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Evaluation of the Danish Aerospace Corporation Portable Pulmonary Function System

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ABSTRACT

A research project designed to investigate changes in maximal oxygen consumption (VO_2max) during and following long duration flight on the International Space Station (ISS) has recently been completed. The device used to measure oxygen consumption (VO_2) on board ISS, the Portable Pulmonary Function System (PPFS) manufactured by the Danish Aerospace Corporation (DAC), is based on previous-generation devices manufactured by DAC, but the PPFS has not been validated for analyzing metabolic gases or measuring cardiac output (Qc). The purpose of the present evaluation is to compare PPFS metabolic gas analysis measurements to measurements obtained using a clinically-validated system (ParvoMedics TrueOne© 2400 system; Parvo). In addition, Qc data collected with the PPFS were compared to Qc measurements from echocardiography. **METHODS:** Ten subjects completed three cycle exercise tests to maximal exertion. The first test was conducted to determine each subject's VO_2max and set the work rates for the second and third (comparison) tests. The protocol for the two comparison tests consisted of three five-minute stages designed to elicit 25%, 50%, and 75% VO_2max (based upon results from the initial test), followed by one-minute stages of increasing work rate (25 watts/minute) until the subject reached maximal effort. During one of the two comparison tests, metabolic gases and Qc were assessed with the PPFS; metabolic gases and Qc were assessed with the Parvo and by echocardiography, respectively, during the other test. The order of the comparison tests was counterbalanced. VO_2max and maximal work rate during the comparison tests were compared using *t* tests. Mixed-effects regression modeling was used to analyze submaximal data. **RESULTS:** All of the data were within normal physiological ranges. The PPFS-measured values for VO_2max were 6% lower than values obtained with the Parvo (PPFS: 3.11 ± 0.75 L/min; Parvo: 3.32 ± 0.87 L/min; mean ± standard deviation; $P = 0.02$); this difference is probably due to flow restriction imposed by the PPFS Qc accessories. Submaximal VO_2 values were slightly lower when measured with the PPFS, although differences were not physiologically relevant. The PPFS-measured values of submaximal carbon dioxide production (VCO_2) were lower than the data obtained from Parvo, which could be attributed to lower fractions of expired carbon dioxide measured by the PPFS. The PPFS Qc values tended to be lower than echocardiography-derived values. **CONCLUSIONS:** The results of the present study indicate a need to further examine the PPFS and to better quantify its reproducibility; however, none of the findings of the current evaluation indicate that the PPFS needs to be modified.

INTRODUCTION

The National Aeronautics and Space Administration (NASA) Human Research Program (HRP) has developed an integrated research plan to address the health risks that might impede human exploration beyond Earth's orbit (Human Research Program Integrated Research Plan, NASA HRP 47065). One of the risks identified by NASA's Integrated Research Plan is the "Risk of reduced physical performance capabilities due to reduced aerobic capacity."

Maximal oxygen uptake (VO_2max), also known as aerobic capacity, is the maximal rate at which a person can consume oxygen (O_2) during exercise, and is directly related to the ability to perform prolonged and strenuous work (1, 2). There is clear evidence from bed rest studies (10) and short-duration spaceflight that VO_2max is reduced after exposure to both simulated and actual microgravity (12, 16), particularly when minimal or no exercise is performed during the exposure period. However, results from longer spaceflight missions, based upon submaximal exercise test results, have been less clear. During the Skylab missions, submaximal exercise testing was performed approximately every six days, and there appeared to be no overall trend (increase or decrease) in the heart rate (HR) response to standard exercise work rates (up 75% of pre-flight VO_2max). These results were interpreted to indicate that VO_2max was unchanged during missions up to three months in duration (14, 15, 21). Similar submaximal exercise tests were performed each month during early ISS missions. In contrast to Skylab results, ISS crewmembers experienced an elevated HR response to exercise in the first weeks of the mission, which suggested that VO_2max may have been compromised, but there appeared to be some recovery over the course of a six-month mission (18). In the first week after landing, the HR responses to exercise of both the Skylab and ISS crew members were elevated, which is consistent with a decline in VO_2max. Multiple factors other than aerobic deconditioning can influence the HR response to exercise and given the error in estimating VO_2max from submaximal exercise data (11), it was unclear until recently (16) how much, or even if, VO_2max is affected by long-duration spaceflight.

Oxygen uptake during exercise (VO_2) is influenced by both central (related to the heart) and peripheral (related to O_2 extraction and distribution of blood flow in the muscle tissues) factors. The relationship between these factors is expressed in a relation commonly known as the Fick equation (20):

$$VO_2 = Q_c\ (a\text{-}v)O_2 \text{ difference}$$

in which cardiac output (Qc) is the amount of blood pumped from the heart's left ventricle per minute and is the product of HR and the volume of blood ejected from the left ventricle per beat (also known as stroke volume [SV]). Arterial to venous O_2 difference "$(a\text{-}v)O_2$" is the difference between O_2 levels in the arterial and venous blood, i.e. O_2 extraction of the tissues. Thus, any factor that influences HR, SV, or O_2 extraction may influence VO_2 or VO_2max.

A contractor to the European Space Agency, Damec Research ApS (currently named Danish Aerospace Corporation [DAC]), developed a metabolic gas analysis system capable of measuring VO_2 on board ISS. This device, named the Portable Pulmonary Function System (PPFS), was used to measure astronauts' VO_2max during long-duration space flight (16). The current report describes our efforts to validate measurements obtained from the PPFS by comparing PPFS measurements of metabolic gas analysis obtained during exercise tests with equivalent measurements obtained using the ParvoMedics TrueOne© 2400 system (ParvoMedics, Sandy, UT). The ParvoMedics system has been validated (8) for accurate measurement of VO_2 and has been used in the Exercise Physiology Laboratory at NASA Johnson Space Center since 2004 but was not designed for use on ISS. The second purpose of the present study was to compare the non-invasive measurements of Qc obtained by the PPFS to measurements obtained using echocardiography.

