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Scaling Submaximal Exercise Cardiac Output and Stroke Volume: The HERITAGE Family Study

Abstract

This study investigated different methods of scaling submaximal cardiac output (Q) and stroke volume (SV) to best normalize for body size (body surface area [BSA], height [Ht], weight [Wt], and fat-free mass [FFM]). Q and SV were measured at both an absolute (50 W) and a relative power output (60% of $\dot{V}O_{2max}$) in 337 men and 422 women, 17 to 65 years of age. Traditional ratio scaling was examined in addition to allometric scaling, where scaling exponents (b) were determined for each body size variable (x) that best normalized the physiological outcome variables (y) for body size ($y = ax^b$). With ratio scaling, regardless of the body size variable (x = BSA, Ht, Wt, FFM), there was no evidence of a linear relationship between x and y (y = Q or SV). A linear relationship is a necessary condition for appropriate normalization. Further, when ratio-scaled variables (e.g., Q/BSA) were correlated to the body size variable (e.g., BSA) by which they were scaled, significant ($p \leq 0.05$) relationships still existed for BSA, Ht, Wt, and FFM. Thus, ratio scaling did not meet either criteria for normalizing Q and SV for body size. In contrast, when allometrically-derived scaling exponents were used to normalize Q and SV (e.g., Q/BSA^b), the resulting scaled values were uncorrelated (i.e., size-independent) with BSA, Ht, Wt, or FFM. These results were independent of age, sex or race. In summary, ratio scaling did not appropriately normalize Q and SV for differences in body size, while allometric scaling did result in size-independent values. Thus, individually-derived allometric exponents should be applied to body size variables to most appropriately adjust Q and SV for body size.

Key words
Allometric scaling · ratio scaling · cardiac index · stroke volume index

Introduction

Physiological variables are often scaled or normalized to account for differences in body size. The use of scaling is important in comparing individuals against a standard or to other individuals or groups differing in body size, investigating the longitudinal effects of growth, and examining relationships between physiological variables and performance.

Traditionally, cardiac output (Q) and stroke volume (SV) have been scaled relative to body surface area (BSA [m^2], ratio scaling) to create size-independent variables (e.g., cardiac index [QI, $l \cdot min^{-1} \cdot m^{-2}$] and stroke volume index [SVI, $ml \cdot beat^{-1} \cdot m^{-2}$]). This form of scaling cardiovascular data has been used for nearly 75 years, with Grollman [6] reporting in 1929 that the resting Q of men and women was a function of their body surface area. The physiological appropriateness of ratio scaling of cardiovascular

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variables was first questioned by Tanner [9] in 1949. Further, Burch and Giles [3] questioned the accuracy of estimating BSA. Ratio scaling continues to be questioned [4,8]. Despite this, clinicians and researchers continue to use ratio scaling of Q and SV.

An alternative to ratio scaling is allometric scaling as expressed in the following relationship: $y = ax^b$ (e.g., $Q = aBSA^b$), where a is a constant and b is the scaling exponent. Only if $b = 1.00$ would ratio scaling be appropriate for normalizing data. Otherwise, the newly calculated scaling exponent must be applied to accurately normalize the data for body size.

Recent studies investigating the appropriateness of ratio versus allometric scaling of Q and SV report conflicting results. De Simone et al. [4] investigated both ratio and allometric scaling in 970 children and adults. They reported that ratio scaling was appropriate for normalizing resting Q and SV in adults (> 17 years of age), but not in children (< 18 years of age). Rowland et al. [8] also concluded that ratio scaling of Q and SV during maximal exercise was not appropriate in premenarcheal girls.

From these studies, it is unclear which method of scaling is most appropriate for normalizing Q and SV. Ratio scaling is simple and widely used, but might not be as accurate as allometric scaling for normalizing data for body size. A major problem with allometric scaling is that many different scaling exponents have been reported in the literature which is likely due to the use of small sample sizes [7]. Thus, the present study was undertaken to investigate which method of data normalization is most appropriate for scaling submaximal Q and SV in a large subject pool (n = 759) using data from the HERITAGE Family Study (HFS). The HFS is a large multicenter clinical trial investigating the genetic basis for the variability in physiological and cardiovascular disease and type 2 diabetes risk factor changes as a consequence of 20 weeks of endurance training [2].

