Validation of the Pulmonary Function System for Use on the International Space Station

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Introduction

Aerobic deconditioning occurs during long duration space flight despite the use of exercise countermeasures (Convertino, 1996). As a part of International Space Station (ISS) medical operations, periodic tests designed to estimate aerobic capacity are performed to track changes in aerobic fitness and to determine the effectiveness of exercise countermeasures. These tests are performed prior to, during, and after missions of greater than 30 days in duration.

Crewmembers selected for missions aboard the ISS perform a graded exercise test on a cycle ergometer approximately 270 days prior to their scheduled launch date in order to measure peak oxygen consumption (VO_{2PK}) and peak heart rate (HRpk). Approximately 30 to 45 days prior to launch, crewmembers perform a submaximal cycle ergometer test at work rates set to elicit 25, 50 and 75% of their pre-flight VO_{2PK}. This test, known as the Periodic Fitness Evaluation (PFE), serves as a baseline measure to which subsequent in-and post-flight exercise tests are compared. While onboard the ISS, crewmembers are normally scheduled to perform the PFE beginning with flight day (FD) 14 and every 30 days thereafter. The PFE is also conducted 5 and 30 days following flight.

Using PFE data, aerobic fitness is estimated by quantifying the VO_2 vs. HR relationship using linear regression and calculating the VO_2 that would occur at the crewmember's previously measured HRpk. Currently, for data collected during flight, this technique assumes that the pre- vs. in-flight oxygen consumption per given cycle workload is similar. However, the validity of this assumption is based upon a sparse amount of data collected during the Skylab era (Michel, et al. 1977). The method of using heart rate and cycle ergometer work rates has been used to estimate aerobic fitness in normal gravity (Astrand and Ryhming, 1954; Lee, 1993). Due to spaceflight induced physiological alterations, such as shifts in extracellular fluid (e.g. plasma) volume, this method may not be valid during space flight. In addition, the ergometer onboard ISS is vibration-isolated and moves with the astronaut's application of force into the pedals. The effect of this movement on the VO_2 of cycle exercise on ISS has not been quantified.

Though the measurement of VO_2 during ISS flight has not been conducted to date, it has been a long-waived requirement found within the International Space Station Medical Operations Requirement Document (ISS MORD), Rev C. An attempt to meet this requirement was made using accessories for the Gas Analyzer System for Metabolic Analysis Physiology (GASMAP). The GASMAP is a mass spectrometer and was developed by the NASA's ISS Human Research Facility (HRF) to support multiple studies on-board ISS, including measurements of VO_2 during exercise. However, ground-based laboratory testing showed that, though the GASMAP mass spectrometer performed well in the analysis of static gas samples, the software used to measure VO_2 was not accurate (A. Moore, personal communication, February 2000). Subroutines within the software were unable to calibrate the turbine flowmeter using a standard three liter calibration syringe. Further, the delay calculation required to measure breath by breath VO_2 was continuously out of phase and unable to align the expired gas fractions with the corresponding expired ventilation measurement. When compared to the Johnson Space Center Exercise Physiology Lab's (EXL) reference metabolic gas analysis system,

the GASMAP was 24 and 11% higher for submaximal workloads of 25 and 50% VO_2 peak, respectively. It was concluded that without further design and software modifications, the GASMAP was not an adequate device for measuring VO_2 on ISS. The expense of engineering support and hardware modifications required to configure the GASMAP to perform accurate measures of VO_2 was considered prohibitive at the time and were not implemented.

A device capable of measuring exercise VO_2 on-board ISS has recently been developed by a contractor to the European Space Agency. The device, known as the Pulmonary Function Module/Photoacoustic Analyzer Module (PFM/PAM) is part of the ISS Pulmonary Function System (PFS). For the purposes of this report, the PFS/PAM and PFS will be referred to simply as the PFS. The PFS is located in the Human Research Facility (HRF) Rack 2 of the Destiny Laboratory on-board the ISS. The manufacturer of the PFS, Damec, (Damec Research ApS, Odense, Denmark) has a history of developing equipment designed to measure the effects of microgravity on the human respiratory system. Previous products by this company include the Respiratory Monitoring System (RMS) for the Anthrorack used during the Space Lab missions, the RMS-II used during the EuroMir 95 mission, and the Advanced Respiratory Monitoring System used aboard STS-107.

