

## Inaccuracy of Estimated Resting Oxygen Uptake in the Clinical Setting

**Running title:** *Narang et al.; Errors in resting oxygen uptake estimation*

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## Abstract

**Background**—The Fick principle (cardiac output ( $Q_c$ ) = oxygen uptake ( $\dot{V}O_2$ ) / systemic arterio-venous oxygen difference) is used to determine  $Q_c$  in numerous clinical situations. However, estimated rather than measured  $\dot{V}O_2$  is commonly used due to complexities of the measurement, though the accuracy of estimation remains uncertain in contemporary clinical practice.

**Methods and Results**—From 1996 to 2005, resting  $\dot{V}O_2$  was measured via the Douglas bag technique in adult patients undergoing right heart catheterization. Resting  $\dot{V}O_2$  was estimated by each of 3 published formulae. Agreement between measured and estimated  $\dot{V}O_2$  was assessed overall, and across strata of body mass index, sex, and age. The study included 535 patients, with mean age 55 yrs, mean BMI 28.4 kg/m<sup>2</sup>; 53% women; 64% non-white. Mean ( $\pm$  standard deviation) measured  $\dot{V}O_2$  was 241  $\pm$  57 ml/min. Measured  $\dot{V}O_2$  differed significantly from values derived from all 3 formulae, with median (interquartile range) absolute differences of 28.4 (13.1, 50.2) ml/min, 37.7 (19.4, 63.3) ml/min, and 31.7 (14.4, 54.5) ml/min, for the formulae of Dehmer, LaFarge and Bergstra, respectively; ( $p < 0.0001$  for each). The measured and estimated values differed by  $>25\%$  in 17% to 25% of patients depending on the formula used. Median absolute differences were greater in severely obese patients (BMI  $> 40$  kg/m<sup>2</sup>), but were not affected by sex or age.

**Conclusions**—Estimates of resting  $\dot{V}O_2$  derived from conventional formulae are inaccurate, especially in severely obese individuals. When accurate hemodynamic assessment is important for clinical decision-making,  $\dot{V}O_2$  should be directly measured.

**Key words:** cardiac output, cardiac catheterization, hemodynamics, Oxygen Uptake

## Introduction

Accurate determination of cardiac output ( $Q_c$ ) is important in the hemodynamic evaluation of valve area, pulmonary and systemic vascular resistance, and severity of heart failure. The Fick method [ $\text{cardiac output } (Q_c) = \text{oxygen uptake } (\dot{V}O_2) / \text{systemic arterio-venous oxygen difference}$ ]<sup>1,2</sup> is the time-honored gold standard for determining  $Q_c$ , and has been used to validate other techniques such as indicator dilution and foreign gas rebreathing<sup>3</sup>. Application of the Fick method requires measurement of  $\dot{V}O_2$ . However, direct measurement of  $\dot{V}O_2$  through (a) mass spectrometry analysis of timed Douglas bag collections of exhaled air; or (b) breath-by-breath analysis of exhaled air using indirect calorimetry or metabolic cart analysis<sup>4,5</sup> is time consuming and involves specific equipment that requires frequent calibration and is expensive to maintain.

As a result, resting  $\dot{V}O_2$  is commonly estimated rather than measured using derived formulae available in the peer-reviewed literature<sup>6-9</sup>. However, the accuracy of the formulae and nomograms most commonly used to estimate resting  $\dot{V}O_2$  is questionable, with most estimating methods derived from limited samples of highly selected, ethnically homogenous populations consisting of similarly aged, lean adults,<sup>10-12</sup> populations that differ substantially from contemporary adult cardiology practice. Other formulae were derived from clinical populations comprised exclusively or primarily of infants and children<sup>6,8</sup>. Hence, we assessed the accuracy of estimated resting  $\dot{V}O_2$  compared with measured  $\dot{V}O_2$  obtained by the gold-standard analysis of timed collections of exhaled air by the method of Douglas in a large population of consecutive adult patients who underwent right-heart cardiac catheterization for clinical indications at our hospital.

## Methods

We conducted a retrospective study of consecutive patients who underwent right heart cardiac catheterization with direct measurement of resting  $\dot{V}O_2$  at Parkland Memorial Hospital between 1996-2005. Charts were reviewed for demographic, anthropometric, and baseline clinical characteristics. This study was approved by the University of Texas Southwestern Medical Center Institutional Review Board.

### Calculating estimated $\dot{V}O_2$

Estimated resting  $\dot{V}O_2$  was calculated by the formula of Dehmer, et al.<sup>7,9</sup>:  $\dot{V}O_2$  (ml/min) = 125 (ml/min/m<sup>2</sup>) x body surface area (BSA, m<sup>2</sup>), with BSA calculated according to the formula of Dubois<sup>13</sup>:  $BSA (m^2) = 0.007184 \times \text{Weight (kg)}^{0.425} \times \text{Height (cm)}^{0.725}$ . For sensitivity analysis, estimation of  $\dot{V}O_2$  was also calculated using the formula of LaFarge<sup>6</sup>:  $\dot{V}O_2$  (ml/min) = 138.1 – (X × log<sub>e</sub>age) + (0.378 × Heart Rate) × BSA (Men: X – 11.49; Women: X – 17.04); and the formula of Bergstra<sup>8</sup>:  $\dot{V}O_2$  (ml/min) = 157.3 × BSA + X – (10.5 × log<sub>e</sub>age) + 4.8 (Men: X = 10; Women = 0).

### Direct measurement of $\dot{V}O_2$

Resting  $\dot{V}O_2$  was measured in all patients using the gold-standard technique of Douglas<sup>1</sup>, with analysis of a three-minute collection of exhaled air collected through a properly fitted mouth piece with a three-way valve. Exhaled volume was measured with a Tissot spirometer and concentrations of oxygen, carbon dioxide and nitrogen were determined by mass spectrometry (Marquette MGA 1100), calibrated prior to every measurement, and all testing was completed while patients remained in the supine position.

