Exercise-induced arterial hypoxemia in healthy young women; role of mechanical constraints to ventilation

by

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Abstract

Many young adult male athletes with a high maximal O_2 consumption ($\dot{V}O_{2Max}$) show exercise-induced arterial hypoxemia (EIAH). In women, EIAH may occur at submaximal exercise intensities and at lower fitness levels, but this is controversial. Greater EIAH in women may be attributed to their increased mechanical constraints to ventilation owing to smaller airway diameters. Accordingly, the purpose of this study was to characterize EIAH, gas exchange and respiratory mechanics during exercise in young healthy women. Subjects (n=31, $\dot{V}O_{2Max}$ =48±1, range 28-62 mL/kg/min) completed a step-wise maximal test on a treadmill. A 3-stage constant load exercise test was also completed where the inspired gas was switched between room air and heliox (21% O_2: 79% He). Arterial blood gases (P_aO_2, P_aCO_2, pH), corrected for esophageal temperature, and oxyhemoglobin saturation (S_aO_2) were measured at rest and during the last 30 s of each exercise stage. The work of breathing (WOB) was obtained using an esophageal balloon-tipped catheter. Expiratory flow limitation (EFL) was determined by superimposing tidal flow-volume loops on the maximum expiratory flow-volume curve. Twenty of the 31 women developed some degree of EIAH with a nadir P_aO_2 and S_aO_2 ranging from 58-103 mmHg and 87-98%; respectively. Subjects with EIAH were fitter ($\dot{V}O_{2Max}$ 51±1 vs. 42±2 mL/kg/min), had a greater $\dot{V}_{EMax}$ (91±3 vs. 77±4 L/min) and had an increased resistive WOB (30±2 vs. 19±1 cmH_2O/breath); for the EIAH and non-EIAH groups respectively ($P<0.05$). Six untrained subjects ($\dot{V}O_{2Max}$ <50 mL/kg/min) developed EIAH and 18/20 of the EIAH group were hypoxemia at submaximal intensities. Six distinct patterns of hypoxemia were observed indicating multiple mechanisms are responsible for EIAH in women. Fourteen subjects developed EFL and 12/14 who showed flow limitation also displayed EIAH. Inspiring heliox gas decreased the WOB by ~32% and partially reversed any EIAH. In conclusion, the pulmonary system response to progressive treadmill exercise in healthy young women is variable and distinct patterns of EIAH exist. EIAH appears to start at submaximal intensities and untrained women can develop hypoxemia. Mechanical ventilatory constraints can lead to or exacerbate EIAH in women, while inspiring heliox gas can partially reverse EIAH.

Preface

This thesis contains original data collected and analyzed for partial fulfilment of the author's Master of Science degree. All protocols were approved by the Clinical Research Ethics Board (Approval number: H10-03237) at the University of British Columbia.

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List of Abbreviations

Symbol	Definition
A	Alveolar
a	Arterial
A-aDO_2	Alveolar to arterial oxygen difference
a-vDO_2	Arterial to venous oxygen difference
ATPS	Atmospheric temperature pressure saturated
BMI	Body mass index
BSA	Body surface area
BTPS	Breathe temperature pressure saturated
C_aO_2	Oxygen content of arterial blood
C_vO_2	Oxygen content of venous blood
DLCO	Lung diffusion capacity for carbon monoxide
E_{el}	Expired elastic
E_{res}	Expired resistive
EFL	Expiratory flow limitation
EELV	End-expired lung volume
EILV	End-inspired lung volume
f	Breathing frequency
FRC	Functional residual volume
FV	Flow-volume
FEF_{75}	Forced expiratory flow at 75% forced vital capacity
FEF_{50}	Forced expiratory flow at 50% forced vital capacity
FEF_{25}	Forced expiratory flow at 25% forced vital capacity
FEV_1	Forced expiratory volume in 1 second
F_iO_2	Fraction of inspired oxygen
F_iCO_2	Fraction of inspired carbon dioxide
FVC	Forced vital capacity
gFVC	Graded forced vital capacity
Hct	Hematocrit

HR	Heart rate
Hb	Hemoglobin
I_{el}	Inspired elastic
I_{res}	Inspired resistive
IC	Inspiratory capacity
IFL	Inspiratory flow limitation
MFV	Maximal flow-volume
MEFV	Maximal expiratory flow-volume
MIP	Maximal inspiratory pressure
MVV	Maximal voluntary ventilation
ODC	Oxygen disassociation curve
P	Partial pressure
P_B	Barometric pressure
P_{eso}	Esophageal pressure
P_{H_2O}	Water vapour pressure
P_{mt}	Mouth pressure
P_{tp}	Transpulmonary pressure
$P_{st(50)}$	Static recoil pressure at 50% lung volume
P_aO_2	Partial pressure of oxygen in arterial blood
P_aCO_2	Partial pressure of carbon dioxide in arterial blood
P_AO_2	Partial pressure of oxygen in alveolar gas
P_ACO_2	Partial pressure of carbon dioxide in alveolar gas
PA	Pulmonary artery
PAV	Proportional assist ventilator
PAP	Pulmonary artery pressure
$P_{ET}CO_2$	Mixed end-tidal carbon dioxide tension
PEF	Peak expiratory flow
PV	Pressure-volume
$\dot{Q}$	Cardiac output
RER	Respiratory exchange ratio