The PFS system was initially launched to the ISS aboard STS-114 (LF 1) in July 2005, followed by a hardware upgrade, which was launched on a Russian Progress supply vehicle on April 2006. A collaborative effort has been initiated between NASA and ESA Life Sciences personnel to integrate the use of the PFS into the PFE tests for the support of Medical Operations objectives. Jensen et al. (2002) performed an in depth comparison of the AMIS 2001, the commercial version of the PFS, versus the standard Douglas bag method and found that the system was reliable and accurate for measuring VO_2. However, prudence dictates that an evaluation of the flight-like PFS device is required to determine if it provides valid metabolic gas analysis prior to implementation on-board ISS.

Purpose

The purpose of this investigation was to compare exercise metabolic gas analysis measurements (including VO_2) obtained by the PFS to those collected using a reference metabolic gas analysis system (the ParvoMedics TrueOne© 2400 system). The ParvoMedics TrueOne© 2400 system has been extensively validated (Basset, et al, 2001; Crouter, et al, 2006) and is currently utilized by the NASA's Exercise Physiology Laboratory for pre- and post-flight testing astronauts assigned to ISS flights.

Methods

Subjects

Eight healthy male subjects volunteered to perform two peak cycle tests over a period of 12 days (Table 1). All subjects completed a modified Air-Force Class III physical exam prior to participation and received written and verbal explanations of test protocols before

providing written informed consent. Test protocols and procedures were reviewed and approved by the NASA-Johnson Space Center Committee for the Protection of Human Subjects.

Table 1. Subject Characteristics (mean ± SD)

Characteristic	n = 8
Age (yrs)	33 ± 6
Height (cm)	181.9 ± 5.0
Weight (kg)	82.2 ± 9.1
$VO_{2\ PK}$ ($l \cdot min^{-1}$)	4.55 ± 0.82
$VO_{2\ PK}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	55.9 ± 14.9

Protocol

Each subject performed two peak cycle ergometer tests. The ergometer used for testing was a LODE Excalibur Sport (LODE, AN Groningen, The Netherlands). Metabolic gas analysis was accomplished using one of two systems in random order: the ParvoMedics TrueOne© 2400 (ParvoMedics, Salt Lake City, UT) metabolic gas analysis system or the PFS. Subjects completed the two tests within a 12 day period. A minimum of 48 hours was allowed between each test to prevent residual soreness and fatigue. Sessions were conducted at approximately the same time of day, limiting variance to within ± 2 hours of the initial testing session to limit any circadian effect on physiological variance (Carter, 2002). Subjects were also requested to maintain the same dietary and sleeping habits throughout the testing period. Compliance was monitored through a subject screening form that was completed by the subject before each test.

Metabolic gas analysis was conducted continuously throughout the cycle test protocol (Figure 1). The cycle work rate was increased according to the protocol until the subject indicated that they could no longer continue. Each subject was allowed to choose their desired pedal cadence (revolutions per minute; RPM) and was required to maintain that same cadence throughout the two tests. Lepers, et al. (2001) found no difference in VO_2 when subjects were allowed to choose their optimal cadence between 70 and 100 RPMs. All test subjects in the current evaluation maintained a pedal cadence within a range of 80-100 RPMs.

