Estimated vs Actual Values for Dead Space/Tidal Volume Ratios During Incremental Exercise in Patients Evaluated for Dyspnea*

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The physiologic dead space/tidal volume ratio (VD/VT) at rest and during exercise is a sensitive measurement of gas exchange that reflects matching of ventilation to perfusion, but requires an invasive measurement for its calculation. Determining VD/VT noninvasively uses estimations of arterial PCO₂ based on the end-tidal PCO₂. To further standardize incremental cardiopulmonary exercise testing, we compared actual VD/VT with estimated VD/VT in 35 patients referred for evaluation of dyspnea. Estimates of VD/VT used the Jones’ equation (VD/VT[J]) derived from healthy subjects during steady-state exercise or PETCO₂ alone (VD/VT[JET]) to approximate PaCO₂. At rest, mean values for VD/VT(J) and actual VD/VT were not different: 0.372 ± 0.08 vs 0.376 ± 0.09, p=not significant (NS). Each method identified 61 percent of values ≥0.36. In 26 subjects who achieved higher work rates, the mean difference between actual VD/VT and VD/VT(J) increased from 0.009 ± 0.04 (NS) at low work rate (VO₂=28.3 percent pred max) to 0.040 ± 0.06 at high work rate (VO₂=54.7 percent pred max), p=0.006. Actual VD/VT identified 18 (69 percent) patients as abnormal vs 13 (50 percent) so identified by VD/VT(J). With exercise, VD/VT(J) was no better than VD/VT(E). We conclude that during incremental exercise in a patient population, methods for estimating VD/VT progressively underestimate this measurement; and therefore, “normal” estimated VD/VT values may fail to identify underlying pulmonary and/or pulmonary vascular impairment.

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DCO=carbon monoxide diffusion; J=Joule; NS=not significant; PETCO₂=end-tidal pressure of carbon dioxide; r=correlation coefficient; TV=tidal volume; VD/VT=physiologic dead space/tidal volume; VO₂=oxygen uptake

The physiologic dead space/tidal volume ratio (VD/VT) is a useful indicator of the matching of ventilation to perfusion both at rest and during exercise.1 An increased VD/VT at rest, or the failure of VD/VT to decrease appropriately with exercise, serves to identify uneven ventilation-perfusion relationships. This finding, in turn, suggests the presence of primary pulmonary vascular disease or pulmonary vascular involvement secondary to intrinsic lung disease.2 We,3,4 and others,4 have reported the greater sensitivity of VD/VT than alveolar-arterial Po₂ difference or diffusion capacity in various types of patients.

The VD/VT can be derived from the modified Bohr’s equation under steadystate conditions (equation 1):

\[ \frac{V_D}{V_T} = \frac{PaCO_2-PETCO_2}{PaCO_2} \cdot \frac{VDM}{VT} \]

where PaCO₂=arterial PCO₂, PETCO₂=mixed expired PCO₂, VDM=mechanical dead space (in liters) and VT=tidal volume (in liters).

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Because arterial blood must be obtained to determine PaCO₂, efforts have been made to avoid this procedure by estimating PaCO₂ noninvasively. One such estimate simply uses the end-tidal PCO₂ (PETCO₂) in place of the arterial value. Jones and colleagues5 derived an equation by multiple regression analysis to predict PaCO₂ during steady-state exercise using the PETCO₂ and tidal volume (VT) (equation 2): Estimated PaCO₂=5.5+0.90 . PETCO₂−0.0021 . VT(ml).

They studied healthy subjects and acknowledged that in patients with abnormal pulmonary function this equation may be misleading. The PETCO₂ may rise farther above PaCO₂ than expected in zones with low ventilation/perfusion relationships or may be lower in zones with diminished perfusion. Robbins and associates6 compared several methods of estimating PaCO₂ during exercise and concluded that Jones’ equation was the best method of estimating PaCO₂ during steady-state exercise in healthy subjects.

