our understanding of ventilatory limitations during exercise (21, 25), particularly in those with congenital heart disease (42). Importantly, it remains to be determined whether ventilatory limitations contribute to increased levels of exertional dyspnea in Fontan patients.

The purpose of the present study was to provide a comprehensive characterization of the ventilatory and sensory responses to exercise in adults that have undergone the Fontan procedure. We hypothesized that Fontan participants would have higher dyspnea intensity ratings at standardized absolute submaximal work rates and would experience greater mechanical constraints on tidal volume (V_T) expansion at lower work rates compared with healthy age-, sex-, and physical activity-matched healthy controls.

METHODS

Participants. This study included 17 Fontan participants and 17 controls with each group having 8 women and 9 men. Fontan participant inclusion criteria included a history of the Fontan operation, age of $\geq$18 yr, nonsmoking (currently or history of $<$10 pack-years), clinically stable, and free of contraindications to exercise testing according to the treating cardiologist. Fontan participants were recruited from the St. Paul's Hospital Pacific Adult Congenital Heart Clinic. Sedentary control participants with no history of cardiopulmonary disease were recruited from the community and university population through poster advertisements. Control participants were recruited after data was collected for Fontan participants to facilitate matching based on age and sex. Women were tested randomly throughout their menstrual cycle and were permitted to use oral contraceptives because the ventilatory response to exercise does not appear to be affected by menstrual cycle phase (6, 13, 31) or oral contraceptive use (8).

Experimental overview. This study received institutional ethical approval from the University of British Columbia and Providence Health Care Research Ethics Board. All participants provided written informed consent before participation, and all experimental testing took place on a single visit to a dedicated research laboratory (Cardiopulmonary Exercise Physiology Laboratory) at St. Paul's Hospital. Participants first completed questionnaires followed by pulmonary function testing and a symptom-limited incremental cardiopulmonary cycle exercise test. All participants were thoroughly familiarized with testing procedures and symptom scales before completing the tests.

Questionnaires. All participants completed demographic, medical history, medication, dyspnea [oxygen cost diagram (34), modified Medical Research Council dyspnea scale (33), and baseline dyspnea index (32)] and physical activity [International Physical Activity Questionnaire-Short Form (12)] questionnaires. A Physical Activity Readiness Questionnaire (https://eparmedx.com) was completed by healthy controls only.

Exercise protocol. The incremental exercise test was performed using an electronically braked cycle ergometer (ergoselect 200, Ergoline). The exercise test began with a steady-state resting period while the participant was seated on the cycle ergometer for 7 min followed by a 1-min warmup of unloaded pedaling and 20-W stepwise increases in work rate every 2 min until symptom limitation.

Pulmonary function. Spirometry, plethysmography, diffusing capacity of the lungs for carbon monoxide, and maximum respiratory pressures were measured according to standard recommendations (4, 30, 35, 48) using a commercially available cardiopulmonary testing system (Vmax Encore 229 with V62J Autobox, CareFusion). Pulmonary function measurements are expressed in absolute values and relative to predicted values (9, 23, 46).

Cardiorespiratory responses to exercise. Standard cardiorespiratory measures were recorded on a breath-by-breath basis and averaged over 30-s epochs (Vmax Encore 229, CareFusion). Arterial oxygen saturation, heart rate, and blood pressure were monitored at rest and throughout the exercise test using pulse oximetry (Radical-7 Pulse CO-Oximeter, Masimo), 12-lead electrocardiography, and manual sphygmomanometry, respectively. Operating lung volumes were derived from dynamic inspiratory capacity maneuvers (21). Specifically, end-expiratory lung volume (EELV) was calculated as the difference between total lung capacity (TLC) and inspiratory capacity, and end-inspiratory lung volume (EILV) was calculated as the sum of EELV and V_T. Figure 1*A* shows an example of an operating lung volume plot in an individual Fontan participant. All cardiorespiratory measurements were averaged between 60 and 90 s of each 120-s stage of exercise and were then linked with the symptom ratings and inspiratory capacity-derived variables that were collected between 90 and 120 s. This was done to prevent potential breathing pattern alterations that could occur during the performance of inspiratory capacity maneuvers and/or when participants rate their sensory responses to exercise. The degree of expiratory flow limitation (EFL) was estimated by superimposing tidal flow-volume loops within a preexercise maximum flow-volume loop according to EELV. The percentage of EFL was then quantified as the volume of the tidal breath that met or exceeded the expiratory limb of the maximum flow-volume loop divided by the V_T of those breaths (21), as shown in Fig. 1*B*.

Dyspnea evaluation. Dyspnea intensity (defined as "the sensation of labored or difficult breathing") and perceived leg discomfort were evaluated at rest, every minute during exercise, and at peak exercise using the modified 0–10 category ratio Borg scale (7). The end points of the scale were described as follows: 0 represents "no breathing or leg discomfort" and 10 represents "the most intense breathing or leg discomfort you have ever experienced or could ever imagine experiencing." Slopes relating dyspnea intensity and $\dot{V}_E$ (using only Borg ratings $>$0) were also calculated. Immediately after stopping exercise, participants were asked to *1*) state their primary reason(s) for stopping exercise (e.g., breathing discomfort, leg discomfort, a combination of breathing and leg discomfort, or another reason), *2*) attribute a percentage between breathing and leg discomfort leading to exercise cessation, and *3*) choose applicable qualitative descriptors of breathlessness using a modified list of descriptors from Simon et al. (43), as we have used previously (11).