### Statistical analysis

The magnitude of agreement between directly measured and estimated resting  $\dot{V}O_2$  was assessed by median absolute difference, ordinary least products regression<sup>14</sup> and typical error analysis<sup>15</sup>. Median absolute difference (ml/min) for the overall cohort was calculated as a median of the absolute value of the differences between measured and estimated resting  $\dot{V}O_2$  determined for each patient. The degree of disagreement between measured and estimated resting  $\dot{V}O_2$  was calculated as a percent error, dividing the absolute difference by the corresponding measured oxygen uptake, and multiplying by 100. Ordinary least products regression was used to assess both fixed and proportional error for the overall cohort<sup>14</sup>. Variance of comparative plot data points for estimated vs. measured  $\dot{V}O_2$  in the overall cohort was assessed by intra-class correlation coefficient. Typical error estimation, expressed as a coefficient of variation derived from the standard deviation of the mean absolute difference divided by the square root of 2<sup>15</sup>, is reported for BMI (body mass index) strata. Median absolute difference between measured and estimated resting  $\dot{V}O_2$  was assessed in the overall cohort and in patients stratified by (a) BMI using clinical categories (<25, 25-29.9; 30-34.9; 35-39.9;  $\geq 40$  kg/m<sup>2</sup>); (b) sex; and (c) age stratified by median split. The one-sample Wilcoxon signed-ranks test was used to determine statistical significance for the median of the raw difference of values between estimated and measured  $\dot{V}O_2$  in the overall cohort and in patients stratified by sex, age, and BMI categories. Tests for interaction were used to assess statistical significance for median absolute difference amongst BMI categories. The clinical relevance of errors of  $\dot{V}O_2$  estimation is demonstrated in a hypothetical clinical context of aortic valve area (AVA) calculation, comparing results using  $\dot{V}O_2$  estimated by each of the 3 formulae versus measured  $\dot{V}O_2$ . Diagnostic performance was

assessed by receiver operator curve analysis comparing area under the curves, and by calculation of optimal cutpoints via Youden's index<sup>16</sup> for each estimating formula to identify AVA <1.0 cm<sup>2</sup> derived from direct  $\dot{V}O_2$  measurement. Sensitivity, specificity and positive and negative predictive values were conventionally defined and compared to assess diagnostic accuracy. Attempts to develop a more accurate estimating equation using the present data included piecewise linear models, restricted cubic splines, additive models, variable transformations, including interaction terms and higher-order variables. Cross-validated samples were obtained in 100 iterations, with 75% used as the training set and 25% used as the validation set. All testing was 2-tailed at a significance level of 0.05, with analyses performed using SAS Version 9.1.3 (Cary, NC, USA) and no corrections made for multiple comparisons.

## Results

Patient characteristics for the overall cohort and selected strata are shown in **Table 1**. The overall cohort comprised 535 patients, with mean age 55 years, 53% were women, and the mean BMI was 28.4 kg/m<sup>2</sup>. The mean measured  $\dot{V}O_2$  for the overall cohort was 241 ± 56.6 ml/min (mean ± standard deviation; **Table 2**), with a range of 108 to 457 ml/min. Using the Dehmer formula, the mean estimated  $\dot{V}O_2$  was 235.4 ± 32 ml/min, with a range of 162 to 356 ml/min; it differed significantly from the direct measurement with a median absolute difference of 28.4 (13.1, 50.2) ml/min [median (25<sup>th</sup>, 75<sup>th</sup> percentile)] (**Table 2** and **Figure 1A**; p<0.0001).

Analysis of agreement in the overall cohort between directly measured  $\dot{V}O_2$  and  $\dot{V}O_2$  estimated by the Dehmer formula using ordinary least products regression demonstrated significant fixed error [reflected by y-intercept >0 (95% CI 92.4, 106.1)] and proportional error

[reflected by slope <1.0 (95% CI 0.53, 0.61)] (**Figure 1A**). Poor agreement between directly measured and estimated  $\dot{V}O_2$  was also observed when the LaFarge and Bergstra formulae were used (**Table 2; Figure 1B and 1C**). Intraclass correlation coefficients were similar and slightly higher in the LaFarge and Bergstra formulae, when compared with the Dehmer formula, demonstrating slightly more consistency overall in intra-test measurement (**Figure 1**).

The magnitude of error between measured and estimated  $\dot{V}O_2$  expressed as a percent error for the overall cohort is shown in **Figure 2**. For all three formulae used to estimate  $\dot{V}O_2$ , the degree of error ranged from 10 to 25% in approximately 40% of the overall cohort, and the error was >25% in 17-25% of the cohort, depending on the estimating formula used.

The median absolute difference between measured and estimated  $\dot{V}O_2$  using the three formulae was stratified by BMI, sex, and age, as shown in **Table 2**. When estimating  $\dot{V}O_2$  using the Dehmer formula, the difference in measured and estimated  $\dot{V}O_2$  widened as BMI increased, with significant disagreement between measured and estimated  $\dot{V}O_2$  observed in all BMI strata. Patients with BMI <40 kg/m<sup>2</sup> had a median absolute difference ranging from 24.6 (11.6, 43.7) ml/min to 29.3 (14.8, 57.8) ml/min, while median absolute difference was significantly higher at 47.0 (29.5, 83.4) ml/min in the ≥ 40 kg/m<sup>2</sup> group when compared with the other strata, ( $p_{\text{interaction}} < 0.0001$ ). Similar results were observed in both the LaFarge and Bergstra formulae ( $p_{\text{interaction}} = 0.001$  and  $p_{\text{interaction}} = 0.005$ ; respectively). When analyzed using typical error analysis, the error associated with estimating resting  $\dot{V}O_2$  was similarly magnified in the ≥ 40 kg/m<sup>2</sup> (**Table 2**).

Both measured and estimated  $\dot{V}O_2$  were higher in men compared with women (**Table 2**).

In sex-stratified analyses, median absolute differences between measured and estimated resting  $\dot{V}O_2$  were large in both men and women for all 3 formulae tested. Although statistically significant, the difference in error between sexes was small (<10 ml/min) and varied in direction depending on the estimating formula used.

In analyses stratified by median age, median absolute difference between estimated and measured  $\dot{V}O_2$  comparisons for age groups  $\leq 55$  years and  $>55$  years were both large [31.7 (13.5, 55.2) ml/min and 26.5 (12.7, 46.6) ml/min, respectively,  $p < 0.0001$  for each] when calculated by the Dehmer formula, though the differences between the two groups did not reach statistical significance ( $p = 0.13$ ). In assessment of both LaFarge and Bergstra formulae, the median absolute difference for both age strata were  $>30$  ml/min, and the differences between age groups similarly did not reach statistical significance (**Table 2**;  $p = 0.92$  and  $p = 0.20$ ; respectively).