Although such use is widespread in computerized commercial systems, the validity of using estimates of PaCO₂ to obtain VD/VT in incremental or ramp (as opposed to steady-state) cardiopulmonary exercise testing has only recently been studied in patient
populations.7,8 The reliability of an estimated value for Vd/Vt is crucial in the interpretation of exercise studies since arterial cannulation is frequently not feasible and an abnormality in Vd/Vt is often the only finding during exercise testing.2-4,9

In this investigation, we compared two estimated Vd/Vt values (using Jones’ equation and PetCO2 alone) with actual Vd/Vt values calculated from measurement of arterial PCO2 during incremental exercise testing of patients referred for the evaluation of dyspnea. Even though the Bohr’s equation is intended for steady states, the Vd/Vt values calculated from it are the same during steady-state and incremental exercise at the same Vo2. The actual and estimated values for Vd/Vt are correlated, since they differ only in the source of the PaCO2 term in equation 1; nevertheless, the extent and conditions of their difference are of practical concern to clinicians and physiologists who may use the readily available estimated values to evaluate patients. By comparing a readily available measurement with a standard but invasive measurement of Vd/Vt, we are heeding the call for standardization of cardiopulmonary exercise testing 10

METHODS

Data were collected from 35 consecutive patients referred for cardiopulmonary exercise testing in the evaluation of dyspnea. Baseline spirometry and single breath diffusing capacity were performed (MedGraphics CAD/NET System 1070); (Medical Graphics Corp, St. Paul, Minn). Symptom-limited, breath-by-breath, 1 minute incremental exercise tests on a cycle ergometer were performed (MedGraphics System 2000) using an incremental work protocol (19 patients) and later on a system (MedGraphics CPX) using a ramp work protocol (16 patients). The mechanical dead space of each system was 100 ml. Both systems use the same infrared CO2 analyzer and pneumotachograph and a fuel cell O2 sensor. Both use the same algorithms for acceptable tidal volume (TV) and calculated and estimated Vd/Vt, and correct for gas transit and analysis times. Whipp et al11 showed the similarity of various incremental and ramp protocols for VO2max, anaerobic threshold and ∆VO2/∆work and Furuki and colleagues showed that actual Vd/Vt and alveolar-arterial P02 difference were the same in incremental and steady state exercise.

Oxygen saturation was monitored by ear-probe pulse oximetry (Ohmeda Bios 3700) and the electrocardiogram was monitored continuously (Series 2310, Marquette Electronics, Inc). Blood pressures were taken manually both at rest and at intervals throughout exercise.

Radial artery cannulation was performed using local anesthesia (1 percent lidocaine). One to two milliliter samples of arterial blood were drawn into heparinized syringes via a stopcock after 2 ml of waste blood were drawn and discarded. Samples were immediately placed on ice and analyzed within 15 min on electrodes located at the exercise station (ABL 30, Radiometer, Copenhagen) whose readings were validated by regular quality-check solutions.

Exercise protocols included 2 min of resting baseline, 1 min of unloaded cycling, and subsequent incremental or ramp increases in work rates of 5 to 30 W/min. Increments were estimated to achieve a total of 6 to 12 min of exercise. Termination of exercise was determined either by the patient, because of limiting symp-
toms (eg, dyspnea or leg fatigue), or by the physician if the patient’s rate of pedaling could not be sustained above 50 revolutions per minute, if a plateau in VO2 had been reached, or if clinically indicated (eg, because of ectopy).

The system was configured to report data in a tabular format, in 1 min intervals, with each entry representing the average breath-by-breath value of the final 20 s for a given minute interval. Resting values were averaged for the final 60 s of the rest period. Arterial blood specimens were drawn at rest, and during the final 20 s of each minute of exercise, when the data were tabulated. To estimate Vd/Vt from PetCO2 alone, the latter value was taken from the tabular report and entered into the modified Bohr equation as the PaCO2.