Statistical analysis. Between-group comparisons (Fontan participants vs. healthy controls) for descriptive characteristics (e.g., age, height, pulmonary function, etc.) and peak exercise responses were performed using unpaired *t*-tests when data were normally distributed. Nonparametric permutation tests were performed on data that showed marked deviations from normality, as indicated by density plots and Shapiro-Wilk tests. Comparisons for cardiopulmonary and sensory responses to exercise at standardized absolute submaximal work rates

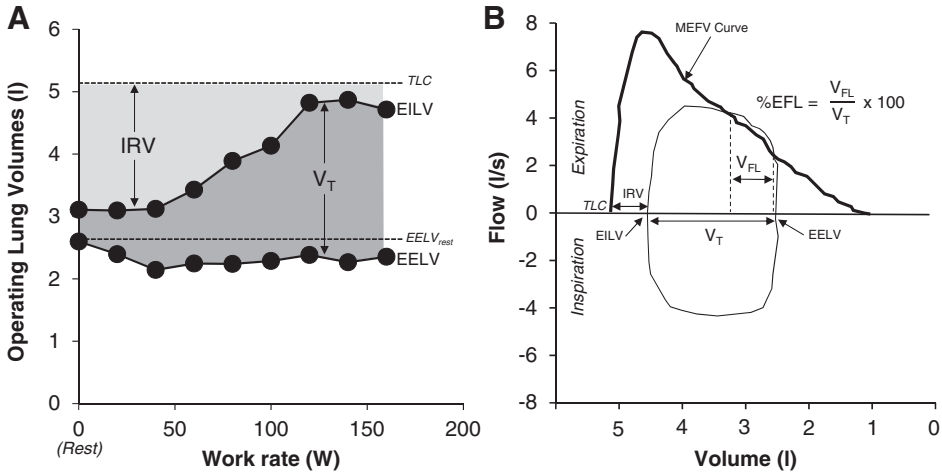

Fig. 1. *A*: operating lung volume plot in an individual Fontan participant. End-expiratory lung volume (EELV) decreased relative to resting values and stayed below resting values throughout all exercise intensities. An increase in EELV relative to rest would be indicative of dynamic lung hyperinflation, which did not occur in any Fontan participant. End-inspiratory lung volume (EILV) progressively increased throughout exercise and then reached a plateau at 120 W. The tidal volume (V_T), represented in the dark gray shaded region (i.e., the difference between EELV and EILV), continually increased throughout exercise but became constrained at 120 W. At this point, the patient's EILV is approaching 95% of their total lung capacity (TLC), at which the elastic loading on the inspiratory muscles should be elevated. The light gray shaded region represents the inspiratory reserve volume (IRV). The IRV is large during light intensity exercise but progressively decreases, particularly when V_T becomes constrained. *B*: schematic representation of a preexercise maximum expiratory flow-volume (MEFV) curve in the same Fontan participant. The thin black flow-volume loop represents a breath at maximal exercise and is positioned along the volume axis according to the measured EELV. The percentage of expiratory flow limitation (EFL) was calculated by dividing the volume of the maximal exercise breath that met or exceeded the MEFV curve (i.e., V_{FL}) by V_T.

were performed using repeated-measures ANOVA with the Greenhouse-Geisser correction. To determine whether group differences were present at various work rates, the interaction between group and work rate was tested followed by Bonferroni-adjusted post hoc comparisons when results were significant. Statistical comparisons were primarily focused on absolute instead of relative (e.g., percentage of maximal) submaximal work rates because the primary aim was to determine whether Fontan participants experience more dyspnea and ventilatory abnormalities to perform the same standardized absolute physical task, similar to what they might experience during their daily activities. This also avoids the need to interpolate data, particularly dyspnea and inspiratory capacity-derived measurements because these measurements were not obtained at precise relative work rates (e.g., 25%, 50%, and 75% of peak work rate). Group differences in the reasons for stopping exercise and the qualitative descriptors of dyspnea were analyzed using Fisher's exact test. Spearman correlation coefficients were determined to explore the relationship between dyspnea intensity ratings and select ventilatory data at peak exercise in Fontan participants. Statistical significance was set at $P < 0.05$. Data are presented as means ± SD. Data analysis was performed using SPSS version 25 and R version 3.4.4.

RESULTS

Participant characteristics. Baseline characteristics of Fontan and control participants are shown in Table 1. Both groups were closely matched for age, sex, height, body mass index, and body surface area. Despite the numerically higher self-reported value for physical activity levels in Fontan participants, there was no statistically significant difference between groups ($P = 0.42$). The numerically higher value was due exclusively to one extreme outlier who reported unusually high levels of walking attributable to his occupation. When removed from this analysis, mean physical activity levels were nearly identical between Fontan versus control participants (1,819 ± 406 vs. 1,941 ± 376 MET-min/wk, respectively, $P = 0.83$). Fontan participants had significantly higher chronic activity-related dyspnea according to all three dyspnea questionnaires (Table 1). Fontan participants had significantly reduced absolute and percent-predicted values for FEV_1, FVC, MVV, and diffusing capacity of the lungs for carbon monoxide relative to controls. Eleven (65%) and thirteen (76%) Fontan participants were below the lower limit of normal (LLN) for FVC and FEV_1, respectively, compared with only 1 (6%) and 2 (12%) controls, respectively. There was no difference in FEV_1/FVC between groups, and no participant had a FEV_1/FVC of <80% predicted, although three Fontan participants and four controls were below the LLN. Twelve (71%) Fontan participants had TLC values below the LLN with only one of these participants having a FEV_1/FVC below the LLN. Thus, 11 (65%) Fontan participants were classified as having a restrictive abnormality according to established criteria (41). Maximal inspiratory pressure was similar between groups, but maximal expiratory pressure was significantly lower in Fontan participants when expressed as a percentage of predicted ($P < 0.05$) and tended to be lower when expressed in absolute values ($P = 0.06$). Clinical characteristics of Fontan participants are shown in Table 2. In addition, two patients had scoliosis, three patients had pectus deformities, no patients had documented diaphragmatic paralysis, and the group had an average of 4 ± 2 procedures that involved a sternotomy or thoracotomy.