We were unable to resolve or improve upon the discordance between measured and estimated resting  $\dot{V}O_2$  using data-derived estimating equations, which we explored using a variety of methods of multivariable linear regression. In all cases of the exploratory models, the mean bias was unacceptably large, and the median percent difference was no less than 15%.

Additionally, the predicted  $R^2$  based on the PRESS statistic<sup>17</sup> yielded values no larger than 0.27 (data not shown), demonstrating unacceptably poor model performance.

To demonstrate the clinical importance of error in resting  $\dot{V}O_2$  estimation, we calculated hypothetical Fick-derived  $Q_c$  based on resting and estimated  $\dot{V}O_2$  from all three formulae for each patient in the study. Fick-derived  $Q_c$  values were used to derive hypothetical aortic valve areas (AVA) by the Hakki equation<sup>18</sup>, as a clinical example to determine the effect of errors in resting  $\dot{V}O_2$  estimation. For this analysis, each patient was assigned an hypothetical mean aortic



valve gradient of 40 mmHg and an arteriovenous oxygen difference of 4.5. An AVA of  $<1.0 \text{ cm}^2$  is classified as severe stenosis and warrants consideration for surgical correction. Using AVA  $<1.0 \text{ cm}^2$  derived from directly measured  $\dot{V}\text{O}_2$  as the outcome, the Dehmer formula had a sensitivity of 93% (95% confidence interval [CI], 90- 95%) with a specificity of 33% (95% CI 25-40%) and an area under the curve (AUC) of 0.79 (95% CI 0.75-0.84) (**Table 3**). The LaFarge formula had similar sensitivity, specificity and AUC when compared to the Dehmer formula; the Bergstra formula had the lowest sensitivity of 75% (95% CI 71-79%) of the formulae tested, but was significantly more specific (77%; 95% CI 68-86%) with a slightly greater AUC of 0.82 (95% CI 0.77-0.87) when compared with the other formulae (**Figure 3**). Similarly, the optimal ROC cutpoint for the Bergstra formula ( $0.94 \text{ cm}^2$ ) was the closest of the three formulae to the clinically important diagnostic cutoff of  $1.0 \text{ cm}^2$  (**Table 3**). Expanded clinical application of the errors encountered in resting  $\dot{V}\text{O}_2$  estimation are shown in **figures 4 and 5** represented by theoretical Fick cardiac output and systemic vascular resistance (hypothetical mean arterial pressure of 75 mmHg, central venous pressure of 8 mmHg, arteriovenous oxygen difference if 4.5), where a large majority of data points deviate notably from the line of equality.

## Discussion

This study demonstrates that in a large, consecutive sample of adult patients undergoing right-heart cardiac catheterization, estimation of resting  $\dot{V}\text{O}_2$  by commonly used formulae is inaccurate compared with the gold-standard analysis of timed collections of exhaled air.

Estimated  $\dot{V}\text{O}_2$  was most inaccurate in morbidly obese patients with  $\text{BMI} \geq 40 \text{ kg/m}^2$ . To put the degree of inaccuracy of resting  $\dot{V}\text{O}_2$  estimation into clinical context, the observed error and

variance in estimated  $\dot{V}O_2$  applied to Fick-calculated  $Q_c$  yields up to 38% error within 1 standard deviation (SD) and up to 64% error within 2 SD's. Since Fick-calculated  $Q_c$  and resting  $\dot{V}O_2$  are directly proportional, error in estimation of resting  $\dot{V}O_2 > 25\%$ , a magnitude of error observed in 17% of the present study cohort, can dramatically alter clinical decision-making.

Formulae and nomograms for the estimation of resting  $\dot{V}O_2$ , published as early as 1954, were derived from highly selected cohorts of homogeneous ethnicity and age<sup>12</sup>. More recently published estimating formulae presently in broader clinical use, such as that by LaFarge and colleagues<sup>6</sup>, were derived primarily from pediatric patients. Similarly, many of the patients used to derive the Bergstra formula<sup>8</sup> were infants and children with congenital heart disease, possibly confounding the application of these methods in adult patients. Prior studies have demonstrated errors in  $\dot{V}O_2$  estimation using these and other formulae in pediatric<sup>19-22</sup> and adult<sup>23-25</sup> populations. However, these analyses have limitations including small sample size with homogeneity of patient population, lack of sub-group analysis in determining other variables that may influence errors in estimation, and use fewer analytic methods to explain the errors observed. Our study builds upon prior analyses by better addressing the above-mentioned limitations, allowing for a comprehensive assessment of errors in resting  $\dot{V}O_2$  estimation not seen to date. In the present study, we observed a substantial fixed and proportional error when  $\dot{V}O_2$  was estimated by each of the 3 formulae compared with analysis of timed collections of exhaled air, with error in excess of 25% in many patients.

We previously demonstrated the inaccuracy of resting  $\dot{V}O_2$  estimation in a smaller cohort of research participants<sup>25</sup>. The present observations confirm and extend these prior findings of exaggerated error in the most obese patients, now in a larger sample of adult patients in a clinical

setting where such methods are commonly applied. Several of the contemporary formulae for estimating  $\dot{V}O_2$ <sup>6, 8</sup> incorporate weight or body surface area without taking into account the degree of adiposity, which may impact the accuracy of estimation, since fat has little impact on oxygen consumption. In addition, there is a metabolic requirement for accommodating excess weight, including physical support and respiratory efforts, all of which may materially influence resting  $\dot{V}O_2$ . While predictive formulae for maximal  $\dot{V}O_2$  have adjusted for the metabolic cost associated with excess adiposity to improve accuracy<sup>26, 27</sup>, whether similar adiposity adjustments for the estimation of  $\dot{V}O_2$  at rest could improve accuracy remains to be determined.

In contrast to our previous study where estimation with mean absolute difference was exaggerated in men compared with women, we found no significant difference in observed disagreement between measured and estimated  $\dot{V}O_2$  at rest when stratified by sex in the present study. We postulate that results from our previous study may be explained by the fact that on average, men have greater absolute and proportional fat-free mass than women, which likely contributed to the sex-based error of the estimating formula. In the present analyses, the error was numerically greater in men compared with women using the Dehmer and Bergstra formulae, whereas with the LaFarge formula the error was numerically greater in women. However, the magnitude of differences was not statistically significant between the groups, and none of the formulae yielded a significant statistical interaction between error and sex, challenging the necessity of inclusion of sex as is done in the LaFarge and Bergstra formulae.