Methods

Subjects

The HFS subjects were from families that included the natural mother and father (not older than 65 years) and at least three offspring 17 years of age or older in Whites, while Black families were as small as two first-degree relatives (e.g., mother and daughter or two siblings). Subjects were recruited independently by each of four clinical centers, located at Indiana University (formerly at Arizona State University), Laval University, the University of Minnesota and the University of Texas at Austin. Exclusion and inclusion criteria have been previously reported [2]. The Institutional Review Boards for each clinical center approved the study protocol and written informed consent was obtained from each subject. The subjects included in this study were those who completed all pre-training exercise tests. Subjects physical characteristics are presented in Table **1**.

Table **1** Subjects physical characteristics (mean ± SD)

	Women (n = 422)	*Men (n = 337)*	*Total (n = 759)*
Age (yr)	34.1 ± 12.8	35.2 ± 14.3	34.6 ± 13.5
Weight (kg)	70.5 ± 16.2	84.2 ± 16.7	76.6 ± 17.7
Height (cm)	163.2 ± 6.6	177.2 ± 6.4	169.5 ± 9.5
Body fat (%)	32.4 ± 9.9[a]	22.7 ± 8.7[b]	27.9 ± 10.5[c]
Fat mass (kg)	23.8 ± 12.3[a]	20.0 ± 10.8[b]	22.1 ± 11.7[c]
Fat free mass (kg)	45.9 ± 5.7[a]	63.6 ± 8.0[b]	54.0 ± 11.2[c]
BSA (m^2)	1.79 ± 0.22	2.04 ± 0.22	1.90 ± 0.26

a – n = 371; b – n = 313; c – n = 684

Exercise testing

All subjects completed a maximal graded exercise test, a submaximal test, and a combination submaximal/maximal test on an Ergo-Metrics 800S cycle ergometer (SensorMedics, Yorba Linda, CA, USA). Each of the three tests was separated by a minimum of two days. The maximal graded test started at an initial power output (PO) of 50 watts (W) for three minutes, followed by an increase of 25 W every two minutes thereafter until volitional fatigue. For less fit, smaller or older subjects, the test started at 40 W with an increase of 10 to 20 W every two minutes. The results from this test were used to calculate the PO necessary to elicit 60% of maximal oxygen uptake ($\dot{V}O_{2max}$). The submaximal test began at an absolute PO of 50 W for 12 – 15 minutes, then a 4 – 8 minute rest period, followed by 12 – 15 minutes at a relative PO of 60% $\dot{V}O_{2max}$. The first two stages of the submaximal/maximal test were identical to the submaximal test (i.e., 50 W followed by 60% $\dot{V}O_{2max}$), except that subjects also exercised at 80% $\dot{V}O_{2max}$ and then progressed to volitional fatigue.

Cardiac output, stroke volume and metabolic measurements

All metabolic variables and Q were measured using a SensorMedics 2900 metabolic measurement cart (SensorMedics, Yorba Linda, CA, USA). Oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and ventilation ($\dot{V}E$) were assessed every 20 seconds and recorded as a rolling minute average of the three most recent 20-second values. Two cardiac output and heart rate measures were obtained and averaged from both the 50 W and 60% $\dot{V}O_{2max}$ POs during both the submaximal and submaximal/maximal tests. Pre- and post-test calibration procedures have been published [13]. The data for each PO from both the submaximal and submaximal/maximal test were then averaged and used in this analysis. Cardiac output was determined using the Collier equilibration CO_2 rebreathing technique, as described by Wilmore et al. [12]. Heart rate was obtained from standard electrocardiography during the last 15 seconds of each exercise stage. SV was derived from Q and heart rate. Reliability data for these metabolic and cardiovascular data have been reported previously [13], with intraclass correlations ranging from 0.76 – 0.99.

Body size and body composition measurements

Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively using a balance-beam scale and a stadiometer. BSA was calculated using the equation of DuBois and DuBois [5]. Relative body fat was estimated from body density, determined by hydrostatic weighing, using population-specific equations for black men and women, and Caucasian men and women. Fat-free mass (FFM) was calculated by subtracting fat mass (kg)

from body mass (kg). Details of these procedures have been described in detail in a prior publication [11].