Peak exercise responses are shown in Table 3. Fontan participants had markedly reduced peak oxygen uptake values compared with both controls and normative values based on age, sex, and height (26). Similarly, average peak work rate was 46% lower in Fontan participants relative to controls. Both groups achieved respiratory exchange ratios that were, on average, >1.05 with no significant difference between groups.

Cardiopulmonary responses. Selected cardiopulmonary variables during exercise are shown in Fig. 2. Fontan participants

Table 1. *Descriptive characteristics of Fontan and control participants*

	Fontan Participants	Control Participants
Age, yr§	31.8 ± 11.0	30.1 ± 10.8
Sex (men:women)	9:8	9:8
Height, cm	167 ± 10	167 ± 8
Body mass index, kg/m^2§	25.8 ± 6.2	24.9 ± 3.1
Body surface area, m^2	1.80 ± 0.22	1.78 ± 0.16
Physical activity, MET-min/wk	2,983 ± 1224	1,941 ± 376
Modified Medical Research Council dyspnea scale (scale: 0–4)	0.8 ± 0.1†	0.2 ± 0.1
Oxygen cost diagram, mm	75 ± 3*	85 ± 2
Baseline dyspnea index focal score (scale: 0–12)	9.1 ± 0.4†	10.9 ± 0.4
Oxygen saturation, %	93 ± 5‡	99 ± 1
FEV_1, l (% predicted)	2.74 ± 0.59† (74 ± 11‡)	3.49 ± 0.64 (94 ± 12)
FVC, l (% predicted)	3.38 ± 0.79† (76 ± 13‡)	4.39 ± 0.93 (98 ± 12)
FEV_1/FVC, % (% predicted)	82 ± 7 (98 ± 8)	80 ± 6 (96 ± 7)
Maximum voluntary ventilation, l/min (% predicted§)	105 ± 28‡ (71 ± 18‡)	143 ± 31 (95 ± 15)
Functional residual capacity, liters (% predicted)	2.21 ± 0.59 (73 ± 16)	2.59 ± 0.75 (85 ± 19)
Total lung capacity, liters (% predicted)	4.50 ± 0.86† (74 ± 9‡)	5.62 ± 1.31 (91 ± 12)
Diffusing capacity of the lungs for CO, ml·min^{-1}·mmHg^{-1} (% predicted)	17.5 ± 4.2‡ (67 ± 12‡)	25.7 ± 7.5 (98 ± 18)
Maximal inspiratory pressure, cmH_2O§ (% predicted)	100 ± 42 (89 ± 31)	99 ± 41 (87 ± 27)
Maximal expiratory pressure, cmH_2O (% predicted)	102 ± 43 (84 ± 32*)	136 ± 56 (111 ± 36)

Values are means ± SD; values in parentheses are % predicted values. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity. Predicted maximum voluntary ventilation was calculated as predicted $FEV_1 \times 40$. *$P < 0.05$, †$P < 0.01$, and ‡$P < 0.001$ relative to healthy controls; §P values determined using nonparametric permutation testing.

achieved significantly reduced peak heart rate values relative to controls with no differences between groups at absolute submaximal work rates (Fig. 2*A*). Fontan participants achieved peak heart rate values of 77 ± 13% predicted compared with 95 ± 12% predicted for controls ($P < 0.001$; Table 3). Similarly, peak oxygen pulse was significantly lower at peak exercise in Fontan participants relative to controls but was not different at standardized absolute work rates (Fig. 2*B*). Arterial oxygen saturation (via pulse oximetry) was consistently lower in Fontan participants at rest and throughout all exercise intensities (Fig. 2*C*).

Ventilatory responses. The ventilatory response to exercise is shown in Fig. 3. $\dot{V}_E$ was consistently elevated in Fontan participants at standardized submaximal work rates and tended to be higher at rest ($P = 0.08$). The higher $\dot{V}_E$ during submaximal work rates appeared to be driven by both a modestly higher V_T (Fig. 3*B*) and significantly higher breathing frequency (Fig. 3*C*). However, the peak $\dot{V}_E$ in Fontan participants was significantly reduced relative to controls, and this was primarily due to their significantly lower peak V_T (Fig. 3 and Table 3). $\dot{V}_E$/MVV was not different between groups at peak exercise (Table 3) with five (29%) Fontan participants and three (18%)

Table 2. *Clinical and echocardiographic characteristics of Fontan participants*

Characteristic	Fontan Participants (n = 17)
Clinical	
Fontan anatomy	
Atriopulmonary	2 (12)
Lateral tunnel	8 (47)
Extracardiac conduit	7 (41)
Predominant ventricular morphology	
Left	13 (76)
Right	4 (24)
Cardiac medications	
Coumadin	9 (53)
Aspirin	8 (47)
Angiotensin-converting enzyme inhibitor	7 (41)
β-Blocker	7 (41)
Echocardiographic	
Systemic ventricular function	
Normal/mild dysfunction	16 (94)
Moderate/severe dysfunction	1 (6)
Moderate/severe atrioventricular valve regurgitation	2 (12)

Data are number of participants with percentages in parentheses.