Although early nomograms for estimating  $\dot{V}O_2$  at rest, some of which were derived from pediatric populations, were stratified by age<sup>10, 11</sup>, we found no age-based error association in this study. No association between the degree of error of the estimating formula and age was present

when assessing  $\dot{V}O_2$  using each of the three formulae. Similar results were found in studies of both older adults with mean age 60 years<sup>24</sup> and younger adults with mean age 39 years<sup>25</sup>.

The errors encountered when resting  $\dot{V}O_2$  is estimated instead of directly measured can potentially impact clinical decision making, including determining the initiation and titration of inotropic support, decision for mechanical ventricular support, determining eligibility and monitoring response of pulmonary vasodilator therapy, and determining candidacy for valve procedures, among others.

### Clinical Implications

The clinical relevance of the observed errors in  $\dot{V}O_2$  estimation as depicted by hypothetical hemodynamic calculations demonstrates the potential impact on critical clinical decision making, as derivations of AVA by all three estimating formulae revealed substantial inaccuracies in diagnostic performance. The Dehmer and Large formulae were adequately sensitive in detection of potential severe aortic stenosis but were poorly specific. Using the Dehmer and LaFarge formulae, a significant number of subjects with AVA  $>1.0 \text{ cm}^2$  derived from directly measured  $\dot{V}O_2$  were found to have estimated AVA's  $<1.0 \text{ cm}^2$ , reflecting the high false positive rate. The Bergstra formula was significantly more specific than the other formulae tested, but overall had the largest combined proportion of false negative and false positive results, leading to potential clinical misclassification of AVA when estimated to be both greater and less than  $1.0 \text{ cm}^2$ . We similarly observed this critical degree of potential clinical error in our prior study, which was composed of research study participants and not actual patients, contrasted with the present study of patients who underwent cardiac catheterization for clinical indications.

From a drug regulatory standpoint, estimation versus measurement of  $\dot{V}O_2$  is also an

important consideration. In 2010, the FDA Cardiovascular and Renal Drugs Advisory Committee convened to discuss the potential role of using pulmonary vascular resistance index (PVRI) and its change in response to therapy as a surrogate for drug efficacy in pediatric patients with pulmonary arterial hypertension (PAH). Therapy in these pediatric patients would consist of drugs with approved indications in adults<sup>28</sup>. In this context, in both pediatric and adult PAH patients, virtually all of the available data from clinical trials had been compiled using estimating formulae for resting  $\dot{V}O_2$ , a key parameter in the calculation of PVRI<sup>29</sup>. Given the degree of error of the estimation of resting  $\dot{V}O_2$  in the present study, and the absence of validation or critical assessment in the pediatric population, the routine use of resting  $\dot{V}O_2$  estimation in the calculation of hemodynamics and their response to therapy for drug registration studies should be closely scrutinized, if not abandoned.

### Limitations

Our study has limitations. Differences in methods between operators with regard to exhaled air collection and analysis could have influenced the accuracy of resting  $\dot{V}O_2$  measurement using the method of Douglas. However, to address this, a specific protocol was followed by all operators and the equipment was routinely maintained and calibrated. In addition, while patients were stationary and in a steady state condition prior to timed collections of exhaled air, it is unlikely that this method equates to a true resting  $\dot{V}O_2$  measurement given the anxiety associated with cardiac catheterization and the variable clinical stability across a population of patients undergoing right heart catheterization for clinical purposes.

## Conclusions

Errors in hemodynamic assessment may adversely impact clinical assessment and therapeutic decision-making across a spectrum of serious cardiovascular conditions. Given the imperative in such situations for accuracy of assessment, if the Fick method is to be used for Qc estimation, resting  $\dot{V}O_2$  should be directly measured and not estimated.

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**Conflict of Interest Disclosures:** None.

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**Table 1.** Baseline descriptive characteristics

	Overall (n=535)	Men (n=252)	Women (n=283)	BMI (kg/m <sup>2</sup> )				
				< 25 (n=187)	25-29.9 (n=174)	30-34.9 (n=94)	35-39.9 (n=41)	≥ 40 (n=39)
Age, mean (SD), yr	55 (13.5)	55 (13.6)	55 (13.5)	54 (15.4)	57 (12)	54 (13.1)	54 (12.7)	55 (11.2)
Women, No (%)	283 (53)	—	—	93 (49.7)	88 (47.1)	51 (54.3)	25 (61)	32 (82.1)
Race/Ethnicity, No (%)								
White	192 (36)	101 (40)	91 (32)	65 (34.8)	65 (37.4)	38 (40.4)	11 (26.8)	13 (33.3)
Black	168 (31)	72 (29)	96 (34)	46 (24.6)	53 (30.4)	32 (34)	19 (46.3)	18 (46.2)
Hispanic	143 (27)	64 (25)	79 (28)	58 (31)	47 (27)	20 (21.3)	10 (24.4)	8 (20.5)
Other	32 (6)	15 (6)	17 (6)	18 (9.6)	9 (5.2)	4 (4.3)	1 (2.4)	—
Height, mean (SD), in	66.0 (4.2)	68.9 (3.4)	63.4 (2.9)	66.2 (4.1)	66.2 (4.1)	66.1 (4.5)	65.9 (4)	64.5 (3.9)
Weight, mean (SD), kg	79.9 (21.3)	83.7 (19.7)	76.5 (22.1)	61.9 (10.1)	78 (10)	90.8 (12.7)	104 (13)	123.2 (19.7)
BMI, mean (SD), kg/m <sup>2</sup>	28.4 (7.1)	27.2 (5.5)	29.4 (8.2)	21.8 (2.1)	27.5 (1.4)	32.1 (1.4)	37.1 (1.3)	45.8 (5.4)
Valvular Heart Disease, No, (%)	383 (72)	177 (70.2)	213 (65.3)	136 (72.7)	135 (77.6)	59 (62.8)	26 (63.4)	27 (69.2)
Pulmonary Hypertension, No (%)	166 (31)	68 (27)	100 (35.3)	65 (34.8)	49 (28.2)	26 (27.7)	10 (24.4)	16 (41)
CVD, No (%)	143 (27)	90 (35.7)	57 (20.1)	50 (26.7)	52 (29.9)	26 (27.7)	10 (24.4)	9 (22)
Heart Failure, No (%)	102 (19)	64 (25.4)	40 (14.1)	33 (17.6)	37 (21.3)	21 (22.3)	5 (12.2)	6 (15.4)
Hypertension, No (%)	114 (21.3)	55 (21.8)	59 (20.8)	23 (12.3)	37 (21.3)	27 (28.7)	13 (31.7)	14 (35.9)
Diabetes, No (%)	63 (11.8)	32 (12.7)	31 (11)	13 (7)	16 (9.2)	17 (18.1)	6 (14.6)	10 (25.6)
Primary Indication for RHC (%)								
Valvular Heart Disease	292 (54.6)	131 (52)	161 (56.9)	106 (56.7)	100 (57.5)	43 (45.8)	20 (48.8)	23 (59)
Heart Failure	177 (33.1)	97 (38.5)	80 (28.3)	54 (28.9)	59 (33.9)	32 (34)	20 (48.8)	12 (30.8)
Congenital Heart Disease	46 (8.6)	21 (8.3)	25 (8.8)	22 (11.8)	8 (4.6)	13 (13.8)	—	3 (7.7)
Pulmonary Hypertension	20 (3.7)	3 (1.2)	17 (6)	5 (2.7)	7 (4)	6 (6.4)	1 (2.4)	1 (2.6)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; in, inch; kg/m<sup>2</sup>, kilogram per square meter; RHC, right heart catheterization; No, number; %, percent; SD, standard deviation; yr, year.