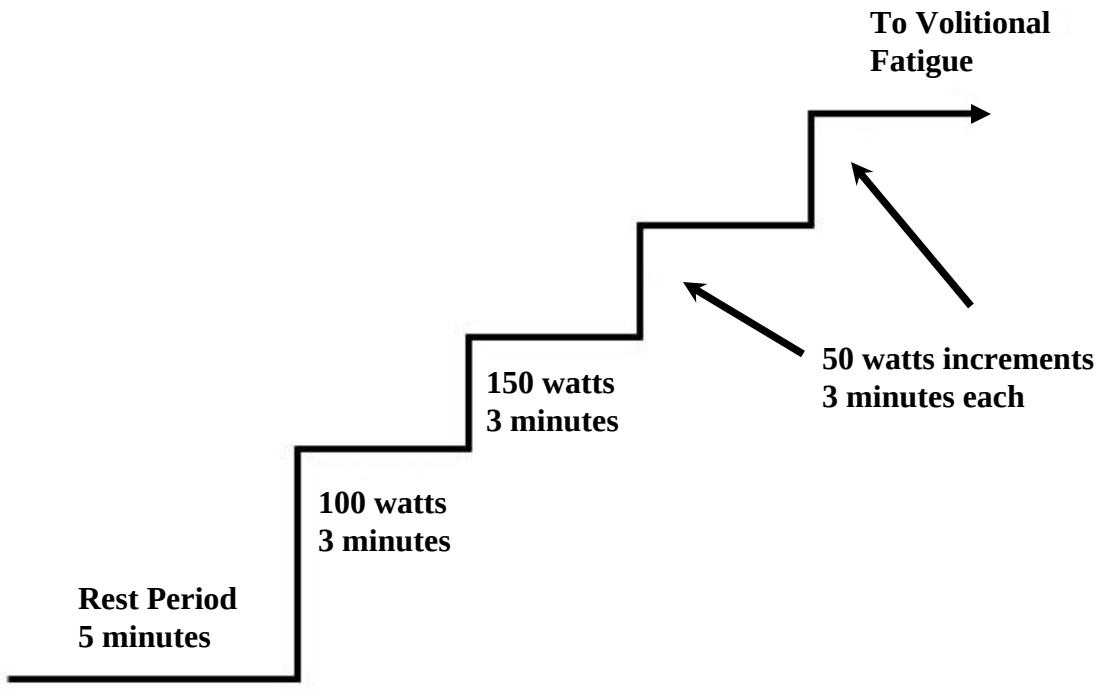

Figure 1. Peak Cycle Protocol

Heart rate was measured electrocardiographically (Q-Stress, Quinton Instruments, Seattle, WA) and blood pressure was measured using a mercurial sphygmomanometer and stethoscope. Ratings of Perceived Exertion (RPE) were reported during the last 30 seconds of each stage. Blood pressure was not recorded above 250 watts (W) if the subject showed a normal blood pressure response to increases in workload for workloads below 250 W. Immediately post exercise, blood pressure was recorded and the subject was monitored for any adverse effects caused by maximal exertion.

Metabolic Gas Analysis Systems Description

The ParvoMedics TrueOne© 2400 metabolic gas analysis system uses a paramagnetic oxygen analyzer (operating range 0-25% O_2) and an infrared single beam, single wave length carbon dioxide analyzer (operating range 0-15% CO_2) to measure the composition of expired gasses. The subject inspires through a two-way non-rebreathing valve (Hans Rudolph Model 2700, Kansas City, MO, USA) and expired air composition is analyzed in a 4 liter mixing chamber. The inspired gas composition is assumed to be standard atmospheric values (i.e. 20.93% O_2 and 0.03% CO_2). Expired ventilation is measured using a Hans Rudolph Model 3813 linear pneumotach (operating flow range 0-800 L/min). Computational software is provided with the system and runs with the Windows XP Professional operating system.

The Damec Pulmonary Function System uses two types of technology for gas analysis. For carbon dioxide, a photo-acoustic method of gas analysis is utilized. In this technique, the gas sample is exposed to intermittent infrared light. The gas sample absorbs the light

and the absorbed energy results in a rise in pressure by heating. The intermittent infrared light is divided into different pulsation frequencies and is filtered optically. Each optical filter allows only a specific wavelength of light to pass through and the wavelengths correspond to the infrared absorption spectra of the sample gasses. When the light-source is removed, the gas cools down, resulting in a pressure fluctuation. By choosing a pulsation frequency in the audible range, the pressure fluctuation becomes an acoustic signal which is detected by a microphone. The audible sounds recorded by the microphone are analyzed and the amplitude of each signal is used to calculate the gas concentration. The operating range for carbon dioxide is from 0-12%. Gasses other than carbon dioxide can be detected utilizing the photo-acoustic method, but an evaluation of these was beyond the scope of our investigation. For oxygen analysis, an Oxigraf™ sensor is used in the PFS. The Oxigraf™ technology is based on a laser diode absorption spectroscopy technique. The sample gas is exposed to a laser tuned to a wavelength of 760 nm (the peak of oxygen absorption). The laser signal is attenuated in proportion to the concentration of oxygen present in the sample. The operating range is from 0-100%.