Table 3. *Peak exercise data*

	Fontan Participants	Control Participants
Work rate, W	98 ± 33‡	156 ± 40
$\dot{V}_{O_2}$, ml·kg^{-1}·min^{-1}	22 ± 7‡	33 ± 8
$\dot{V}_{O_2}$, l/min	1.51 ± 0.48‡	2.32 ± 0.63
$\dot{V}_{O_2}$, % predicted§	65 ± 14‡	99 ± 27
$\dot{V}_{CO_2}$, l/min	1.64 ± 0.56‡	2.61 ± 0.68
Respiratory exchange ratio	1.09 ± 0.09	1.14 ± 0.11
$\dot{V}_E$, l/min	66 ± 23*	89 ± 32
V_T, l	1.60 ± 0.50*	1.99 ± 0.45
Breathing frequency, breaths/min	41 ± 6	44 ± 9
$\dot{V}_E/\dot{V}_{CO_2}$§	41 ± 8†	34 ± 6
$\dot{V}_E/\dot{V}_{O_2}$§	45 ± 11	38 ± 9
End-tidal P_{CO_2}, mmHg	27 ± 5†	34 ± 6
Estimated dead space/V_T	0.13 ± 0.04*	0.11 ± 0.02
Change in IC from resting values, liters	0.30 ± 0.36	0.26 ± 0.36
End-expiratory lung volume, %TLC	50 ± 8	48 ± 6
End-inspiratory lung volume, %TLC§	86 ± 6	84 ± 5
Inspiratory reserve volume, l	0.63 ± 0.33*	0.92 ± 0.35
V_T/IC, %	72 ± 11	69 ± 8
$\dot{V}_E$/maximum voluntary ventilation, %	65 ± 19	62 ± 16
Heart rate, beats/min	138 ± 24‡	171 ± 22
Heart rate, % predicted	77 ± 13‡	95 ± 12
Oxygen pulse, ml/beat	11 ± 3*	14 ± 4
Oxygen saturation, %§	90 ± 7†	97 ± 4
Breathing discomfort (Borg scale: 0–10)§	5 ± 3	6 ± 3
Dyspnea intensity/$\dot{V}_E$ slope, Borg 0–10 scale/l/min§	0.14 ± 0.12	0.12 ± 0.10
Leg discomfort (Borg scale: 0–10)§	6 ± 3	8 ± 3

Values are means ± SD. $\dot{V}_{O_2}$, oxygen uptake; $\dot{V}_{CO_2}$, carbon dioxide output; $\dot{V}_E$, minute ventilation; V_T, tidal volume; IC, inspiratory capacity; TLC, total lung capacity. $\dot{V}_{O_2}$ and heart rate prediction equations are from Jones et al. (26). *$P < 0.05$, †$P < 0.01$, and ‡$P < 0.001$ relative to healthy control participants; §P values determined using nonparametric permutation testing.

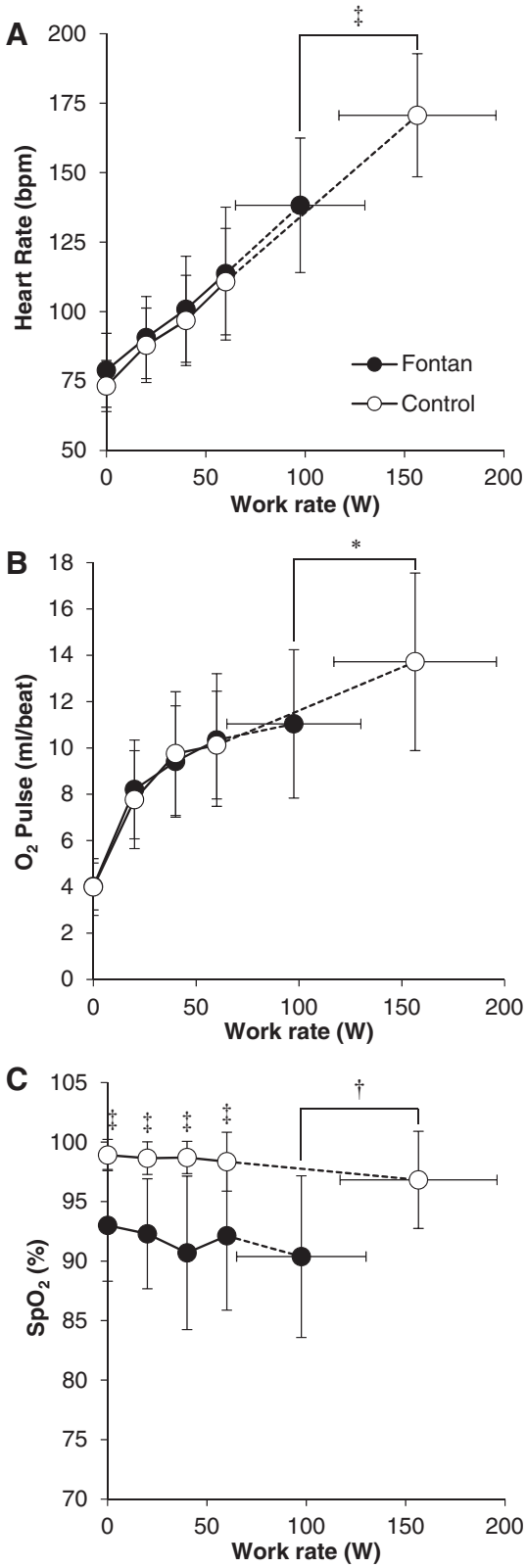

Fig. 2. Cardiovascular responses and arterial oxygen saturation at rest and during exercise. *A*: heart rate. *B*: oxygen pulse. *C*: arterial oxygen saturation by pulse oximetry (SpO_2). Dashed lines connect the highest equivalent submaximal work rate to peak exercise. Values are means ± SD. $^*P < 0.05$, $\dagger P < 0.01$, and $\ddagger P < 0.001$ relative to healthy controls.