METHODS

Subjects

Ten healthy volunteers participated in the ground-based study described here (**Table 1**). Subjects passed a modified Air Force Class III physical exam before they participated in the study and received written and verbal explanations of test protocols before providing written informed consent. The NASA Johnson Space Center Committee for the Protection of Human Subjects reviewed and approved the test protocols and procedures.

TABLE 1: SUBJECT CHARACTERISTICS (MEAN ± SD) BY SEX.

	Male	Female
n	6	4
Age (yr)	37.5 ± 9.5	36.0 ± 9.2
Weight (kg)	80.1 ± 10.6	55.6 ± 2.6
Height (cm)	180.8 ± 4.3	162.6 ± 4.1
VO_2max (ml/kg/min)	48.7 ± 9.3	46.2 ± 5.0

Overall Protocol

Subjects performed three peak cycle tests to measure VO_2max. The LODE Excalibur Sport (Groningen, NL) cycle ergometer was used for all testing.

The initial peak cycle test used the same protocol used to measure the pre-flight VO_2max in astronauts before early ISS missions (18). During the initial test, subjects with a body mass of > 65 kg cycled for three minutes each at 50, 100, and 150 watts (W), after which work rate was increase 25 W/minute until maximal exertion. If the subject's body mass was < 65 kg, the subjects cycled for three minutes each at 50, 75, and 100 W, after which work rate increased 25 W/minute until maximal exertion. If an individual who was <65 kg reported that they regularly participated in cycle exercise, the first protocol described above was used for this initial test. For either protocol, the work rate was increased until subjects indicated that they could no longer continue or until they could no longer maintain a pedal cadence of 75 revolutions per minute. During this initial test, the ParvoMedics TrueOne© (ParvoMedics, Salt Lake City, UT) system was used to perform metabolic gas analysis. The VO_2 and work rate data from the initial test were used to design the protocol for the second and third (comparison) tests.

The second and third tests were designed to compare the metabolic gas analysis and Qc measurements from the two different devices. The testing protocol for these comparison tests was based on the submaximal cycle test used by Skylab astronauts (14, 15, 21) and for the ISS Periodic Fitness Evaluation during early ISS mission (18), but the protocol was extended to achieve VO2max. Specifically, the protocol for the comparison tests consisted of three five-minute stages designed to elicit 25%, 50%, and 75% of the individual's VO_2max that was previously determined from the initial peak cycle test. The three initial stages were followed by work rate increases of 25 W/minute until subjects reached their maximal effort. This is the same exercise protocol that was used in a study of ISS astronauts (16). Comparison tests were performed in a counterbalanced order; one test was performed using the ParvoMedics TrueOne© system paired with echocardiography to measure Qc, and one test was performed using the PPFS to obtain metabolic gas analysis data and Qc measurements using a rebreathing technique. These tests were repeated within one month of the initial test, and the two tests were separated by at least one week to minimize the potential effects of residual soreness or fatigue.

Before starting the exercise, the subjects rested quietly for five minutes in supine and seated positions while measurements of HR, heart rhythm, and blood pressure (BP) were taken. HR and rhythm were measured electrocardiographically (Q-Stress, Quinton Instruments, Seattle, WA), and BP

was measured using a mercurial sphygmomanometer and stethoscope. HR, heart rhythm, and metabolic expired gas were measured continuously throughout the test. BP was measured once during each submaximal exercise stage, and ratings of perceived exertion (5) were reported during the last 30 seconds of each stage. BP was recorded during the recovery period after the test, and the subject was monitored for any adverse effects caused by maximal physical exertion.

Metabolic Gas Analysis Systems

The dependent variables for comparisons between the two systems were VO_2, carbon dioxide production (VCO_2), expired ventilation (V_E), and fractions of expired oxygen and carbon dioxide (FEO_2 and $FECO_2$).

ParvoMedics TrueOne© system uses a paramagnetic O_2 analyzer (operating range 0-25% O_2) and an infrared single-beam, single-wavelength, carbon dioxide (CO_2) analyzer (operating range 0-15% CO_2) to measure the composition of expired gases. The subjects inspired through a two-way non-rebreathing valve (Hans Rudolph Model 2700, Kansas City, MO) and expired air composition was sampled from a four-liter mixing chamber. The inspired gas composition was assumed to be standard atmospheric values (i.e., 20.93% O_2 and 0.03% CO_2). V_E was measured using a Hans Rudolph Model 3813 linear pneumotachometer (operating flow range 0-800 L/min). Computational software was provided with the system. Data were collected continuously by the ParvoMedics system and were averaged in 30-second intervals to the nearest whole breath. VO_2max was accepted as the highest VO_2 attained for a single 30-second period.

The PPFS uses two types of technology for gas analysis. A photoacoustic method of gas analysis is used to measure CO_2 concentration. In this technique, the gas sample is exposed to intermittent infrared light. The gas sample absorbs the light, and the heat from the absorbed energy results in an increase in pressure in the sample chamber. The intermittent infrared light is divided into different pulsation frequencies and is filtered optically. Each optical filter allows only specific wavelengths of light to pass through. The wavelengths correspond to the infrared absorption spectra of the sample gases. When the light source is removed the gas cools down, resulting in a pressure fluctuation. Because the pulsation frequency is in the audible range, the pressure fluctuation becomes an acoustic signal that is detected by a microphone. The sounds recorded by the microphone are analyzed, and the amplitude of each signal is used to calculate the gas concentration. The PPFS operating range for CO_2 concentration is from 0% to12%. An Oxigraf™ sensor in the PPFS is used for O_2 analysis. The Oxigraf™ uses a spectroscopy technique for laser diode absorption in which the sample gas is exposed to a laser with a wavelength of 760 nm (the peak of O_2 absorption). The laser signal is attenuated in proportion to the concentration of O_2 present in the sample. The PPFS operating range for O_2 is from 0% to 100%. When using the PPFS during exercise testing, the subject inspires through a DAC custom-designed two-way non-rebreathing valve and the expired gases are sampled in a 15-liter anesthesia bag that serves as a mixing reservoir. Ventilation is measured on the inspired side of the non-rebreathing valve using a DAC custom-designed pneumotach (operating flow range 0-900 L/min). The technologies used for PPFS metabolic gas analysis are further described by Clemensen and colleagues (6). A proprietary software package developed by DAC, named ADAM, was used to compute metabolic gas analysis variables. Similar to the Parvomedics data reduction, the data were averaged in 30-second intervals to the nearest whole breath.