When the PFS is used during exercise testing, the subject inspires through a custom-designed (Damec Research Aps., Odense, Denmark) two-way non-rebreathing valve and the expired gasses are sampled in a 15 liter anesthesia bag, which serves as a mixing reservoir. Inspired gas concentrations are measured on the inspired side of the respiratory circuit. This is done because inspired gas concentrations on board the spacecraft typically deviate slightly from normal atmospheric values. Ventilation is measured on the inspired side of the non-rebreathing valve using a Damec custom-designed pneumotach (operating flow range 0-900 L/min).

Metabolic Gas Analysis Data Reduction

Data were collected continuously by the ParvoMedics and PFS systems. Data were averaged in 30-second intervals to the nearest whole breath. Peak VO_2 was accepted as the highest VO_2 attained for a single 30-second period. The dependent variables in this investigation were VO_2, carbon dioxide production (VCO_2), pulmonary ventilation (V_E), and fractions of expired oxygen and carbon dioxide (F_EO_2 and F_ECO_2). Custom data reduction templates were created using Microsoft Excel (Microsoft Corporation, Redmond, WA).

Data collected using the ParvoMedics were automatically reduced to 30-second intervals by the ParvoMedics software. The exported data were further reduced using a data reduction template and averaged over the last 30-seconds of each stage. The ParvoMedics sampled the QRS signal directly from the Q-Stress ECG system and calculated heart rate. Heart rate data were reduced in the same fashion as the metabolic gas analysis variables.

Damec provided a Ground Support Equipment (GSE) software package to calculate the dependent measures from the raw data signals measured by the PFS. Similar to the ParvoMedics data, all PFS data were reduced in 30-second intervals and exported to Excel. A data cable to collect heart rate data from the Q-Stress ECG system directly by

the PFS was not available; therefore HR data were entered into the PFS data reduction template from the Q-Stress ECG printout.

Data Analysis

Data analysis for each dependent variable was conducted as a series of pre-planned comparisons (dependent T-tests with a Bonferroni adjustment made for multiple comparisons). This data reduction strategy was selected instead of the more traditional analysis of variance for two reasons. The first is that the dependent measurements (VO_2, VCO_2, and V_E) will increase with exercise intensity – there was no need for a statistical test to corroborate a physiological certainty. The second is that the primary question of interest involves determining if the measured metabolic gas analysis variables differed between the devices at any stage of exercise. Testing of this question is much more straightforward using preplanned comparisons. A significant difference was deemed to occur if $p<0.05$. A linear regression analysis comparing the VO_2 data collected from both devices across all exercise stages was also performed and confidence intervals developed for the slope and intercept of the relationship. Finally, a comparison of the peak VO_2 data attained from each of the devices was performed using a paired T-test.

Results

The average work rate attained by the subjects was 319 ± 53 W. All subjects completed each exercise stage through 250 W. Therefore, the planned comparisons of the dependent variables were conducted at 100, 150, 200 and 250 W.

Oxygen Consumption (VO_2)

Oxygen consumption did not differ between devices at 100, 200, and 250 W; however, a statistically significant difference between the devices was observed at the 150 W stage (Figure 2). The percent difference in VO_2 between the two devices was 5.4% at this stage. When the VO_2 values measured on the ParvoMedics and the PFS were compared using linear regression, the Pearson-Product moment correlation was high ($r=0.987$), indicating that 97.5% of the variance observed in the measure was shared between the two devices (Figure 3). In addition, the intercept of the relationship was not significantly different than 0 and the slope of the relationship did not differ from 1.0. The peak oxygen consumption of the subjects did not differ between the two systems (ParvoMedics: 4.47 ± 0.73 L/min; PFS: 4.64 ± 0.77 L/min, a 3.8% difference).