Analysis

Ratio standards were calculated by dividing Q and SV by each of the four body size variables: Ht, Wt, FFM and BSA. Ratio scaling assumes a linear relationship between physiological (y) and body size (x) values [10]. The existence of a linear relationship was assessed statistically by comparing the coefficient of variation (CV = [SD/mean] · 100) for x (CVx) divided by CVy to the Pearson's Product Moment (PPM) correlation coefficient (r) between the variables, and graphically by comparing the ratio and regression lines. The ratio line was created by forcing the regression line through zero. The greater the difference between the quotient of the CV and the PPM correlation, and the further the actual regression line is from the ratio line, the greater the error caused by ratio scaling [10]. Further, the ratio-scaled value (e.g., cardiac index – QI) was compared to the body size value by which it was scaled (e.g., BSA) using a PPM correlation. If ratio scaling truly normalizes the data, a correlation not significantly different from zero (r = 0.00) is expected [1]. An unpaired *t*-test was used to determine if the correlation coefficient was significantly different from zero.

Allometric scaling was used to determine scaling exponents (*b*) for each body size variable (x) that most appropriately normalizes the physiological outcome (y) variables for body size ($y = ax^b$). Statistical log transformations were used as follows:

$$\text{Log } y = b \cdot \log x + \log a,$$

where y = the physiological outcome variable, *b* = scaling exponent, x = body size variable and *a* is the proportionality constant. A scaling exponent of 1 indicates that ratio scaling is an appropriate method of normalizing for body size. The significance of scaling exponents was determined by checking for inclusion of 1 in the 95% confidence interval. If the interval does not include 1, there is significant evidence ($p \leq 0.05$) that the scaling exponent is not 1. A PPM correlation was then used to compare the allometrically-scaled physiological outcome variable (y/x^b) with the body size value (x) by which it was scaled to determine if it was unrelated (r = 0.00), and thus, appropriately normalized. An unpaired *t*-test was used to determine if the correlation coefficient was significantly different from 0.00. All statistical analyses were run using a SAS statistical program. Statistical significance is reported at $p \leq 0.05$ unless stated otherwise.

Results

Figs. **1** and **2** show the ratio and regression lines for Q ($l \cdot min^{-1}$) and SV ($ml \cdot beat^{-1}$) versus each body size variable at both 50 W (Fig. **1**) and 60% $\dot{V}O_{2max}$ (Fig. **2**) in the total population. Separate figures for men and women are not shown as the results were nearly identical to those of the total population. Included in the figures are the quotients of the coefficients of variation (CVx/CVy) and the PPM correlation coefficients (r) between the two variables.

Allometric scaling exponents for all body-size variables at each work rate in men, women and the total population are presented in Table **2**. With few exceptions ($SV/BSA^{0.93}$ at 60% $\dot{V}O_{2max}$ in the total population; $Q/Ht^{0.73}$ in women and $Q/Ht^{0.67}$ in men at 50 W; $SV/Ht^{1.29}$ in men at 50 W; and $SV/Ht^{1.36}$ in women at 60% $\dot{V}O_{2max}$), the scaling exponents were significantly different from 1.00, indicating that ratio scaling did not appropriately normalize submaximal Q and SV.

Table **3** presents the PPM correlation coefficients between BSA, Ht, Wt and FFM versus each physiological variable (Q and SV) expressed both as a ratio standard (x-1.0; e.g., $QBSA^{1.0}$) and allometrically scaled (xb; e.g., $QBSA^b$) for both rates of work in men, women, and the total population. For scaling to appropriately normalize the data for body size, the correlation cannot be significantly different from 0.00. With few exceptions (Q/Ht [r = – 0.09] at 50 W and SV/Ht [r = 0.09] at 60% $\dot{V}O_{2max}$ in women; Q/Ht [r = 0.09] and SV/Ht [r = 0.07] at 50 W in men; and SV/BSA at 60% $\dot{V}O_{2max}$ [r = – 0.05] in the total population), significant ($p \leq 0.05$) relationships still existed between the ratio-scaled physio-

Table **2** Allometric scaling exponents (*b*) for women, men, and the total sample