controls having $\dot{V}_E$/MVV values exceeding 80%. Only two Fontan participants and two controls had $\dot{V}_E$/MVV values exceeding 85%. Operating lung volumes are shown in Fig. 4 and Table 3. Fontan participants had similar values for EELV and EILV when expressed in liters (Fig. 3*A*), but Fontan participants had higher EILV values during submaximal exercise when normalized to TLC (Fig. 4*B*). This resulted in a higher V_T/inspiratory capacity ratio at all submaximal exercise intensities (all $P < 0.0001$). Absolute inspiratory reserve volume was also reduced at peak exercise in Fontan participants relative to controls (Table 3). No Fontan participants experienced a reduction in inspiratory capacity ≥ 150 ml at peak exercise, suggesting that our Fontan participants did not experience dynamic lung hyperinflation. There was no statistically significant difference in the degree of EFL between Fontan participants versus controls (29 ± 27% vs. 35 ± 35%, respectively, $P > 0.05$). A total of 10 Fontan participants and 9 controls experienced EFL ≥ 20% at peak exercise. The ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$) was markedly elevated in Fontan participants at rest and throughout all exercise intensities, indicating significantly greater ventilatory inefficiency relative to controls (Fig. 3*D*).

Sensory responses. Intensity ratings for breathing and leg discomfort are shown in Fig. 5. Both symptom ratings were similar at peak exercise but were significantly elevated at 60 W (both $P < 0.05$) and tended to be elevated at 40 W (both $P = 0.05$). There were no differences in slopes relating dyspnea intensity and $\dot{V}_E$ (Table 3). Spearman correlation data relating peak dyspnea ratings and select ventilatory parameters are shown in Table 4. Absolute EILV and the V_T/inspiratory capacity ratio at peak exercise were significantly associated with peak dyspnea ratings, whereas EILV (%TLC) and $\dot{V}_E$/MVV approached statistical significance (Table 4). There were no differences in the selection frequency of the reasons for stopping exercise in Fontan participants versus controls (breathing: 11.8% vs. 5.9%, legs: 58.8% vs. 58.8%, combination of breathing and legs: 17.6% vs. 35.3%, and other: 11.8% vs. 0%, respectively, all $P > 0.05$). There were also no between-group differences in the self-reported relative contribution between breathing and leg discomfort that caused exercise cessation in Fontan participants (breathing: 39 ± 21 vs. legs: 61 ± 21%, respectively) and controls (breathing: 31 ± 18 vs. legs: 69 ± 18%, respectively). Finally, selection frequency of the 15 qualitative descriptors of dyspnea at symptom limitation are shown in Fig. 6. There were no statistically significant differences between groups for any dyspnea descriptor.

DISCUSSION

Here, we present a comprehensive characterization of the ventilatory and sensory responses to exercise in adult Fontan participants. This is the first investigation to assess operating lung volumes, expiratory flow limitation, and simultaneous assessments of both the intensity and qualitative dimensions of exertional dyspnea in Fontan participants compared with healthy individuals. A key strength of this study is the inclusion of a well-matched control group that had similar baseline physical activity levels. This addresses the potentially confounding effects of exercise training and physical activity on physiological and sensory responses to exercise when comparing clinical populations with healthy individuals. The main