Cardiac Output Measurements

To obtain Qc measurements from echocardiography, two-dimensional imaging was used to obtain the aortic annulus diameter (d) from the parasternal long axis during supine rest before the exercise tests. Continuous-wave Doppler from the apical window (2- to 4-MHz phase array probe, iE33, Phillips Ultrasound, Andover, MA) was used to obtain aortic blood velocity time integral in three to five heartbeats during the last minute of rest and each five-minute exercise stage. Images were stored digitally for offline analysis and independently analyzed by two experienced, registered sonographers.

Aortic annulus area ($\pi \bullet d^2/4$), stroke volume (annulus diameter x velocity time integral), and Qc (stroke volume x heart rate) were calculated.

Qc measurements using the PPFS involved subjects rebreathing into and out of a bag containing 2.5-3.5 liters of a gas composed of 1% Freon R-22, 1% sulfur hexafluoride (SF_6), 40% O_2, and 58% N_2. The subjects started the rebreathing procedure after an exhalation at a self-selected time point during seated rest and within the last minute of each five-minute stage of exercise. The rebreathing protocol consisted of eight breaths (approximately 30 seconds during rest and 20 to 25 seconds during exercise). The ADAM software calculated Qc using formulas that are described elsewhere (4). Briefly, Qc was calculated using the rate of disappearance of Freon R-22 (a blood-soluble gas) from the rebreathed air as measured from the end-tidal expiratory gas fractions. Adequate gas mixing in the lungs, required for accurate Qc measurements, was determined by measuring the end-tidal expiratory gas fractions of SF_6 (a blood-insoluble gas). Freon R-22 and SF_6 were sampled through a Nafion® catheter connected to a port adjacent to the mouthpiece of the PPFS.

Statistical Methods

The PPFS measures were compared to those obtained with the Parvomedics device using expected and actual responses to a range of workloads experienced by the subjects during submaximal exercise. To achieve this comparison, we used mixed-effects regression models (7) to estimate the mean output of gas measurements (VO_2, VCO_2, V_E, FEO_2 and $FECO_2$) obtained on the Parvomedics device as either a linear or a quadratic function of work rate (depending on the type of output), allowing for random subject differences and within-subject measurement errors. We then used another mixed-effects regression model to estimate the bias (mean difference between the two devices: PPFS – Parvomedics) as a function of the mean. From this second regression model, we also calculated 95% confidence limits for the bias, which are displayed for each of the measurements. The plots are similar to Bland-Altman plots (3), except that in our case, by modeling the physiological responses as functions of workload, we make allowance for repeated measures on subjects as well as reduce sensitivity to the effect of measurement errors in the standard device (in this case, the Parvomedics). The mean VO_2max and maximal work rate attained during the tests with each device were also compared using paired *t* tests.

The analysis of the PPFS and echocardiographic Qc and SV data followed a strategy similar to that used for the metabolic gas analysis comparisons, with one important difference: because there is no compelling evidence in the literature to suggest that either of the methods should serve as a standard (17), the data collected from each device was modeled as a function of cycle ergometer work rate.

RESULTS

Submaximal Exercise

All of the metabolic gas analysis data, irrespective of the device used for measurement, were within normal physiological ranges. Thus, there were no gross errors in output from either the PPFS or the Parvomedics system.

Comparisons of the absolute VO_2 values measured by the two devices are shown in **Figure 1**. In general, the PPFS-measured values were lower than those measured by the Parvomedics system.

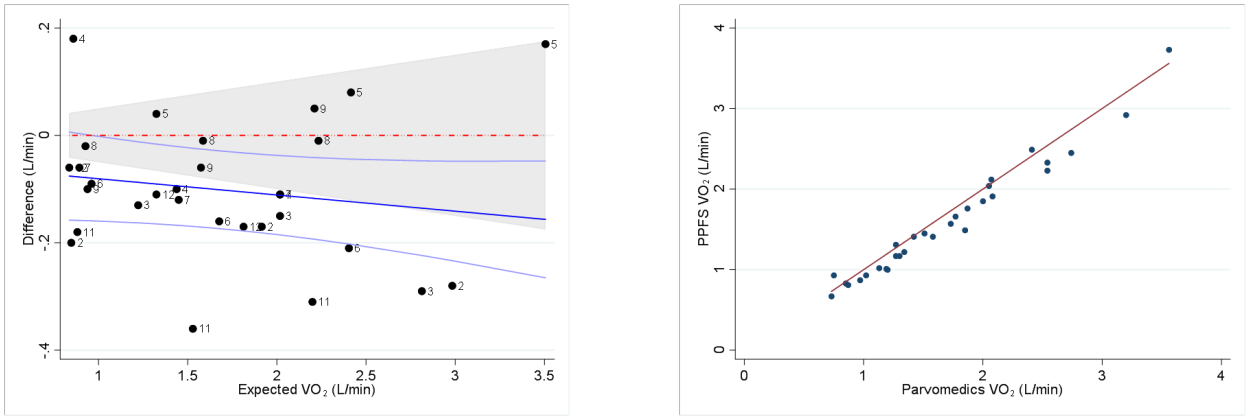

Figure 1. VO_2 values observed during the submaximal stages of testing. The left panel displays the observed differences (PPFS-Parvomedics) between the two devices. Expected VO_2 (x-axis) for each exercise level is predicted from the relationship between VO_2 and work rate for these subjects, as measured by the Parvomedics (the "clinical standard" device). The numbers displayed next to the data points are subject identifiers (three data points for each subject). The gray shaded area indicates ±5% of the expected VO_2. The solid straight line is the mean relationship, and the curves are 95% confidence intervals for the mean difference. The right panel displays the relationship between the VO_2 values of the two devices evaluated. The solid line is the line of identity.