	Women	*Men*	*Total*
Body surface area (m^2)			
Q			
– *50 W*	0.46*	0.21*	0.36*
– *60% $\dot{V}O_{2max}$*	0.36*	0.15*	0.71*
SV			
– *50 W*	0.62*	0.27*	0.80*
– *60% $\dot{V}O_{2max}$*	0.60*	0.43*	0.93
Height (cm)			
Q			
– *50 W*	0.73	0.67	0.60*
– *60% $\dot{V}O_{2max}$*	1.51*	1.94*	2.56*
SV			
– *50 W*	1.47*	1.29	2.18*
– *60% $\dot{V}O_{2max}$*	1.36	1.88*	2.58*
Weight (kg)			
Q			
– *50 W*	0.25*	0.11*	0.20*
– *60% $\dot{V}O_{2max}$*	0.18*	0.04*	0.35*
SV			
– *50 W*	0.33*	0.13*	0.42*
– *60% $\dot{V}O_{2max}$*	0.32*	0.21*	0.49*
Fat free mass (kg)			
Q			
– *50 W*	0.43*	0.33*	0.23*
– *60% $\dot{V}O_{2max}$*	0.69*	0.61*	0.46*
SV			
– *50 W*	0.75*	0.49*	0.69*
– *60% $\dot{V}O_{2max}$*	0.73*	0.70*	0.81*

Q = cardiac output; W = watts; SV = stroke volume, * Significantly different from 1.00 ($p < 0.05$)

Table **3** Pearson Product Moment correlation coefficients between Q and SV and body size variables

Variable#	*Women*				*Men*				*Total Sample*			
	BSA	*Ht*	*Wt*	*FFM*	*BSA*	*Ht*	*Wt*	*FFM*	*BSA*	*Ht*	*Wt*	*FFM*
Q 50 W												
$x^{1.00}$	– 0.49*	– 0.09	– 0.79*	– 0.50*	– 0.53*	– 0.09	– 0.75*	– 0.55*	– 0.56*	– 0.17*	– 0.79*	– 0.77*
x^{b}	0.007	– 0.002	0.012	0.009	0.002	0.003	0.004	– 0.002	– 0.003	0.004	0.006	0.006
Q 60%												
$x^{1.00}$	– 0.41*	0.13*	– 0.70*	– 0.24*	– 0.45*	0.21*	– 0.69*	– 0.29*	– 0.18*	0.47*	– 0.56*	– 0.29*
x^{b}	0.012	0.001	0.005	0.010	0.004	0.007	0.002	– 0.003	0.006	0.005	– 0.010	0.010
SV 50 W												
$x^{1.00}$	– 0.30*	0.12*	– 0.68*	– 0.21*	– 0.46*	0.07	– 0.72*	– 0.42*	– 0.16*	0.39*	– 0.59*	– 0.41*
x^{b}	– 0.003	– 0.004	– 0.013	0.002	0.001	0.001	– 0.004	– 0.002	– 0.010	– 0.006	– 0.022	– 0.011
SV 60%												
$x^{1.00}$	– 0.30*	0.09	– 0.67*	– 0.22*	– 0.35*	0.21*	– 0.66*	– 0.26*	– 0.05	0.48*	– 0.50*	– 0.26*
x^{b}	0.002	– 0.001	– 0.005	0.007	0.003	0.003	– 0.002	0.001	0.001	– 0.001	– 0.015	0.007

*Significantly different ($p < 0.05$) from 0.00; #Expressed to both the ratio standard ($x^{1.00}$) and allometrically derived (x^{b})