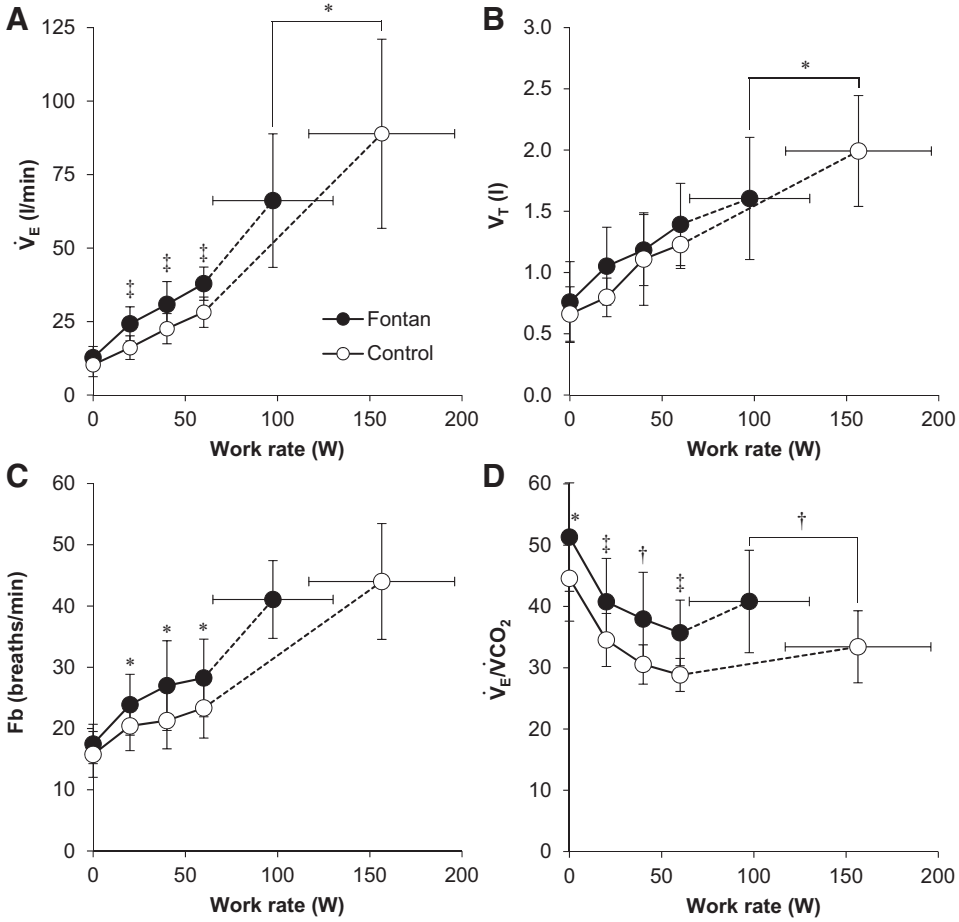

Fig. 3. Ventilatory responses at rest and during exercise. *A*: minute ventilation ($\dot{V}_E$). *B*: tidal volume (V_T). *C*: breathing frequency (Fb). *D*: ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$). Dashed lines connect the highest equivalent submaximal work rate to peak exercise. Values are means ± SD. $*P < 0.05$, $\dagger P < 0.01$, and $\ddagger P < 0.001$ relative to healthy controls.

results of this study are as follows: *1*) the majority of Fontan participants had a restrictive ventilatory impairment; *2*) Fontan participants had greater ventilatory requirements, adopted a more rapid breathing pattern, had greater ventilatory inefficiency, and breathed closer to TLC relative to controls when performing the same absolute work rates; and *3*) Fontan participants had significantly higher dyspnea intensity and leg discomfort ratings at standardized submaximal work rates with no differences at peak exercise. There was also no difference in the selection frequency of various qualitative descriptors of dyspnea at peak exercise and no difference in the subjective reasons for exercise cessation between groups.

The majority (i.e., 65%) of Fontan participants in the present study had evidence of a restrictive ventilatory defect based on a reduced TLC and normal FEV_1/FVC. Other similar studies in Fontan participants have classified restriction according to varying spirometric criteria and found evidence of restriction in ~50–60% of patients (16, 40, 47). Accordingly, it is increasingly recognized that many Fontan patients have abnormal pulmonary function and that these abnormalities may contrib-

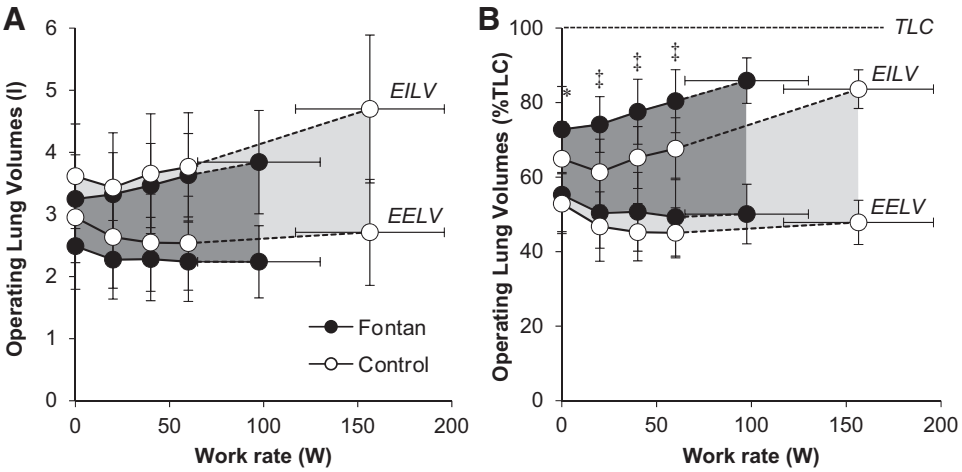

Fig. 4. *A* and *B*: operating lung volumes at rest and during exercise. Dashed lines connect the highest equivalent submaximal work rate to peak exercise. Values are means ± SD. $*P < 0.05$ and $\ddagger P < 0.001$ relative to healthy controls. EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume; TLC, total lung capacity.

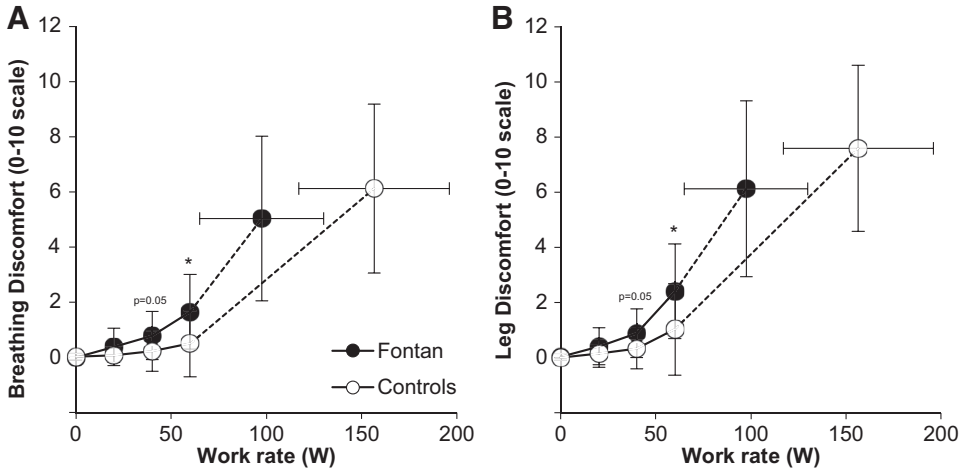

Fig. 5. *A* and *B*: sensory responses at rest and during exercise. Dashed lines connect the highest equivalent submaximal work rate to peak exercise. Values are means ± SD. $*P < 0.05$ relative to healthy controls.

ute to the reduced cardiorespiratory fitness and exercise capacity seen in these patients (19, 40, 47). The mechanisms for the restrictive ventilatory impairment in Fontan participants has not been fully elucidated, but, as previously described (19, 40), there are likely developmental, mechanical, surgical, and functional factors that contribute. Given the evidence of a restrictive ventilatory pattern in Fontan patients, it seems reasonable to speculate that these individuals may experience ventilatory abnormalities during exercise as observed in those with other restrictive respiratory conditions, such as interstitial lung disease (ILD) and obesity (5).