The VCO_2 data are displayed in **Figure 2**. As was the case for VO_2, the PPFS values were lower than the data measured by the Parvomedics system. The disparity between the two devices increased as the values of VCO_2 rose.

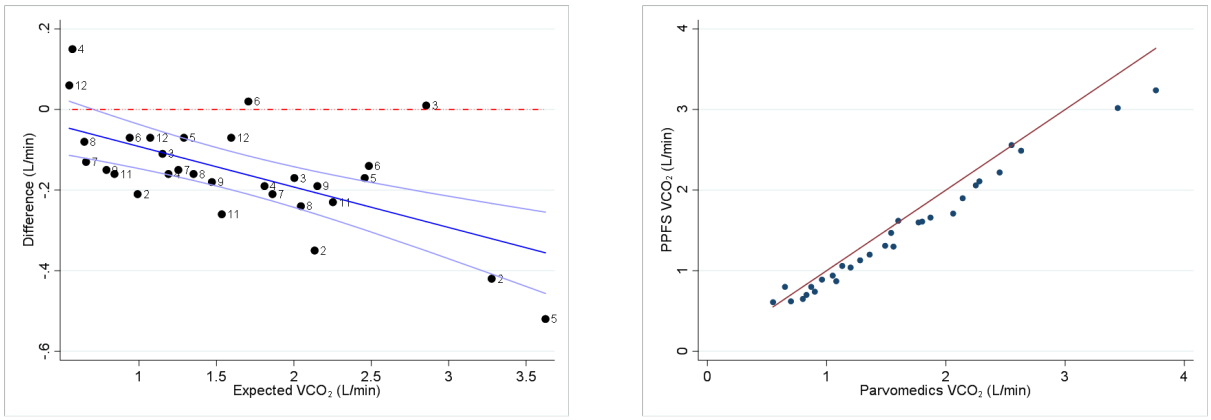

Figure 2. VCO_2 values observed during the submaximal stages of testing. The left panel displays the observed differences (PPFS-Parvomedics) between the two devices. Expected VCO_2 (x-axis) for each exercise level was predicted from the relationship between VCO_2 and work rate for these subjects, as measured by the Parvomedics device. The numbers displayed next to the data points are subject identifiers (three data points for each subject). The solid straight line is the mean relationship, and the curves are 95% confidence intervals for the mean difference. The right panel displays the relationship between the VCO_2 values of the two devices evaluated. The solid line is the line of identity.

Figure 3 illustrates the ventilation data. The values from the PPFS and the Parvomedics were quite close; the 95% confidence intervals of the difference between the two devices contained zero (no difference) throughout the range of data observed in the evaluation.

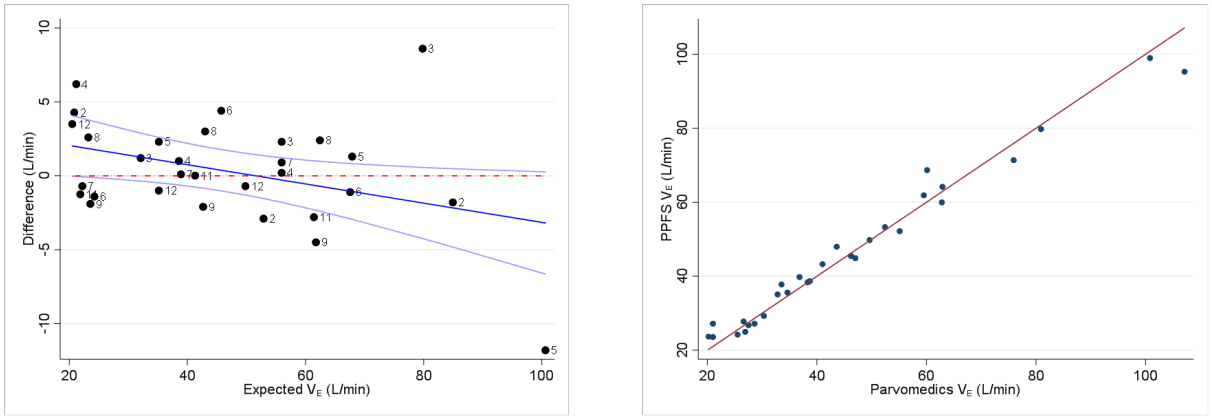

Figure 3. V_E values observed during the submaximal stages of testing. The left panel displays the observed differences (PPFS-Parvomedics) between the two devices. Expected V_E (x-axis) for each exercise level is predicted from the relationship between V_E and work rate for these subjects, as measured by the Parvomedics. The numbers displayed next to the data points are subject identifiers (three data points for each subject). The solid straight line is the mean relationship, and the curves are 95% confidence intervals for the mean difference. The right panel displays the relationship between the V_E values of the two devices evaluated. The solid line is the line of identity.

The FEO_2 measured by each device was fairly comparable (**Figure 4**). At the very lowest levels, the 95% confidence interval was slightly above a difference of zero, which indicates that the PPFS values were slightly higher than the Parvomedics values. This would cause computed VO_2 values from the PPFS to be lower.