**Table 2.** Comparison of median absolute difference and typical error (BMI only) by estimating formulae for overall cohort, and subgroups stratified by sex, age, and body mass index

Group	Dehmer Formula <sup>†</sup>				LaFarge Formula <sup>‡</sup>			Bergstra Formula <sup>§</sup>		
	Mean Measured VO <sub>2</sub> (ml/min)	Mean Calc. VO <sub>2</sub> (SD), ml/min	Median* Absolute Difference [IQR], ml/min	Typical Error (CV)	Mean Calc. VO <sub>2</sub> (SD) ml/min	Median* Absolute Difference [IQR], ml/min	Typical Error (CV)	Mean Calc. VO <sub>2</sub> (SD), ml/min	Median* Absolute Difference [IQR], ml/min	Typical Error (CV)
Overall (n=535)	241 (56.6)	235.4 (32)	28.4 [13.1, 50.2]	—	208 (42.8)	37.7 [19.4, 63.3]	—	254.5 (42.4)	31.7 [14.4, 54.5]	—
Men (n=252)	260.6 (58.3)	248.1 (29.7)	33.1 [15.6, 53.9]	—	241.1 (32.2)	31.6 [15.9, 56.2]	—	275.9 (37.5)	34.8 [17.9, 58.3]	—
Women (n=283)	224.2 (49.1)	224.1 (29.6)	24 [11.3, 47]	—	178.8 (26.6)	41.3 [22.7, 68]	—	235.4 (37.1)	26.8 [10.9, 49.2]	—
Age ≤ 55 years (n=255)	250.1 (61.6)	239.9 (34.3)	31.7 [13.5, 55.2]	—	218.2 (44.9)	36.9 [17.6, 61.7]	—	258.2 (45.5)	34.2 [14.4, 55.8]	—
Age > 55 years (n=280)	233.4 (50.3)	234 (29.6)	26.5 [12.7, 46.6]	—	199 (38.6)	39.2 [19.4, 63.3]	—	250 (39.5)	30.3 [14.6, 50.6]	—
BMI (kg/m <sup>2</sup> )										
<25	218.6 (48)	212.6 (23.3)	24.6 [11.6, 43.7]	13.9	171.7 (22.8)	36.2 [18.6, 54.4]	15.9	226.8 (32.2)	25.7 [13.7, 46]	13.9
25-29.9	242.4 (51.3)	235 (22.8)	26.8 [12.1, 48.6]	13.8	207.3 (38.8)	38 [16.2, 60.7]	15.2	254 (32.4)	31 [15.2, 56.7]	13.7
30-34.9	258.1 (55.5)	250.4 (26.9)	29.3 [14.8, 57.8]	13.9	223.2 (45.4)	40.4 [22, 65.9]	14.2	273.4 (37.6)	35.9 [13.4, 56.5]	13.5
35-39.9	265.3 (63.3)	264.6 (25.7)	27 [10.3, 52.9]	13.4	228.3 (46.7)	30.7 [14.4, 61.1]	12.4	290.5 (36.4)	40.8 [14.6, 67.8]	12.6
≥ 40	280.1 (67.8)	279.5 (28.8)	47 [29.5, 83.4]	18.0	233.7 (43.6)	63.9 [30.9, 106.1]	19.1	307 (38.9)	48.6 [26.5, 72.3]	17.9

Abbreviations: BMI, body mass index; Calc, calculated; CV, coefficient of variation; IQR, interquartile range; ml/min, milliliter per minute; SD, standard deviation; VO<sub>2</sub>, oxygen uptake. \* = p<0.005 for median raw difference for overall cohort and subgroups determined by one-sample Wilcoxon signed-ranks test

<sup>†</sup>Dehmer Formula: VO<sub>2</sub> (ml/min) = 125 × Body Surface Area

<sup>‡</sup>LaFarge Formula:

VO<sub>2</sub> (ml/min) = 138.1 – (11.49 × log<sub>e</sub>age) + (0.378 × Heart Rate) × Body Surface Area (Men)

VO<sub>2</sub> (ml/min) = 138.1 – (17.04 × log<sub>e</sub>age) + (0.378 × Heart Rate) × Body Surface Area (Women)

<sup>§</sup>Bergstra Formula:

VO<sub>2</sub> (ml/min) = 157.3 × Body Surface Area + 10 – (10.5 × log<sub>e</sub>age) + 4.8 (Men)

VO<sub>2</sub> (ml/min) = 157.3 × Body Surface Area – (10.5 × log<sub>e</sub>age) + 4.8 (Women)

**Table 3.** Diagnostic performance by estimating formula for calculation of AVA <1.0 cm<sup>2</sup>

	Dehmer	LaFarge	Bergstra
Optimal ROC Cutpoint (cm <sup>2</sup> )	0.87	0.78	0.94
AUC	0.79 (0.75-0.84)	0.79 (0.74-0.84)	0.82 (0.77-0.87)
Sensitivity	93% (90.1-95.3)	96% (93.6-97.5)	75% (71.2-79.2)
Specificity	33% (25.2-40.2)	30% (20.3-39.5)	77% (68.2-85.9)
PPV	78% (74.2-81.7)	88% (84.6-90.5)	94% (92-96.8)
NPV	64% (52.9-74.4)	57% (42.2-70.9)	38% (30.5-44.8)
Positive LR	1.4 (1.23-1.55)	1.4 (1.19-1.57)	3.3 (2.22-4.83)
Negative LR	0.2 (0.15- 0.34)	0.15 (0.09-0.26)	0.32 (0.26-0.39)