Most exercise physiology studies in Fontan participants have characterized ventilatory responses during exercise by focusing on standard measurements such as $\dot{V}_E$, V_T, and breathing frequency. These studies demonstrated that Fontan participants have lower values for peak $\dot{V}_E$ and V_T (14, 39) and are more likely to adopt a rapid breathing pattern for a given exercise intensity relative to controls (38). These observations are consistent with the results of the present investigation. However, these variables are insufficient in determining the presence or absence of a ventilatory limitation to exercise. The most common method of evaluating a ventilatory limitation during exercise is to examine $\dot{V}_E$/MVV at peak exercise. A recent study has shown evidence of a ventilatory limitation (defined as $\dot{V}_E$/MVV $> 80\%$) in 26.9% of Fontan participants that had a low FVC. $\dot{V}_E$/MVV is simple to obtain and easy to interpret but has numerous limitations, as previously described (21, 25, 42). To provide a more detailed characterization of ventilatory limitations to exercise, we had participants perform inspiratory capacity maneuvers throughout exercise so that we could evaluate dynamic operating lung volumes and expiratory flow limitation.

Table 4. *Spearman correlations between peak Borg 0–10 dyspnea intensity ratings and select peak ventilatory parameters*

	r	*P*
IC, l	0.41	0.11
$\dot{V}_E$/MVV, %	0.46	0.07
EELV, l	0.40	0.12
EELV, %TLC	0.01	0.97
EILV, l	0.64	0.01
EILV, %TLC	0.49	0.05
V_T/IC, %	0.53	0.03

IC, inspiratory capacity; $\dot{V}_E$, minute ventilation; MVV, maximum voluntary ventilation; EELV, end-expiratory lung volume; TLC, total lung capacity; EILV, end-inspiratory lung volume; V_T, tidal volume.

Despite similarities in $\dot{V}_E$/MVV between groups at peak exercise, Fontan participants had higher EILV (%TLC) values across all submaximal work rates. Thus, to perform the same absolute submaximal physical task, Fontan participants were breathing closer to TLC, resulting in a relatively smaller inspiratory reserve volume (Fig. 4). This abnormality should result in a relatively higher elastic work of breathing in Fontan participants relative to controls for a given work rate. Despite these differences, EILV (%TLC) was similar at peak exercise. The degree of EFL was also similar at peak exercise, but this occurred at a markedly lower $\dot{V}_E$ and work rate in Fontan participants. Increases in EILV (%TLC) and decreases in inspiratory reserve volume during exercise have been observed in other populations, such as those with both restrictive and obstructive pulmonary diseases (15), and are thought to play an important role in the genesis of exertional dyspnea (37). The mechanisms associated with the abnormal ventilatory response in Fontan patients are likely complex and multifactorial. It seems reasonable to suspect that the abnormal ventilatory response to exercise is related, in large part, to the frequent presence of a restrictive pattern on lung function testing. However, other factors could potentially contribute. For example, Greutmann et al. (20) found evidence of respiratory and peripheral skeletal muscle weakness in young adults with congenital heart disease, which could alter the ventilatory response to perform a given absolute work rate. However, absolute respiratory muscle strength was not significantly different between controls and Fontan participants in the present study and likely did not contribute to the abnormal ventilatory response to exercise. Unfortunately, we cannot rule out the possibility that peripheral skeletal muscle weakness partially contributed to the ventilatory responses observed in our Fontan participants because we did not assess this. Exercise-induced arterial hypoxemia could also contribute to the abnormal ventilatory and sensory response to exercise, as previously shown (39). Although Fontan patients were hypoxemic throughout exercise, the change in oxygen saturation from resting values to peak exercise was modest (i.e., 3%) and was not correlated with the resting-to-peak change in $\dot{V}_E$, $\dot{V}_E/\dot{V}_{CO_2}$, or dyspnea

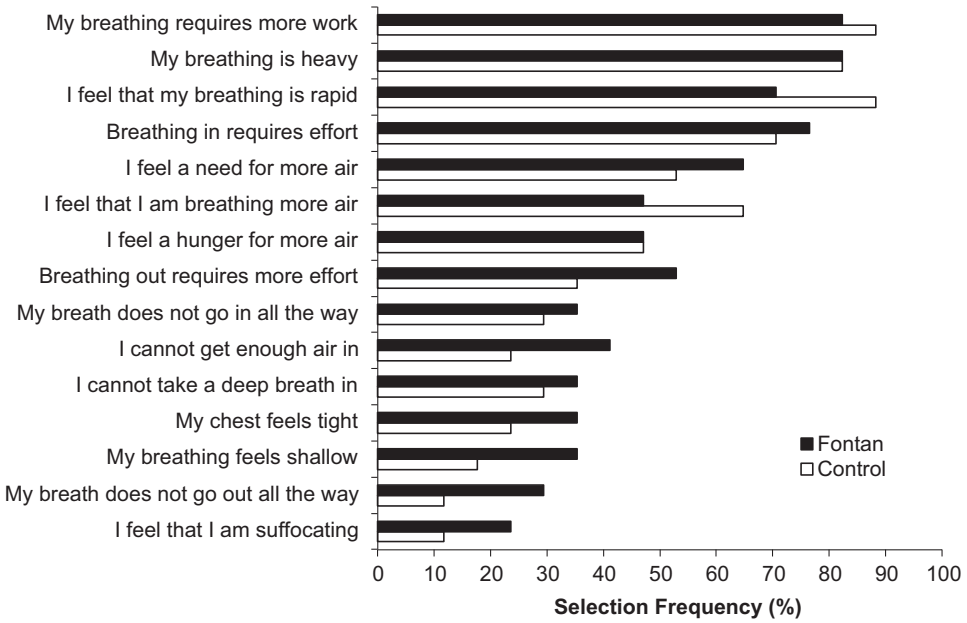

Fig. 6. Selection frequency of qualitative descriptors of dyspnea. There were no significant between-group differences for any dyspnea descriptor.