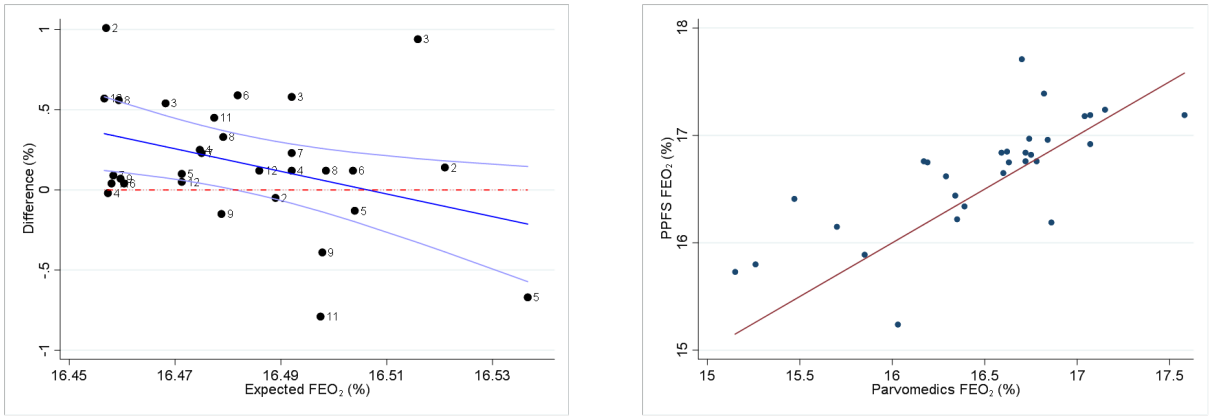

Figure 4. FEO_2 values observed during the submaximal stages of testing. The left panel displays the observed differences (PPFS-Parvomedics) between the two devices. Expected FEO_2 (x-axis) for each exercise level is predicted from the relationship between FEO_2 and work rate for these subjects, as measured by the Parvomedics. The numbers displayed next to the data points are subject identifiers (three data points are present for each subject). The solid straight line is the mean relationship, and the curves are 95% confidence intervals for the mean difference. The right panel displays the relationship between the FEO_2 values of the two devices evaluated. The solid line is the line of identity.

$FECO_2$ values are illustrated in **Figure 5**. The PPFS values were clearly lower than the Parvomedics values across the range of data produced by our subjects.

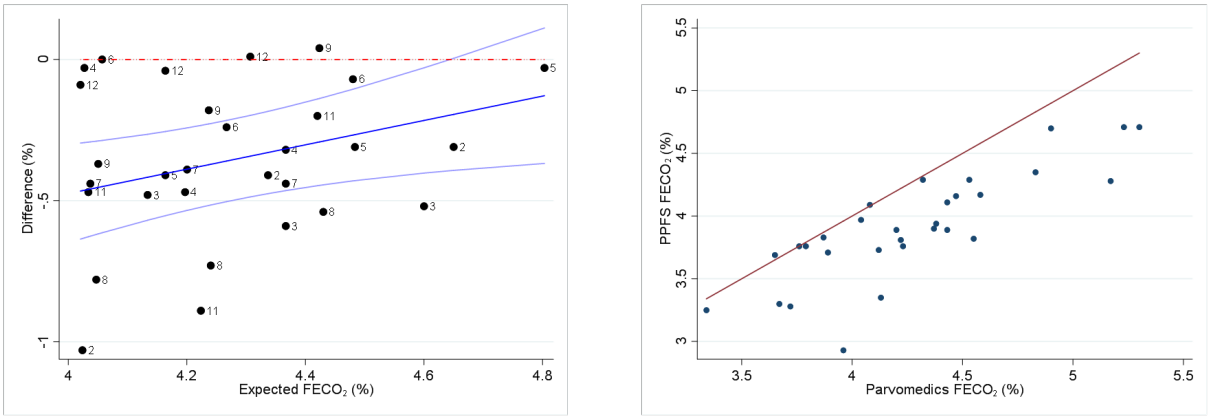

Figure 5. $FECO_2$ values observed during the submaximal stages of testing. The left panel displays the observed differences (PPFS-Parvomedics) between the two devices. Expected $FECO_2$ (x-axis) for each exercise level is predicted from the relationship between $FECO_2$ and work rate for these subjects, as measured by the Parvomedics. The numbers displayed next to the data points are subject identifiers (three data points for each subject). The solid line is the mean relationship, and the curves are 95% confidence intervals for the mean difference. The right panel displays the relationship between the $FECO_2$ values of the two devices evaluated. The solid line is the line of identity.

Maximal Exercise

The average VO_2max attained by the subjects was higher when measurements were obtained with the Parvomedics device (**Figure 6**). The higher Parvomedics VO_2max also was associated with a higher peak work rate attained during testing.

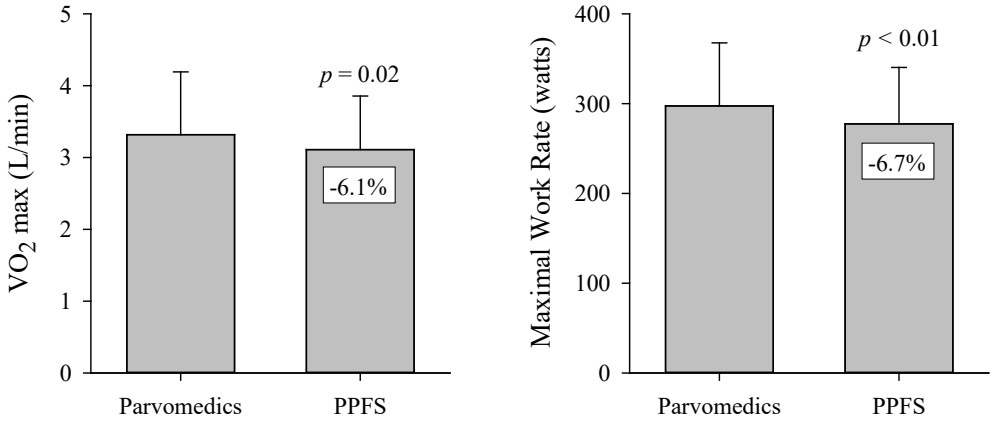

Figure 6. Mean VO_2max (left panel) and maximal cycle work rate (right panel) attained during the tests using the Parvomedics and PPFS devices. Note that the PPFS trial produced a lower VO_2max in almost direct proportion to the lower work rate attained**.**

Cardiac Output

The Qc values obtained from the PPFS and echocardiographically are displayed in **Figure 7**. At resting levels the two methods provided comparable data; however, with increasing exercise work rate the echocardiographic data were lower than the associated PPFS data.