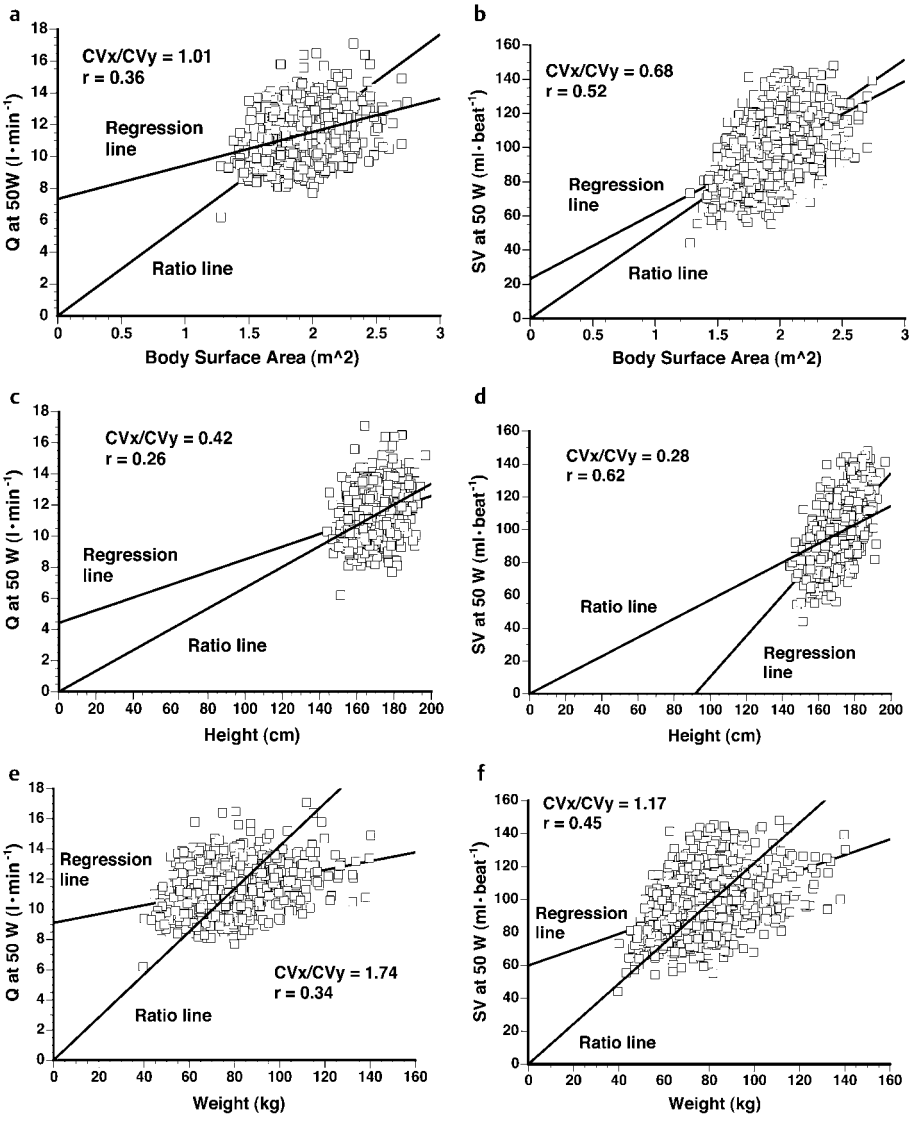

Fig. **1 a** to **f** Ratio and regression lines for body surface area (**a, b**), height (**c, d**), and weight (**e, f**) versus cardiac output (**a, c, e**) and stroke volume (**b, d, f**) at the 50 Watt work rate.