Several cut-off values for an abnormal Vd/Vt at rest were evaluated (0.35 to 0.45); a value greater than 0.25 at high work load (VO2max, 55 percent of predicted) was considered abnormal.12

Statistical Analysis

Statistical analysis was performed using statistic software (StatWorks, no. 1.1, Heydon and Son, Spectrum House, London) on a personal computer (Apple Macintosh SE Personal Computer), and statistical software (Epistat, no. 3.1, 1984, Tracy L. Gustafson) on a personal computer (IBM PC XT). All values are expressed as the mean value ± SD unless specified otherwise. Except as noted, we compared Vd/Vt values from the different methods using Pearson’s correlation coefficient and paired Student’s t test, and we analyzed the prevalence of abnormality using paired χ2 analysis; p<0.05 was considered significant.

RESULTS

Thirty-six studies were performed in 35 patients referred for the evaluation of dyspnea. There were 21 men patients and 14 women patients ranging in age from 24 to 79 years (mean age 53.5 years). The patients carried the following diagnoses: sarcoidosis (n=11), asbestos-related disease (n=10), neurofibromatosis (n=3), Gaucher’s disease (n=2), Parkinson’s disease (n=2), mixed connective tissue disease (n=1), multiple sclerosis (n=1), and dyspnea of unknown cause (n=5). Baseline pulmonary function test data for the group are described in Table 1. Seventeen patients had normal results of spirometry,13 and Dco14, five had reduced Dco only; ten had restrictive impairment with normal Dco; two had restriction and reduced Dco, and only one had (slight) obstructive impairment (with normal Dco). This distribution of pulmonary function findings reflects the fact that these patients were referred for evaluation of dyspnea not readily explained by clinical or functional abnormalities. Patients with obvious airways obstruction were, therefore, conspicuously absent.

Table 1—Baseline Pulmonary Function Test Data in 35 Patients

<table>
<thead>
<tr>
<th>Test Parameter</th>
<th>Mean Value</th>
<th>(Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>82.0%</td>
<td>(47-111)</td>
</tr>
<tr>
<td>FEV1</td>
<td>82.5%</td>
<td>(32-115)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.79</td>
<td>(0.54-0.96)</td>
</tr>
<tr>
<td>Dco</td>
<td>87.0%</td>
<td>(35-144)</td>
</tr>
</tbody>
</table>

*One patient underwent exercise studies twice.
†Values expressed as mean percent predicted values from Miller et al,10 range in parentheses.
‡Mean (range) of actual value.
Table 2—Difference Between Vo2/Vt(J) and Actual Vo2/Vt at Different Work Loads in 26 Patients†

<table>
<thead>
<tr>
<th>Vo2 ( % pred max)</th>
<th>Actual Vo2/Vt</th>
<th>VD/Vt (J)</th>
<th>Actual- (J)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>16.6±7.2</td>
<td>0.37±0.08</td>
<td>0.36±0.07</td>
</tr>
<tr>
<td>Low work load</td>
<td>28.3±5.7</td>
<td>0.33±0.09</td>
<td>0.32±0.08</td>
</tr>
<tr>
<td>High work load</td>
<td>54.7±5.8</td>
<td>0.31±0.09</td>
<td>0.27±0.09</td>
</tr>
</tbody>
</table>

*Values are means ± SD.
†Within columns, all comparisons between work loads are significant (p<0.006) except where noted.
\( p=0\) Not significant.

There were 36 pairs of resting values for VD/Vt. Estimated VD/Vt derived using Jones' equation [VD/Vt(J)] correlated with actual VD/Vt with a correlation coefficient of 0.85 (p<0.001). Mean values for both VD/Vt(J) and actual VD/Vt were not significantly different: VD/Vt(J) 0.372±0.08 vs actual VD/Vt 0.376±0.09, p=NS. Using a cutoff value defining abnormality at rest as greater than 0.35, VD/Vt(J) and actual VD/Vt were each abnormal in 22 of 36 tests (61 percent); 20 pairs were concordant for abnormality. There was no difference in the ability to discriminate an abnormal study between the two methods. Results were similar for cutoff values of 0.40, 0.42 and 0.45.