Parentheses indicate 95% confidence interval. Abbreviations: AUC, area under the curve; cm, centimeters; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

### Figure Legends:

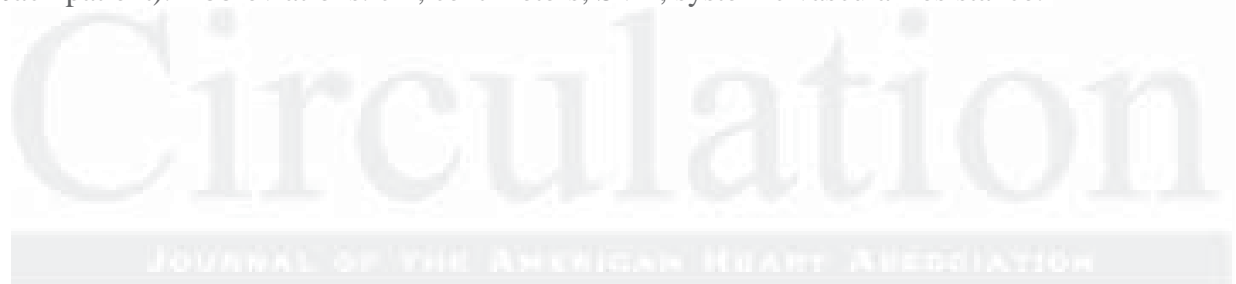
**Figure 1.** Comparative plot of measured  $\dot{V}O_2$  vs. estimated  $\dot{V}O_2$  for overall cohort using A) Dehmer; B) LaFarge; and C) Bergstra formulae. *Dashed line:* line of equality; *solid line:* ordinary least products regression line. Abbreviations: CI, confidence interval; ICC, intraclass correlation coefficient;  $\dot{V}O_2$ , oxygen uptake.

**Figure 2.** Distribution of error related to use of estimated  $\dot{V}O_2$  (n=535) across estimating formulae tested.

**Figure 3.** ROC curves by estimating formula for AVA<1.0 cm<sup>2</sup> (measured  $\dot{V}O_2$ ) as the outcome and AVA<1.0 cm<sup>2</sup> (estimated  $\dot{V}O_2$ ) as the predictor. Abbreviations: AVA, aortic valve area; cm, centimeters; ROC, receiver operating characteristic;  $\dot{V}O_2$ , oxygen uptake.

**Figure 4.** Hypothetical comparison of cardiac output from measured  $\dot{V}O_2$  versus cardiac output derived from estimated  $\dot{V}O_2$  using A) Dehmer; B) LaFarge; C) Bergstra formulae ( $\dot{V}O_2$  data from the present study and assuming arteriovenous oxygen difference of 4.5 for each patient). Abbreviations: L, liters; min, minutes;  $\dot{V}O_2$ , oxygen uptake.

**Figure 5.** Hypothetical comparison of systemic valvular resistance derived from measured  $\dot{V}O_2$  versus systemic vascular resistance derived from estimated  $\dot{V}O_2$  using A) Dehmer; B) LaFarge; C) Bergstra formulae ( $\dot{V}O_2$  data from the present study and assuming arteriovenous oxygen difference of 4.5, mean arterial pressure of 75 mmHg, central venous pressure of 8 mmHg for each patient). Abbreviations: cm, centimeters; SVR, systemic vascular resistance.