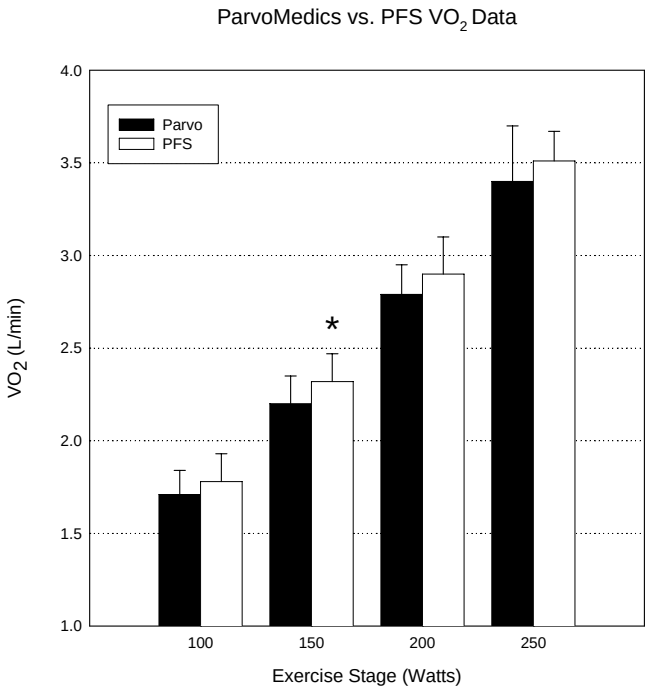

Figure 2. Comparison of ParvoMedics reference system and PFS measured VO_2 at the work-rates that all subjects could complete. * ($p<.05$ – difference between devices at indicated stage)

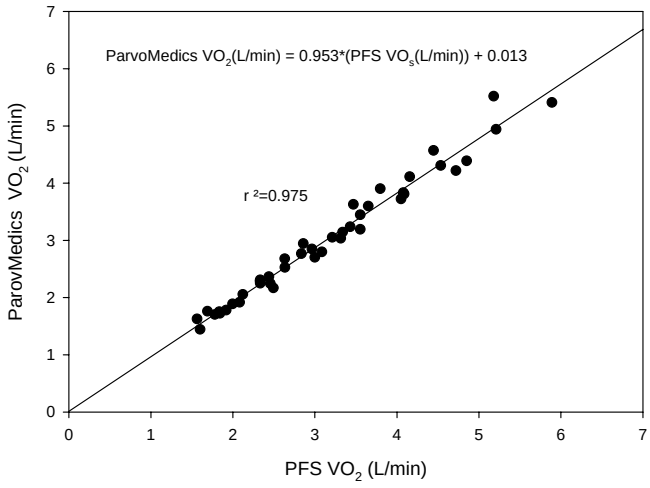

Figure 3. The relationship between all exercise VO_2 measurements collected by the ParvoMedics reference system and those made by the PFS.

Remaining Metabolic Gas Analysis Measures

None of the remaining metabolic gas analysis measures examined, i.e., VCO_2, V_E, FEO_2, and $FECO_2$, demonstrated any statistically significant differences between the ParvoMedics reference system and the PFS within any exercise stage (Figures 4-7).