There were 26 patients who had values for actual Vd/Vt at a low work rate (mean Vo2=28.3 percent of predicted maximum), and a high work rate (mean Vo2=54.7 percent of predicted maximum). We compared the values for VD/Vt(J), as well as the difference between VD/Vt(J) and actual VD/Vt, at these two specific intervals as well as during rest. Mean data are shown in Table 2 and Figure 1, and plots of actual VD/Vt vs VD/Vt(J) are shown in Figures 2 and 3. These figures show the number of patients who would be classified as abnormal by ei-

![Figure 1](image1.png)

**Figure 1.** Actual Vo2/Vt compared to VD/Vt(J) at different work loads in 26 patients. Difference significant at high work load by paired Student's t test. Low work and high work represent 28.3±5.7 percent and 54.7±5.8 percent of Vo2 max pred, respectively. Values expressed as mean±SEM.

![Figure 2](image2.png)

**Figure 2.** Plot of Vd/Vt (actual) vs Vd/Vt(J) at rest.

Other Vd/Vt, eg, at rest, both methods of obtaining Vd/Vt yielded 16 values >0.35, whereas at high work, actual Vd/Vt yielded 18 values (69 percent) >0.25 compared with 13 (50 percent) for Vd/Vt(J).

Starting from rest and progressing through the two levels of Vo2, the decrease in Vd/Vt with increasing workrate was seemingly much greater for Vd/Vt(J). Similarly, the difference between actual and estimated values for Vd/Vt was greatest at the highest work rate, with the estimated value significantly lower than the actual (Fig 1).

Considering all values for Vo2, there were 207 pairs of Vd/Vt throughout all 36 exercise studies. The Vd/Vt(J) correlated with actual Vd/Vt with an r of 0.85 (p<0.001). The mean value for Vd/Vt(J) was significantly lower than the mean value for ac-

![Figure 3](image3.png)

**Figure 3.** Plot of Vd/Vt (actual) vs Vd/Vt(J) at 55 percent of pred Vo2max.
Table 3—Actual vs Estimated (Jones) VD/VT at Rest, Low and High Work Loads in Patients With Normal* and Higher† Resting Actual VD/VT

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Low Work Load (28% pred $V_02_{max}$)</th>
<th>High Work Load (55% pred $V_02_{max}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD/VTact</td>
<td>Normal</td>
<td>0.254 ± 0.06</td>
<td>0.253 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>Incr</td>
<td>0.424 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>VD/VT(J)</td>
<td>Normal</td>
<td>0.292 ± 0.05</td>
<td>0.247 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>Incr</td>
<td>0.410 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>Act(J)</td>
<td>Normal</td>
<td>-0.008 ± 0.05</td>
<td>0.006 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>Incr</td>
<td>0.014 ± 0.04</td>
<td></td>
</tr>
</tbody>
</table>

*≤ 0.35, n=10. †p<0.05. ‡≥ 0.36, n=16. §Not significant. ¶p<0.005.

actual VD/VT: VD/VT(J) was 0.28 ± 0.09 vs actual VD/VT of 0.31 ± 0.09, p<0.001. The VD/VT(J) underestimated actual VD/VT in 133/207 (64 percent), VD/VT(J) was equal to actual VD/VT, to two decimal places, in 26/207 (13 percent) and VD/VT(J) overestimated actual VD/VT in 48/207 (23 percent).

To evaluate whether the differences between the actual VD/VT and Jones' estimate were related to the severity of disease, we selected the degree of ventilation-perfusion imbalance as our criterion and compared patients with normal actual values at rest (≤ 0.35; n=10) with those who had increased (≥ 0.36; n=16) values. The lesser fall in actual than in estimated VD/VT with increasing work load was seen in both groups of patients (Table 3), and the difference between the two methods of obtaining the VD/VT was the same at high work load in both groups (Table 3 and Fig 4).