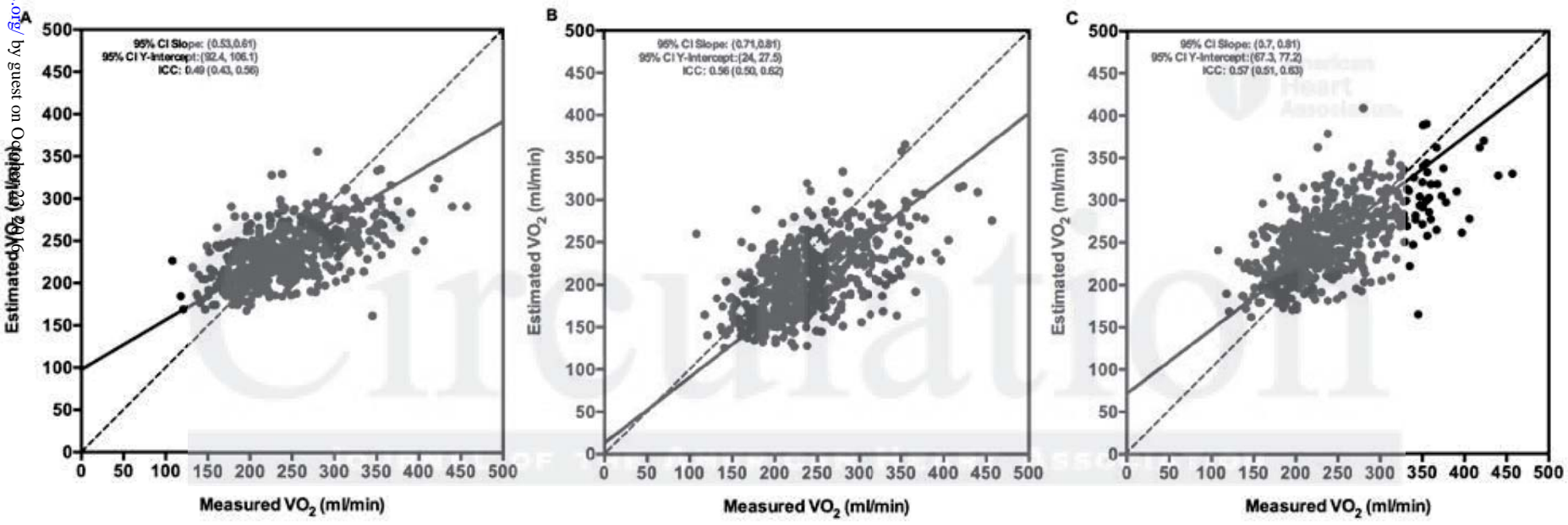


Figure 1

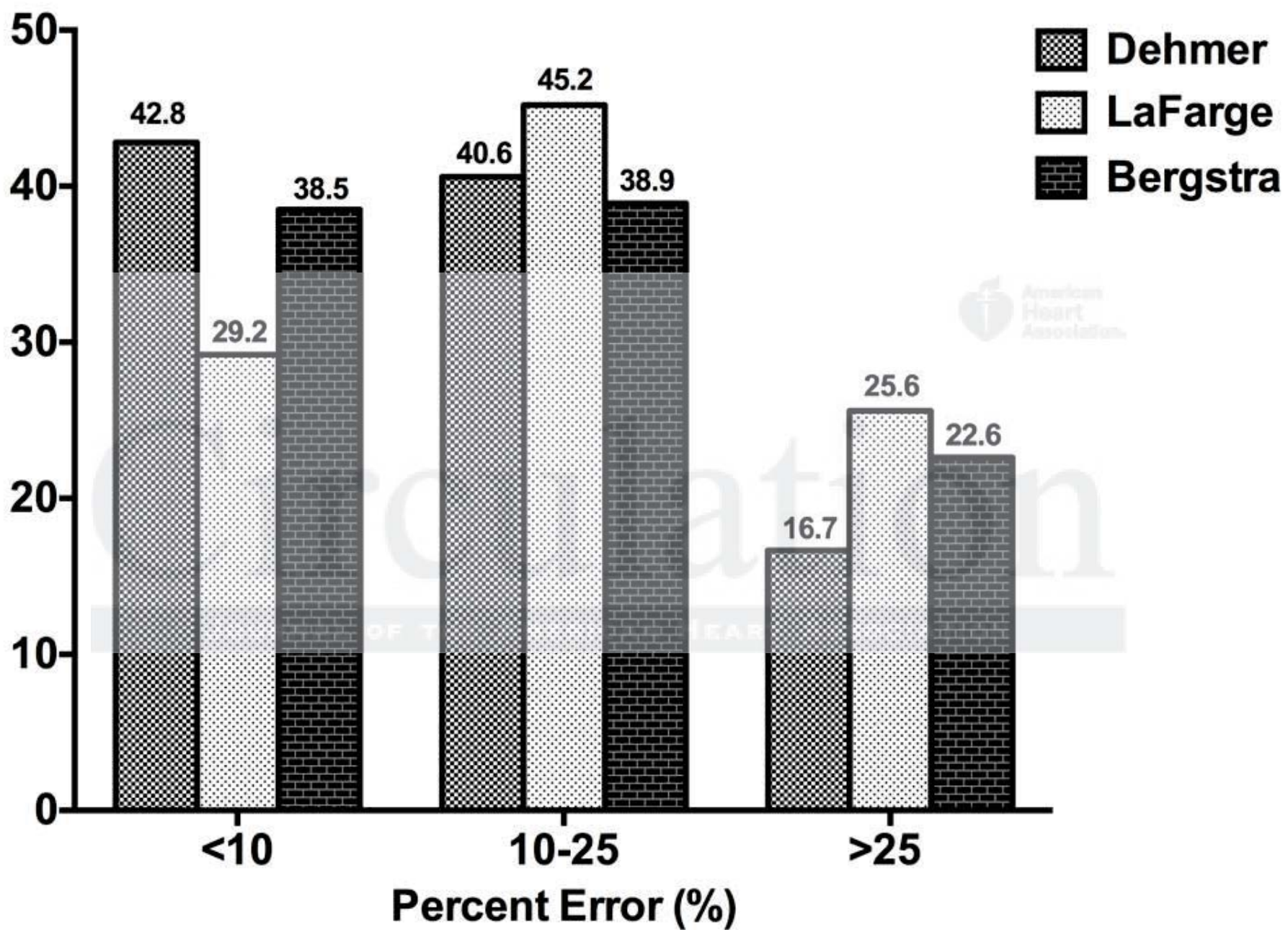


Figure 2



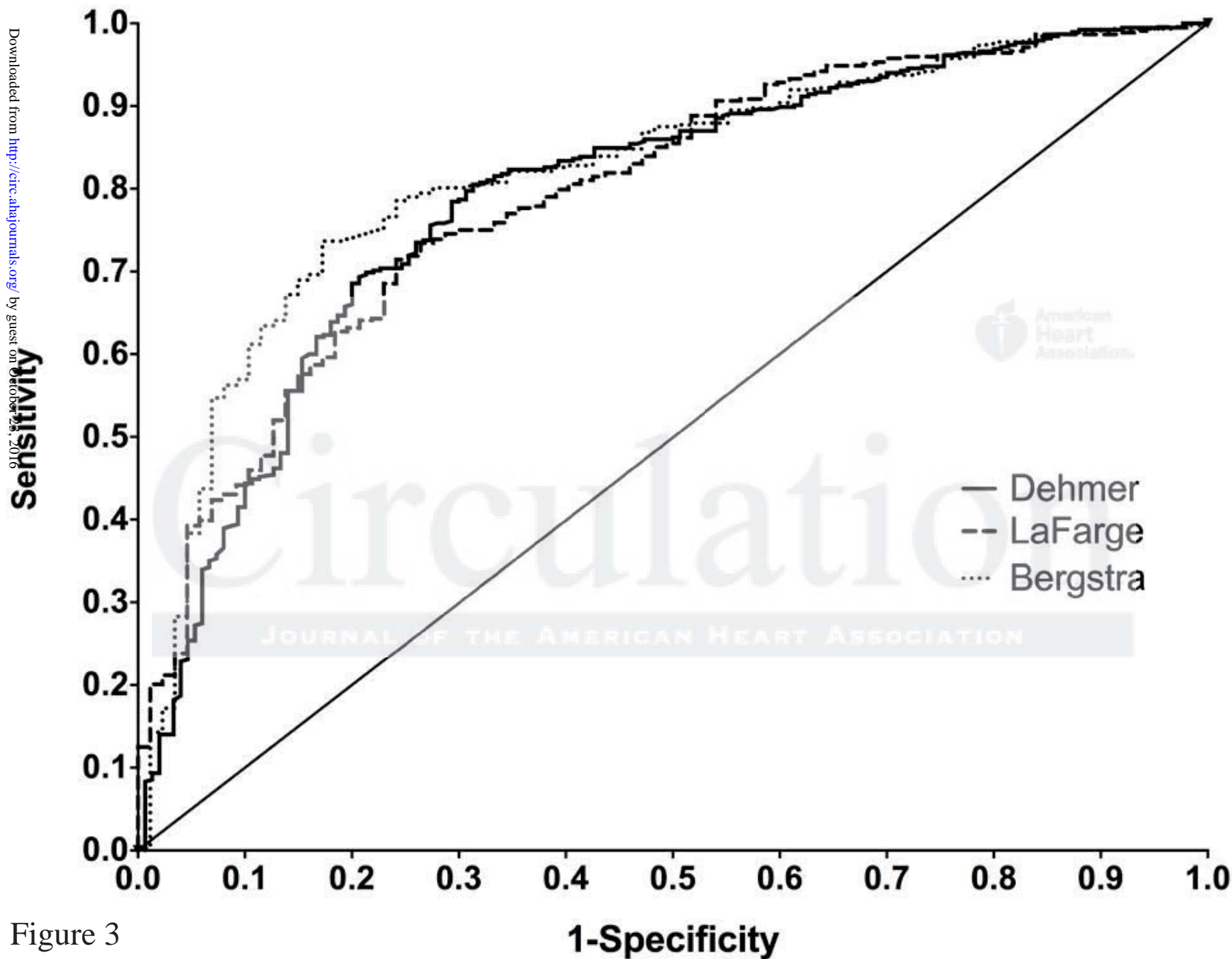


Figure 3

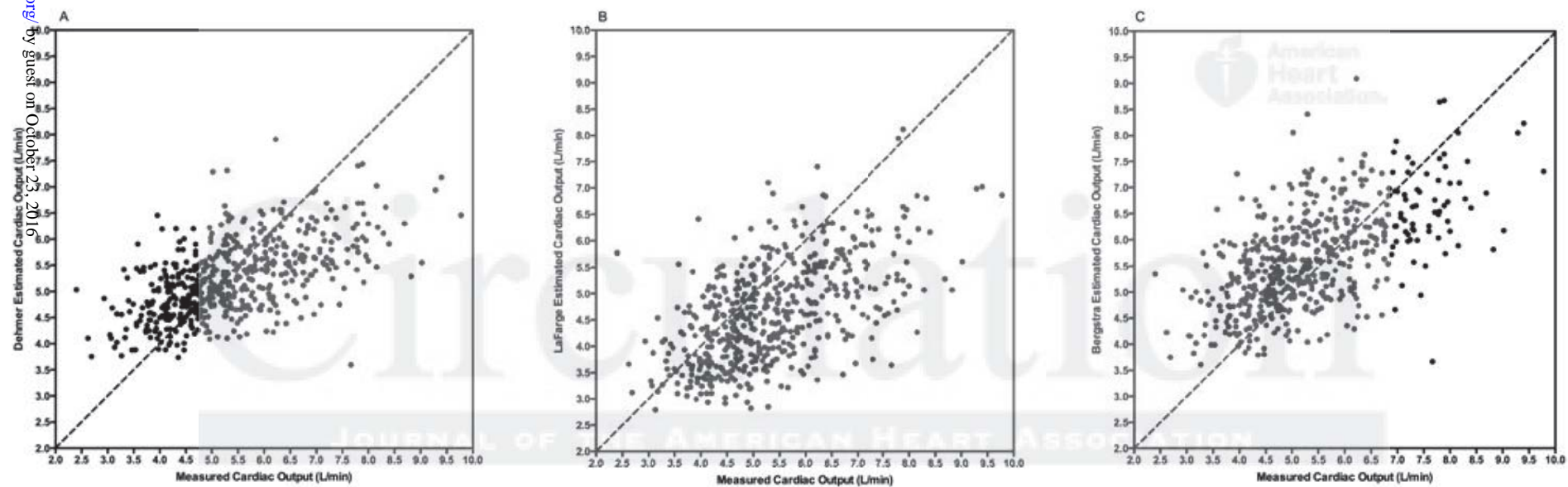