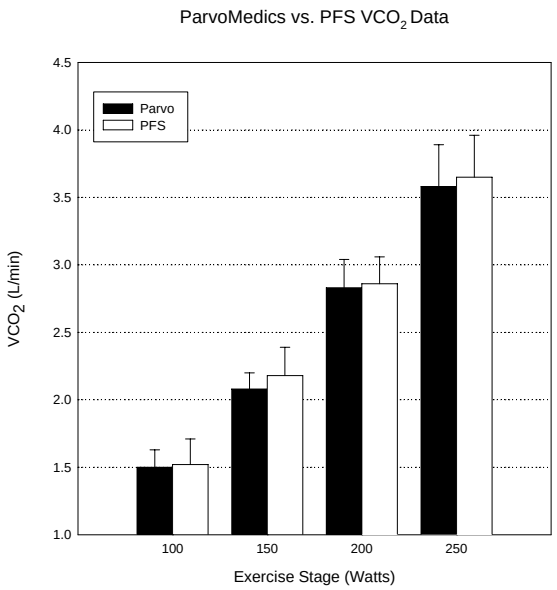

Figure 4. Comparison of ParvoMedics and PFS measured VCO_2 values.

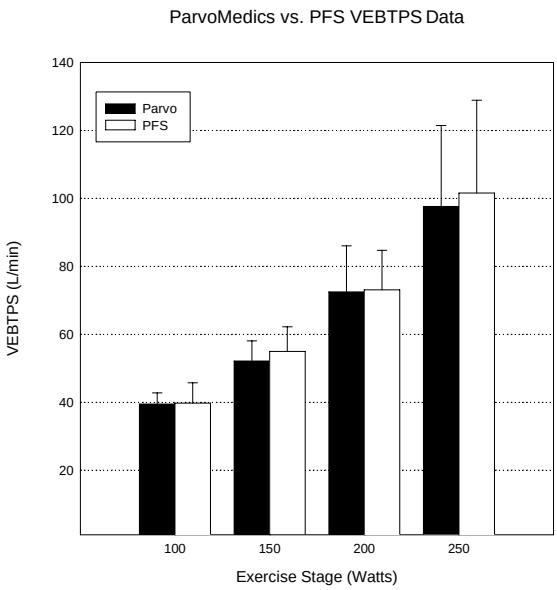

Figure 5. Comparison of ParvoMedics and PFS measured expired pulmonary ventilation values.

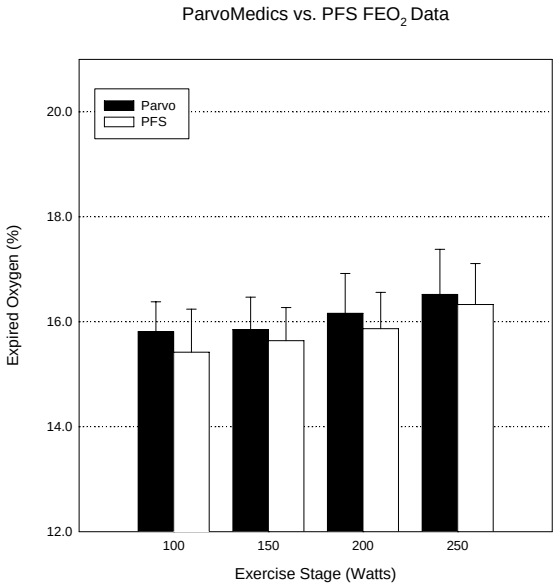

Figure 6. Comparison of ParvoMedics and PFS measured FEO_2 values.

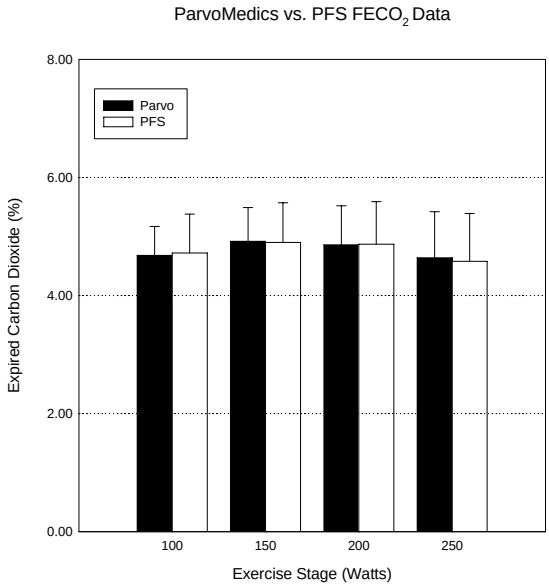

Figure 7. Comparison of ParvoMedics and PFS measured $FECO_2$ data.