We were additionally interested in determining whether the underestimation of actual VD/VT also occurred when VD/VT was estimated from end-tidal $PCO_2$ alone [VD/VT(ET)]. We analyzed a subset of 11 studies performed on the MedGraphics CPX system, which provided minute-by-minute PetCO2. Comparisons were made between VD/VT values derived from PaCO2 (actual VD/VT), Jones’ estimate of PaCO2 [VD/VT(J)], and PetCO2 [VD/VT(ET)] at rest, at low work load (mean $V_02=28.5$ percent pred), and at high work load (mean $V_02=54$ percent pred) (Table 4). At rest, values for VD/VT(J) were slightly lower than actual (p=NS) while values for VD/VT(ET) were similar to actual. During exercise, both estimated values were lower than actual with the difference between actual and estimated values becoming

![Histogram showing the difference between actual and Jones' estimate of VD/VT at rest for patients with normal VD/VT (≤ 0.35, open bars, n=10) vs those with high VD/VT (≥ 0.36, solid bars, n=16); values are evenly distributed around zero for patients with normal VD/VT and slightly to the right (calculated > Jones') for those with high VD/VT. Lower panel. Similar histogram at high work load (55 percent pred $V_02_{max}$) showing similar distributions to the right for patients with normal or high resting VD/VT.](image-url)
greater with increasing work. At the high work load, VD/VT(J) underestimated actual VD/VT to a significantly greater degree than did VD/VT(ET) (p < 0.05).

**DISCUSSION**

Our study undertook to describe the impact on interpretation of incremental cardiopulmonary exercise tests when an estimated value for arterial PCO2 is used to derive VD/VT in a population of patients referred for the evaluation of dyspnea (in whom severe airways obstruction was absent). We found that the use of estimated (as compared with actual) VD/VT values did not affect the interpretation of gas exchange at rest. With incremental exercise, estimated values progressively underestimated the VD/VT, falsely classifying certain patients as normal whose actual values exceeded normal. This is shown in Figure 5 in a representative patient with high VD/VT values at rest.

In discussing possible mechanisms for the difference between estimated and actual VD/VT, we address the two variables in Jones’ equation, namely end-tidal Pco2 and tidal volume. In normal erect subjects at rest, PET is slightly less than PaCO2 due to dilution by gas from poorly perfused apical alveoli.5 The difference is minimal, with a range from 0 to ±4 mm Hg.1,9,12,13 During exercise in normal subjects, PET-PaCO2 increases, varying directly with increasing VCO2 and VT, and inversely with respiratory frequency.5,9 In patients, arterial values, however, may substantially exceed end-tidal values. This has been described in obstructive or restrictive impairments, pulmonary vascular disease including pulmonary emboli and pulmonary hypertension, respiratory failure, myocardial infarction, and shock.1,15-17 The mechanism is thought to be ventilation-perfusion inequality. Areas of high Va/Q contribute gas with lower PCO2 leading to a lowering of end-tidal PCO2 relative to arterial PCO2 by their dilutional effect. While gas from areas with low Va/Q has a higher PCO2, leading to a rise in end-tidal PCO2,17,18 these areas generally have elevated time constants and gas from these units may not have sufficient time during rapid tidal breathing to be fully reflected in the end-tidal sample.

The effect of exercise on ventilation-perfusion matching introduces another variable. Matching generally improves with exercise, although persistence of ventilation-perfusion inequality has been described in exercise.1,10 The effect of incremental exercise on the difference between end-tidal and arterial PCO2 is probably variable and unpredictable.

The second variable in Jones’ equation is tidal volume. It is known that patients with restrictive impairment exhibit a pattern of rapid, shallow breathing during exercise.1 This may affect the distribution of ventilation-perfusion ratios.11 Our patient population reflected the referral pattern for the evaluation of dyspnea in our institution in that it included patients with restrictive impairment and/or decreased DC02, or with normal pulmonary function tests, but no patient with obvious obstructive impairment for whom the attending physicians felt dyspnea to be well explained. Studies of patients with obstructive impairment are needed to determine whether our findings apply to them.