(data not shown). Dynamic hypoxemia, therefore, likely played a relatively minor role in the abnormal ventilatory and sensory response to exercise in these Fontan participants.

To our knowledge, this is the first study to examine the intensity and qualitative dimensions of exertional dyspnea in Fontan participants compared with controls. Given the abnormal pulmonary function and ventilatory response to exercise in Fontan participants, it seems reasonable to speculate that these abnormalities would have important sensory consequences. Indeed, we observed that Fontan participants experience greater dyspnea intensity ratings at a standardized submaximal work rate of 60 W and tended to have higher ratings at 40 W ($P = 0.05$). The clinical significance of this finding is underscored by the fact that the metabolic requirements of these work rates correspond well to important moderate-intensity activities of daily living (1). This observation is consistent with our dyspnea questionnaire data showing that Fontan participants experience greater chronic activity-related dyspnea relative to controls during daily life. It is difficult to definitively determine the reason for the higher dyspnea intensity ratings based on the design of this study. However, we speculate that the restrictive ventilatory impairment that led to higher EILVs and a more rapid breathing frequency may have partially contributed. This is supported indirectly by the correlations between both EILV and V_T/inspiratory capacity and dyspnea intensity ratings at peak exercise (Table 4). Future experimental studies are needed to directly determine the relative contributions of ventilatory, cardiocirculatory, and pulmonary gas exchange factors contributing to dyspnea in Fontan participants. Despite the higher dyspnea ratings at submaximal work rates, there was no difference at peak exercise for both dyspnea intensity ratings and the qualitative descriptors of dyspnea. The lack of difference in the selection frequency of the qualitative descriptors of dyspnea differs in patients with other restrictive respiratory diseases (e.g., ILD) that more frequently select phrases alluding to "rapid breathing," "inspiratory difficulty," and "unsatisfied inspiration" compared with controls (36). This discrepancy likely reflects the greater degree of restriction in patients with ILD and their markedly different respiratory pathophysiology relative to Fontan patients.

There are several limitations of this study that should be acknowledged. First, our assessment of EFL needs to be interpreted with caution, as we did not account for the confounding effect of thoracic gas compression or exercise-induced bronchodilation when generating the maximum expiratory flow volume curve, which is known to overestimate the degree of EFL (22). Whether this potential overestimation was consistent between groups is unknown. Accordingly, we focused our study on the regulation of operating lung volumes and sensory responses to exercise and have not attempted to overstate our EFL findings. Second, we matched groups for self-reported physical activity levels based on questionnaire data rather than objective measures of physical activity. Third, as with most studies in Fontan patients, we had a heterogeneous group of patients that included a small number of participants with moderate/severe ventricular dysfunction ($n = 1$) and moderate/severe atrioventricular valve regurgitation ($n = 2$), which could have influenced some of the cardiovascular responses. In addition, patients in the present study were permitted to continue their regular medications, including β-blockers ($n = 7$), which may have influenced the heart rate and oxygen pulse responses to exercise. Indeed, although heart rate and oxyen pulse were lower at peak exercise in Fontan patients compared with controls, the values were surprisingly similar between groups for a given submaximal work rate. This may be attributed, in part, to β-blocker use in a handful of participants but may also be related to the relatively poor aerobic fitness level of our activity-matched controls. Finally, we did not include an examination of pulmonary gas exchange with arterial blood gasses or detailed measures of cardiovascular function (e.g., cardiac output), as the focus of this study was on the ventilatory and sensory responses to exercise.

These findings suggest that the restrictive pulmonary defect commonly observed in adult Fontan patients likely contributes to an abnormal ventilatory response during submaximal exercise, characterized by rapid breathing and increased EILV

relative to a group of well-matched healthy controls. Interventions that can potentially improve the ventilatory response to exercise [e.g., inspiratory muscle training (29, 50)] should be explored as adjuncts to enhance the beneficial effects of cardiac rehabilitation for Fontan patients (44, 49). Finally, traditional measures of ventilatory limitation (i.e., $\dot{V}_E$/MVV) may be misleading in some Fontan patients. Thus, the inclusion of inspiratory capacity maneuvers to track operating lung volumes and EFL throughout exercise during routine cardiopulmonary exercise testing may provide a more comprehensive assessment of the noncardiac sources of exercise limitation in these patients.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.A.G., A.H.R., S.S.D., and J.H.P. analyzed data; J.A.G., A.H.R., S.S.D., J.H.P., M.R., A.R.O., and J.G. interpreted results of experiments; J.A.G. prepared figures; J.A.G. drafted manuscript; J.A.G., A.H.R., S.S.D., J.H.P., M.R., A.R.O., and J.G. edited and revised manuscript; J.A.G., A.H.R., S.S.D., J.H.P., M.R., A.R.O., and J.G. approved final version of manuscript; A.H.R., S.S.D., and M.R. performed experiments.

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