Discussion

Comparison of metabolic gas analysis systems is complicated by human variability in day-to-day exercise responses and performance. One way to control for day-to-day variation in exercise responses is to test both systems simultaneously, either in series or in parallel. While this is possible using some systems, the investigators of the current study and the designers of the hardware concluded that use of the ParvoMedics system and the PFS simultaneously may induce error related to a novel test set up. For example, if the ParvoMedics was sampling "in-line" past the PFS, the increased pressure of gas passing through the ParvoMedics may change the mixing bag characteristics of the PFS. Thus, two separate tests were performed on the subjects. While every attempt was made to limit variation, including limiting testing for subjects to the same time of day, it has been reported that day to day variability in VO_2 ranges from 4 to 6% (Shephard, et al, 1984), while others have reported variability in VO_2pk as high as 10 to 12% (Versteeg, et al, 1989).

The ParvoMedics reference system and the PFS measures of VO_2 did not statistically differ for the majority of exercise stages examined (Figure 2). For the 150 W stage, the systems did statistically differ by 5.4%. This appears to be a random finding that has no apparent physiological or methodological explanation. One of the subjects did experience an unusually large difference between the two devices at that stage (2.49 L/min PFS vs. 2.17 L/min ParvoMedics, a 14.7% difference), and this undoubtedly contributed to the statistical difference. Consideration was given to removing the subject as an "outlier" from the data set, but because of the small sample size and the fact that all of the other stage data appeared normal for this subject, he was retained in the data set. From a clinical relevance stand-point, a 5.4% difference, i.e., the difference between the mean values of the two systems at 150 W, is within most of the day-to-day variations of VO_2 reported in the literature; therefore, based upon the stages of exercise examined, the two devices exhibited acceptable agreement. In addition, the peak VO_2 of the subjects demonstrated a non-significant difference of 3.8% between the two devices, also within the ranges reported in the literature of day-to-day variation in peak VO_2.

The VO_2 relationship between the two systems shows that the systems exhibit very close agreement. One would expect high agreement between two devices designed to measure the same physiological parameter, thus a high Pearson product moment coefficient of correlation (r); however, a high r alone does not ensure that the results between the two devices are similar (Bland and Altman, 1986). If a high r is coupled with the slope of the relationship being approximately 1.0, and an intercept near 0, the two devices can be judged as yielding similar results (Moore, et al, 1997). In the case of the current evaluation, the slope of the relationship between the ParvoMedics and PFS measurements of VO_2 did not significantly differ from 1.0, nor did the intercept differ from zero.

Interestingly, no differences were seen in expired pulmonary ventilation (V_E), even though the systems compute pulmonary ventilation using differing methods. Both the PFS and ParvoMedics use a differential pressure pneumotach to measure flow; however, the PFS measures flow on the inspiratory side, while the ParvoMedics measures flow on the expiratory side. The software of both systems uses the Haldane Transformation

correction (Luft, 1973) to correct for the differences in inspiratory and expiratory ventilation when calculating VO_2 and VCO_2. The PFS measures inspired ventilation, rather than the more traditional expired measurement, to minimize the chance of condensation or saliva contamination on the pneumotach surface. This design feature is important for space flight because traditional methods to reduce contamination from moisture contained in expired gas rely on gravity and thus would not work in the ISS environment.

Use of the PFS during exercise testing on-board ISS should provide improved accuracy of the estimates of aerobic fitness which currently rely on the assumption that VO_2 per given workload is similar on ISS to preflight measurements. However, the prediction of peak oxygen uptake from the heart rate response to submaximal exercise, even with gas exchange measurements, will still have limited accuracy. If accurate aerobic capacity measurements are desired by NASA, serious consideration must be given to the performance of maximal exercise testing with metabolic gas analysis.

In conclusion, laboratory evaluation of the PFS demonstrated that it provides similar results to those measured by the reference metabolic gas analysis system. It is recommended that the PFS be incorporated into the standard periodic fitness evaluation testing performed on board ISS.

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