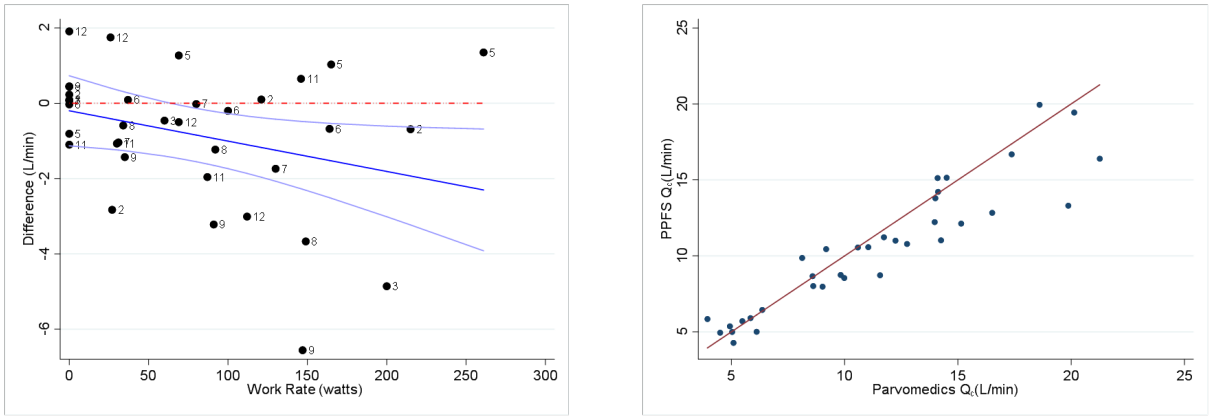

Figure 7. Q_C values observed during the submaximal stages of testing. The left panel displays the differences (PPFS-Echocardiograph) observed between the two devices across exercise work rates (0 W = seated rest). The numbers displayed next to the data points are subject identifiers (three data points for each subject). The solid straight line is the mean relationship, and the curves are 95% confidence intervals for the mean difference. The right panel displays the relationship between the Q_C values of the two methods evaluated. The solid line is the line of identity.

Figure 8 contains the SV data from the echocardiograph and the PPFS. Stroke volume tended to be higher when measured by echocardiography, with the margin of the upper 95% confidence interval falling close to no difference across the range of values measured.

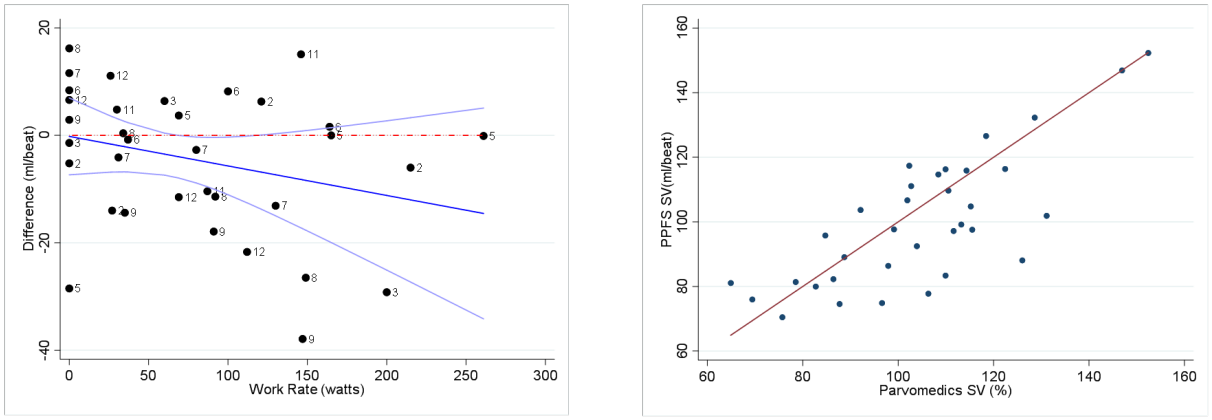

Figure 8. SV values observed during the submaximal stages of testing. The left panel displays the differences (PPFS-Echocardiograph) observed between the two devices across exercise work rates (0 W = seated rest). The numbers displayed next to the data points are subject identifiers (three data points for each subject). The solid straight line is the mean relationship, and the curves are 95% confidence intervals for the mean difference. The right panel displays the relationship between the SV values of the two methods evaluated. The solid line is the line of identity.

DISCUSSION

The primary purpose of this study was to determine whether consistent differences existed between two metabolic gas analysis systems, PPFS and Parvomedics, with respect to measuring VO_2 during submaximal and maximal exercise. We also assessed differences between Qc measurements obtained with the PPFS and by echocardiography.

Our data show statistically significant differences between the PPFS and Parvomedics values of VO_2 during submaximal exercise at loads up to 75% VO_2max (**Figure 1**), but this difference is not of sufficient magnitude to be physiologically important. The average differences observed in submaximal VO_2 were just outside the 4%-6% intra-individual day-to-day variation in VO_2 commonly reported in the literature (19). The upper 95% confidence interval computed from the differences between the two devices was not outside of the 4%-6% range. However, when measurements are repeated across the duration of a longitudinal study, it is important that all measurements (e.g., before, during, and after space flight) be conducted using the same device to avoid potential sources of error associated with different metabolic gas analysis systems.