Figure 4



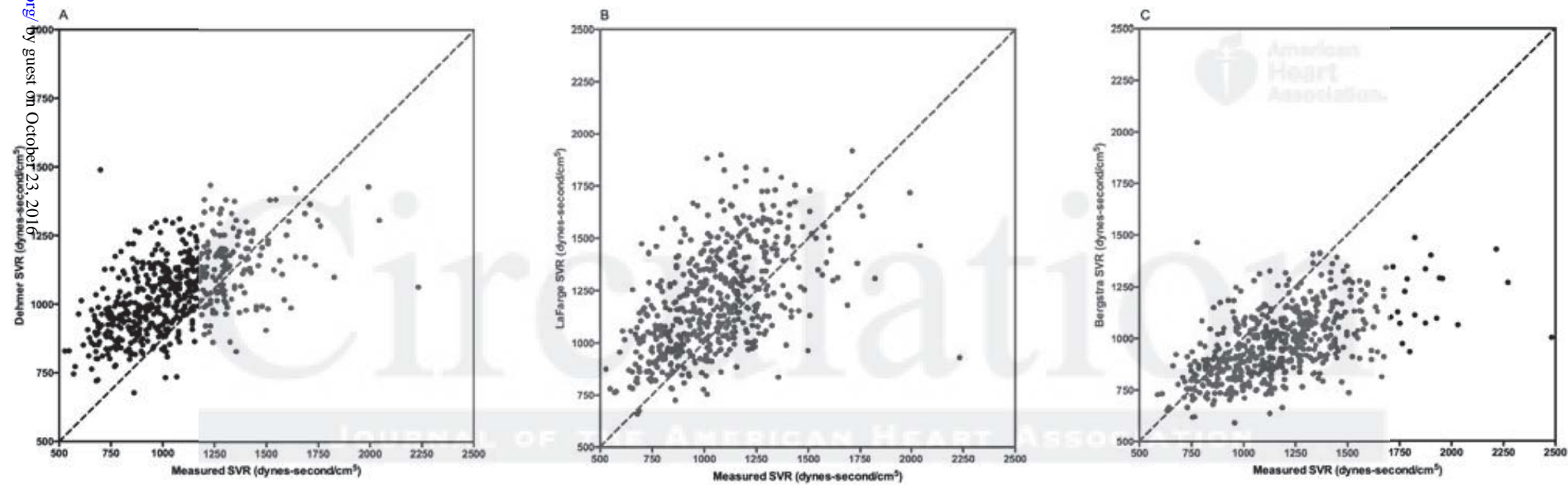


Figure 5

## Inaccuracy of Estimated Resting Oxygen Uptake in the Clinical Setting

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