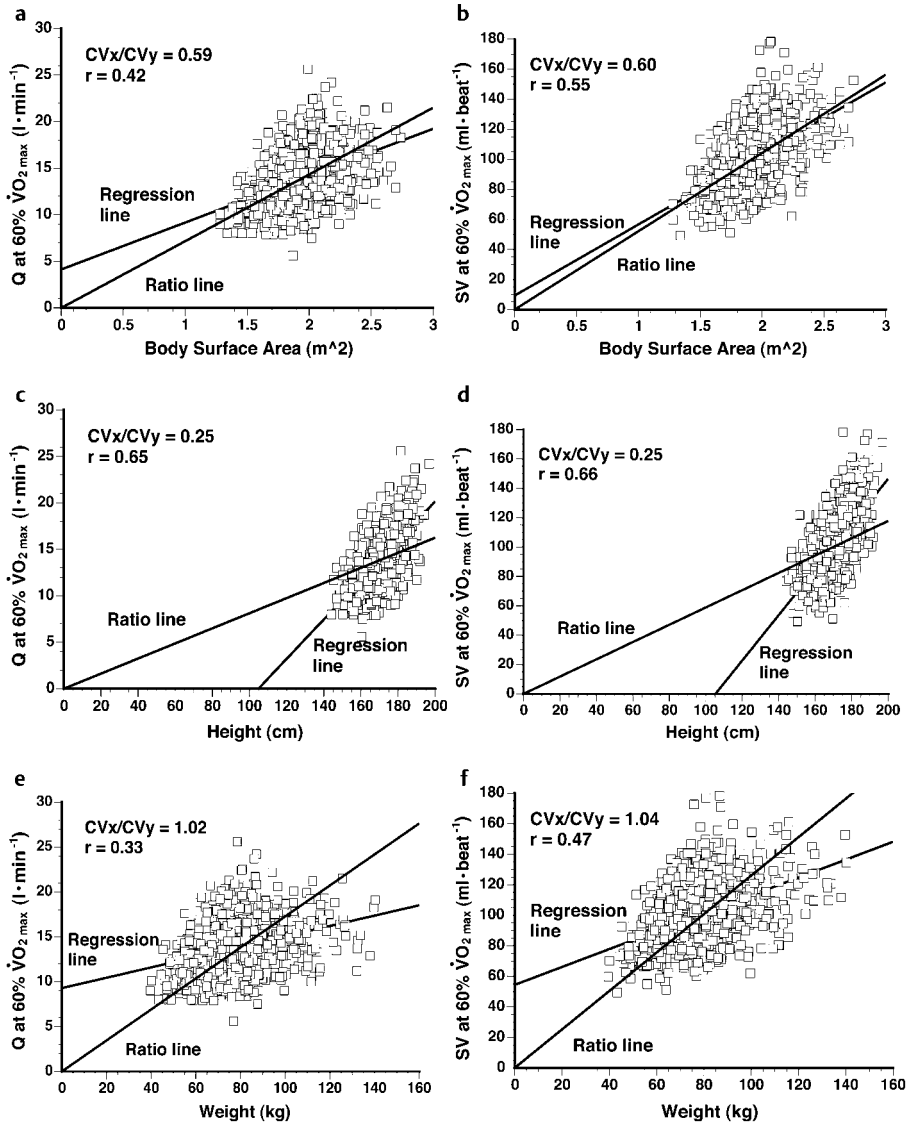

Fig. **2 a** to **f** Ratio and regression lines for body surface area (**a, b**), height (**c, d**), and weight (**e, f**) versus cardiac output (**a, c, e**) and stroke volume (**b, d, f**) at the 60% $\dot{V}O_{2max}$ work rate.

logical outcome variables and the body-size values by which they were scaled, regardless of which body-size value was used. When the appropriate allometric scaling exponent was applied to the Q and SV data, no significant relationships existed between the allometrically-scaled physiological outcome variable and the body-size value by which it was scaled.

Discussion

The results of this study indicate that regardless of the body size variable used, ratio-scaling did not appropriately eliminate the effects of body size from Q and SV at these two submaximal work rates. First, there was no evidence of a significant linear relationship between either Q or SV and any of the body size variables (Figs. **1** and **2**), although there were trends for several variables (e.g., Q and SV at 60% $\dot{V}O_{2max}$ and BSA). A linear relationship must exist between these variables in order for ratio scaling to be appropriate [10]. Second, when the ratio-scaled Q and SV were correlated with the body size variable by which they were scaled, with few exceptions, significant relationships remained (Table **3**) indicating that ratio scaling did not normalize the data for differences in body size. Third, the allometrically-derived scaling exponents for Q and SV were all significantly different from 1.00 (the value necessary if ratio scaling is appropriate) for BSA, Wt, and FFM in men, women and the total population at both 50 W and 60% $\dot{V}O_{2max}$ (Table **2**). Eight of the 12 scaling exponents for Ht were significantly different from 1.00, while only the exponent for Q and SV at 50 W in men and for Q at 50 W and SV at 60% $\dot{V}O_{2max}$ in women were not significantly different from 1.00 (Table **2**). Fourth, when the allometrically-scaled Q and SV values were correlated with the body size variables by which they were normalized, there were no significant relationships, indicating that allometric scaling appropriately scaled Q and SV values (Table **3**).

It is logical to question the need to scale Q and SV values at a constant power output (e.g., 50 W), since the absolute rate of oxygen uptake (l/min) at a given power output is assumed to be relatively independent of body size and highly correlated with Q (l/min). In this study, however, the PPM correlation between $\dot{V}O_2$ (l/min) and Q (l/min) at 50 W was only $r = 0.524$ ($p \leq 0.0001$). Fur-

ther, the correlations between Q (l/min) at 50 W and height ($r = 0.272$), weight ($r = 0.343$) and BSA ($r = 0.363$) were all significant ($p \leq 0.0001$), substantiating the need for scaling Q at 50 W for body size. The PPM correlation between $\dot{V}O_2$ (l/min) and SV (ml/beat) at 50 W was $r = 0.425$ ($p \leq 0.0001$), and the correlations between SV (ml/beat) at 50 W and height ($r = 0.623$), weight ($r = 0.447$) and BSA ($r = 0.519$) were all significant ($p \leq 0.0001$), again substantiating the need for scaling SV at 50 W for body size.