Vincken and Cosio7 performed steady-state exercise in 18 patients with various respiratory disorders at workloads of one-third and two-thirds V02max. They restricted their analysis to VD/VT estimated from end-tidal PCO2, and they found that this underestimated actual VD/VT by a mean value of 0.055, a finding similar to ours. However, in their study, the difference between actual and estimated VD/VT changed little with exercise. Several differences between their study and ours may account for the contrasting results. First, differences in patient popula-

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**Table 4—Difference Between Two Different Vd/VT Estimates and Actual Vd/VT at Different Work Loads in 11 Patients**

<table>
<thead>
<tr>
<th></th>
<th>Actual Vd/VT-J</th>
<th>Actual Vd/VT-ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest (16% pred Vo2max)</td>
<td>0.010±0.003¶</td>
<td>-0.003±0.005¶</td>
</tr>
<tr>
<td>Low work load (29% pred Vo2max)</td>
<td>0.013±0.004§</td>
<td>0.012±0.0048</td>
</tr>
<tr>
<td>High work load (54% pred Vo2max)</td>
<td>0.062±0.068</td>
<td></td>
</tr>
</tbody>
</table>

*Values are means±SD.¶p<0.01, paired Student’s t test.||p=0.04.

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**Figure 5.** Display of Vd/VT versus Vo2 in a representative patient, illustrating the increasing underestimation of actual Vd/VT by Vd/VT(J) with increasing Vo2 (work). The shaded area represents “8 breath averaging” of 439 values (breaths) for Vd/VT(J) during 2 min of rest, 1 min of unloaded cycling, and 9 min of exercise. Actual Vd/VT values were calculated from the PaCO2 after the first minute of rest and after each of the 9 min of exercise.
tion: severity and type of pulmonary dysfunction clearly would have an impact on the magnitude of the difference between actual and estimated VD/VT, as well as their deviation with increasing work. Their mean resting VD/VT of 0.43 ± 0.06 as compared with our mean resting VD/VT of 0.39 ± 0.09 (in the 11 patients whose VD/VT(ET) values were available) suggests that their patients had greater baseline impairment. From this, it may follow that the difference at rest between actual VD/VT and VD/VT(ET) was greater in their group: 0.057 ± 0.04 vs −0.003 ± 0.053 in one group. Second, it is difficult to interpret changes with increasing exercise because their study populations were not the same at different levels of work: only 18 of 23 studies reached one-third V02max, and only 14 reached two-thirds V02max. It is unclear what effect the loss of the presumably sicker patients had on the differences between actual and estimated VD/VT with increasing work. Finally, the differing effects of incremental vs steady-state exercise on the equilibration of arterial and end-tidal Pco2 need to be considered.

In a preliminary report, Lewis et al8 compared actual VD/VT to VD/VT(J) and VD/VT(ET) at peak exercise in 68 patients. They considered the actual values calculated from the Bohr equation to be standard, as did we. Using a normal value ≤0.30, VD/VT(ET) failed to identify 15 of 30 patients with elevated actual VD/VT, whereas VD/VT(J) incorrectly classified 15 of 38 patients with normal actual VD/VT. Separate analyses by pulmonary function impairment did not identify any group for which estimated values were more accurate. They concluded that “non-invasive estimates of arterial Pco2 cannot replace measured PaCO2 for calculation of VD/VT during exercise.”

Weisman and Zeballos10 have called for studies to standardize cardiopulmonary exercise testing to “more clearly define [its] full potential and limitations”.10 We have confirmed that in systems which use Jones’ equation to estimate arterial Pco2 during exercise, an abnormal estimated VD/VT indeed defines an abnormal response. However, a normal estimated VD/VT frequently masks an abnormal actual VD/VT during exercise, thus failing to identify underlying pulmonary vascular impairment. In addition, Jones’ estimation seemed to offer no advantage over PETCO2 in the estimation of VD/VT during incremental exercise.

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