It appears that the difference in submaximal VO_2 values was not caused by different measures of V_E obtained by the two devices (**Figure 3**). This suggests that FEO_2 measurements might explain the VO_2 differences; conceptually VO_2 is simply the product of V_E and the difference in O_2 concentration between ambient air and expired air. However, it is difficult to pinpoint this as the precise cause of the discrepancy in VO_2 values because the preponderance of the FEO_2 data is clustered within a narrow range between 16 and 16.5% O_2 (**Figure 4**). $FECO_2$ also contributes to the calculation of VO_2, but its influence is negligible compared to FEO_2 or V_E. To illustrate, at a VO_2 of 4.68 L/min (a level representative of maximal exercise of our fittest subjects) if $FECO_2$ was reduced by 0.4% (which is the average difference observed in $FECO_2$ between the two devices in our tests; **Figure 5**), the calculated VO_2 would be reduced only to 4.66 L/min.

Mean VO_2max obtained from the two devices was significantly different (**Figure 6**). However, this is not likely due to any measurement problems within the devices *per se*, in light of the fact that the 6.1% lower VO_2max measured with the PPFS was observed in combination with a 6.7% reduction in the peak work rate attained during the PPFS tests. The reduction in work rate achieved by the subjects during the PPFS comparison test might be due to a ventilatory flow restriction imposed by the PPFS. When using the PPFS, the subjects breathe through a valve and a mouth port tube that is lengthened to accommodate the Qc rebreathing bag adapter and the pneumatic valve, which controls flow into and out of the bag. The extended length of the port tube causes more flow limitation and resistance to breathing than the standard Hans Rudolph 2700 valve that is part of the Parvomedics device. Pressures in the respiratory valve up to 13.5 cmH_2O were measured by the PPFS during peak exercise, and the pressure during submaximal exercise ranged from 2 to 5 cmH_2O. A peak pressure of about 8 cmH_2O is expected at peak exercise ventilation values when using the Hans Rudolph 2700 valve (http://www.rudolphkc.com/pdf/691017%201008%20I.pdf). The pressures measured by the PPFS do not seem to be in the range that would cause marked limitation to submaximal exercise, although ventilation at maximal exercise levels may be impaired (9), thus limiting performance.

The differences in VCO_2 values obtained from the two devices (**Figure 2**) are likely to be directly attributable to the different $FECO_2$ data (**Figure 5**). The primary contributing variables used in the calculation of VCO_2 are V_E and $FECO_2$. As noted above, V_E measurements did not differ significantly between the two devices. The disparity between $FECO_2$ values measured by the Parvomedics device and the PPFS are not easily explainable because both systems use infrared measuring techniques for detecting CO_2 concentrations.

Qc and SV values obtained during exercise using the PPFS are lower than the measurements obtained by echocardiography (**Figures 7 and 8**). As noted in the statistical methods section of this report and in previous reports (17), there is no compelling evidence to suggest that one technique is more

accurate or valid than the other. However, in the present study, measurement of SV and Qc using echocardiography involved analysis of as few as three heart beats, whereas about 20 to 40 heart beats would occur during the rebreathing technique used for the PPFS. In addition, it becomes increasingly difficult to attain accurate ultrasound images with increasing cycle work rate because of subject movement. Thus, it is possible that the rebreathing technique was less prone to variation than echocardiography because beat-to-beat differences in SV are averaged over more heart beats and subject movement does not affect the measurement.

Limitations

An ideal comparison of metabolic gas analysis systems would entail the two systems being operated "in series" (i.e., measuring fractions and volumes of the same expired gases or from sensors in close proximity to one another) on the same subject. An "in series" evaluation eliminates day-to-day variation in the subjects' response to exercise as a source of error. However, this type of setup often is not feasible because the two systems can interfere with each other and produce erroneous results. Discussions with the manufacturers of both the Parvomedics system and the PPFS led us to conclude that an evaluation with the two devices in series may lead to errors, particularly in gas sampling, and therefore our tests were performed using the devices on separate days. With this approach, valid comparisons of the VO_2 and VCO_2 data obtained from each device are still possible, although variables associated with the calculation of VO_2 and VCO_2 (i.e., FEO_2, $FECO_2$ and V_E) need to be assessed with caution. For example, an individual should have a similar VO_2 response to a similar exercise load during two separate tests (an expected finding), but V_E could be higher in one trial and resulting in a higher FEO_2 (13). Alternatively, we could have exchanged the PPFS and Parvomedics at the midpoint during a series of prolonged exercise stages. This approach would have eliminated day-to-day variation during submaximal data collections, but it would have introduced the distinct disadvantage of not being able to compare maximal responses; only one device could be used at a time to collect maximal exercise data. Therefore, the approach that we selected appeared to be the best compromise. However, although the data from our evaluation indicate that FEO_2 values may differ, and the $FECO_2$ values certainly differ, there is no way to conclusively prove this using the present data set.

The difference between VO_2max data obtained on the two devices is likely a limitation of the PPFS design. If Qc measurements are not desired, the PPFS can be used without the extended mouth-port adapter. This should reduce the flow limitation and allow subjects to exercise to higher loads. However, because one of the objectives of the ISS study (16) was to measure Qc, this is not viewed as an ideal solution.

It should be noted that throughout this report VO_2 measured at maximal exertion during the peak cycle tests has been referred to as VO_2max. This is technically not the correct terminology for our measurement because we performed no specific verification of a plateau in VO_2 with increasing work rates, which is the criterion for "true" VO_2max (22). However, not all individuals can attain this plateau, and previous comparisons have reported no statistically significant difference between VO_2max and peak VO_2, which is the correct description for the variable reported here. Further, because the terms "VO_2max" and "peak VO_2" have been used interchangeably in various spaceflight and bed rest publications, we have chosen to use only VO_2max in the description of test results contained in this report.

CONCLUSIONS

There were no findings in this evaluation that preclude using the PPFS to obtain data before, during, or after ISS missions. In light of the differences observed in the VO_2 and VCO_2 measurements obtained by the PPFS and the Parvomedics devices, it is imperative that the same device be used for all pre-, in-, and post-flight testing if the data are to be compared across time points.

- The differences observed in submaximal VO_2 were small and are probably not clinically relevant.