Our results are in contrast with the adult data of de Simone et al. [4] who investigated the appropriateness of both allometric and ratio scaling of resting Q and SV in 970 subjects ages 1 day to 85 years old. They concluded that in adults (> 17 years of age) the scaling exponents for both QI ($b = 1.15$) and SVI ($b = 1.19$) were similar to 1.0 and thus ratio scaling was appropriate for normalizing adult resting Q and SV. In contrast, the scaling exponents for the children in their study (< 18 years of age) for both QI ($b = 0.53$) and SVI ($b = 0.82$) were different than 1.0 and thus ratio scaling was not appropriate. Furthermore, when we analyzed our data by age group (e.g., 17 – 29 yrs, 30 – 49 yrs, and 50+ yrs of age; data not presented) regardless of gender or race, ratio-scaling did not eliminate the effects of body size while allometric-scaling did appropriately control for the effects of body size on both the SV and Q.

Rowland et al. [8] examined the use of both allometric and ratio scaling of maximal Q and SV in 24 girls (mean age 12.2 ± 0.5 years). In contrast to our work, they reported BSA scaling exponents of 1.08 and 1.05 for Q_{max} and SV_{max}, respectively. Further, when they correlated QI and SVI to BSA ($r = 0.07$ and 0.08, respectively), there were no significant relationships. In the women in the present study, the PPM correlation coefficients for QI ($r = -0.49, -0.41$) and SVI ($r = -0.30, -0.30$) with BSA at both 50 W and 60% $\dot{V}O_{2max}$, respectively, were nearly all significantly different from zero (Table **3**). Again, for ratio scaling to truly normalize Q and SV, a zero correlation ($r = 0.00$) should result when the scaled value is correlated with the body size value by which it was scaled. Furthermore, Rowland et al. [8] reported that when $Q_{max}/Ht^{1.00}$ ($r = 0.22$) and $S\dot{V}_{max}/Ht^{1.00}$ ($r = 0.28$) were correlated to Ht, no significant relationships remained. This suggests that ratio scaling of maximal Q and SV to Ht results in size-independent values. In the women in our study, however, the PPM correlation coefficients for $Q/Ht^{1.00}$ ($r = -0.09, 0.13$) and $SV/Ht^{1.00}$ ($r = 0.12, 0.09$) to Ht at both 50 W and 60% $\dot{V}O_{2max}$, respectively, were significantly different from $r = 0.00$ for two of the four correlations (Table **3**). Thus, ratio scaling of Q and SV by Ht did not consistently result in size-independent values. In agreement with Rowland et al. [8], the present study indicates that ratio scaling of Q and SV relative to Wt ($Q/Wt^{1.00}$ and $SV/Wt^{1.00}$) is not appropriate. Last, data from both Rowland et al. [8] and the present study indicate that size-independent values result when the empirically-derived exponents from allometric scaling are applied to BSA, Ht, Wt and FFM to adjust Q and SV.

The discrepancy between data from the present study and those of Rowland et al. [8] for girls, and those of de Simone et al. [4] in adults could be explained by a number of factors. First, the data of Rowland et al. [8] were collected during maximal exercise and those of de Simone et al. [4] were collected at rest. Data from the present study were collected during submaximal exercise. Further, age (biological development) could impact study results. Rowland et al. [8] suggested that the difference in scaling exponents between their data and those on children (age < 18 years old) from de Simone et al. [4] is related to differences in hemoglobin concentration that are likely across the age span (one day to 17 years of age) in the study by de Simone et al. [4]. Theoretically, this would impact the a-$\dot{V}O_2$ difference versus body size relationship since $\dot{V}O_2/BSA^{a+b} = Q/BSA^{a}$ x a-$\dot{V}O_2$ $diff^{b}$, and thus could impact scaling exponents [8].

Finally, another technique that has been used to normalize metabolic data is analysis of covariance (ANCOVA). Like any linear model, ANCOVA assumes a linear relationship between variables. In our data, however, linear relationships did not exist between submaximal Q and SV and body size, thus lending support to allometric scaling which does not assume a linear relationship.

In conclusion, these data in 759 adult subjects indicate that individually-derived allometric exponents should be applied to body size variables to most appropriately adjust Q and SV for body size. Linear relationships did not exist between Q and SV and body size and the use of ratio scaling in Q and SV did not result in size-independent values regardless of the body size variable used. Thus, care must be taken when interpreting other studies where ratio scaling is used and size-independent values are assumed.

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