- The differences observed in submaximal VCO_2 are very likely due to differences in $FECO_2$. Although $FECO_2$ has only a small effect on the computation of VO_2, the effect could confound any research projects that examine VCO_2 as a variable of interest. We recommend that PPFS expired gas fraction measurements be further examined.
- The reduced VO_2max and maximal work rate attained by the subjects during PPFS tests are likely due to a ventilatory flow limitation.
- The reproducibility of the PPFS measurements should be quantified.

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REFERENCES

1. **American College of Sports Medicine**. *ACSM's Guidelines for Exercise Testing and Prescription*. Ninth edition. Philadelphia: Lippincott Williams & Wilkins, 2013.
2. **Astrand P-O**, **Rodahl K**, **Dahl HA**, **Stromme SB**. *Textbook of Work Physiology: Physiological Bases of Exercise*. 4th ed. Champaign, IL: Human Kinetics, 2003.
3. **Bland JM**, **Altman DG**. Measuring agreement in method comparison studies. *Stat Methods Med Res* 8: 135–160, 1999.
4. **Bonde-Petersen F**, **Norsk P**, **Suzuki Y**. A comparison between freon and acetylene rebreathing for measuring cardiac output. *Aviat Space Environ Med* 51: 1214–1221, 1980.
5. **Borg G**. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 2: 92–98, 1970.
6. **Clemensen P**, **Christensen P**, **Norsk P**, **Grønlund J**. A modified photo- and magnetoacoustic multigas analyzer applied in gas exchange measurements. *J Appl Physiol Bethesda Md 1985* 76: 2832–2839, 1994.
7. **Cnaan A**, **Laird NM**, **Slasor P**. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. *Stat Med* 16: 2349–2380, 1997.
8. **Crouter SE**, **Antczak A**, **Hudak JR**, **DellaValle DM**, **Haas JD**. Accuracy and reliability of the ParvoMedics TrueOne 2400 and MedGraphics VO2000 metabolic systems. *Eur J Appl Physiol* 98: 139–151, 2006.
9. **Demedts M**, **Anthonisen NR**. Effects of increased external airway resistance during steady-state exercise. *J Appl Physiol* 35: 361–366, 1973.
10. **Lee SMC**, **Moore AD**, **Everett ME**, **Stenger MB**, **Platts SH**. Aerobic exercise deconditioning and countermeasures during bed rest. *Aviat Space Environ Med* 81: 52–63, 2010.
11. **Lee SMC**, **Moore AD Jr**, **Barrows LH**, **Fortney SM**, **Greenisen MC**. *Variability of Prediction of Maximal Oxygen Consumption on the Cycle Ergometer using Standard Equations, NASA Technical Paper 3412*. Houston, TX: NASA Center for AeroSpace Information, 1993.
12. **Levine BD**, **Lane LD**, **Watenpaugh DE**, **Gaffney FA**, **Buckey JC**, **Blomqvist CG**. Maximal exercise performance after adaptation to microgravity. *J Appl Physiol Bethesda Md 1985* 81: 686–694, 1996.
13. **McArdle WD**, **Katch FI**, **Katch VL**. Exercise Physiology: Nutrition, Energy, and Human Performance [Online]. Eighth Edition. Lippincott Williams & Wilkins. https://www.amazon.com/Exercise-Physiology-Nutrition-Energy-Performance/dp/1451191553 [15 Mar. 2017].
14. **Michel EL**, **Rummel JA**, **Sawin CF**. Skylab experiment M-171 "Metabolic Activity"--results of the first manned mission. *Acta Astronaut* 2: 351–365, 1975.
15. **Michel EL**, **Rummel JA**, **Sawin CF**, **Buderer MC**, **Lem JD**. Results of Skylab experiment M171-metabolic activity. In: *Biomedical Results from Skylab, NASASP-377*, edited by Johnson RS, Dietlein LF. Washington, D.C.: National Aeronautics and Space Administration, 1977, p. 372–387.
16. **Moore AD**, **Downs ME**, **Lee SMC**, **Feiveson AH**, **Knudsen P**, **Ploutz-Snyder L**. Peak exercise oxygen uptake during and following long-duration spaceflight. *J Appl Physiol* 117: 231–238, 2014.
17. **Moore AD Jr**, **Barrows LH**, **Rahsid M**, **Siconolfi SF**. *Evaluation of Non-Invasive Cardiac Output Methods during Exercise, NASA Technical Paper 3174*. Washington, D.C.: National Aeronautics and Space Administration, 1992.

18. **Moore AD**, **Lynn PA**, **Feiveson AH**. The first 10 years of aerobic exercise responses to long-duration ISS flights. *Aerosp Med Hum Perform* 86: A78-86, 2015.

19. **Noonan V**, **Dean E**. Submaximal exercise testing: clinical application and interpretation. *Phys Ther* 80: 782–807, 2000.

20. **Rowell LB**. *Human Cardiovascular Control*. New York, NY: Oxford University Press, 1993.

21. **Rummel JA**, **Michel EL**, **Sawin CF**, **Buderer MC**. Medical experiment M-171: results from the second manned Skylab mission. *Aviat Space Environ Med* 47: 1056–1060, 1976.

22. **Shephard RJ**. Tests of maximum oxygen intake. A critical review. *Sports Med Auckl NZ* 1: 99–124, 1984.

APPENDIX A – ACRONYM LIST

BP	Blood Pressure
CO_2	Carbon Dioxide
ECWG	Exploration Clinical Working Group
$FECO_2$	Fractions of Expired Carbon Dioxide
FEO_2	Fractions of Expired Oxygen
HRP	Human Research Program
ISS	International Space Station
MOG	Medical Operations Group
NASA	National Aeronautics and Space Administration
O_2	Oxygen
PPFS	Portable Pulmonary Function System
Qc	Cardiac Output
SF_6	Sulfur Hexafluoride
SV	Stroke Volume
V_E	Expired Ventilation
VCO_2	Submaximal Carbon Dioxide
VO_2	Oxygen Consumption
VO_2max	Maximal Oxygen Consumption
W	Watt