RV	Residual volume
S_aO_2	Arterial oxyhemoglobin saturation
STPD	Standard temperature pressure dry
TLC	Total lung capacity
T_{am}	Ambient temperature
T_{eso}	Esophageal temperature
v	venous
$\dot{V}_A$	Alveolar ventilation
$\dot{V}_E$	Expired minute ventilation
$\dot{V}_{ECAP}$	Theoretical maximal expired minute ventilation
$\dot{V}_{ERES}$	Minute ventilation reserve
$\dot{V}_I$	Inspired minute ventilation
$\dot{V}O_2$	Oxygen consumption
$\dot{V}O_{2Max}$	Maximal oxygen consumption
$\dot{V}CO_2$	Carbon dioxide production
$\dot{V}CO_{2Max}$	Maximal carbon dioxide production
VC	Vital capacity
V_D	Physiological deadspace
V_{DV}	Deadspace of breathing valve
V_{FL}	Volume flow limited
V_T	Tidal volume
WOB	Work of breathing
WOB_{El}	Elastic work of breathing
WOB_{Res}	Resistive work of breathing

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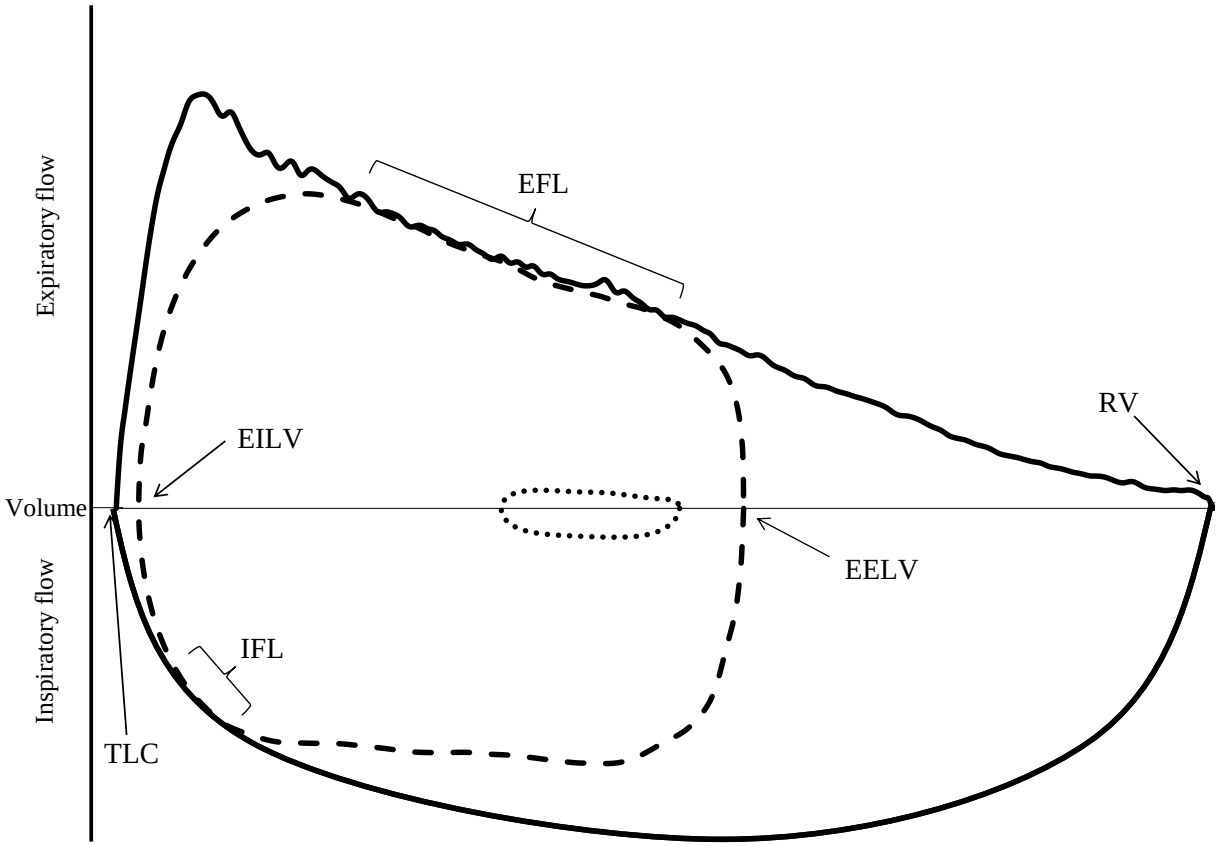
Introduction

When exercising at sea-level, healthy humans have long been thought to maintain arterial blood gases near resting levels throughout all intensities. Sporadic reports between the 1940's and 1960's however indicated that this belief may not be justified in all individuals (32, 46, 72). In the 1980's Dempsey *et al*. (12) confirmed these earlier reports in a study involving highly trained male runners whose arterial oxygen tension (P_aO_2) fell considerably (>20 mmHg) during progressive running exercise. The fall in P_aO_2 was coined exercise-induced arterial hypoxemia (EIAH). Broadly, EIAH can be viewed as a failure of the respiratory system to precisely match the cardiovascular and metabolic systems output (13). This idea of physiological systems mismatching was termed the "Demand vs. Capacity" relationship (11) and relies on the fact that the respiratory system shows little to no positive adaptations in response to exercise training (73). Conversely, the cardiovascular and metabolic systems both show considerable increases in maximal output in response to endurance training (73). The demand vs. capacity concept is able to explain EIAH at maximal exercise, as the respiratory system is functioning at maximal capacity, while the cardiovascular and/or metabolic systems are not. Put another way, the respiratory system can become the limiting factor in exercise. However, EIAH also occurs during submaximal exercise intensities, when the respiratory system has the capacity to increase alveolar ventilation ($\dot{V}_A$) and attempt to reverse the hypoxemia (12, 65). Therefore, while the demand vs. capacity theory can explain EIAH during intense exercise, it cannot describe why hypoxemia would be tolerated during submaximal exercise. To date, the mechanism(s) responsible submaximal hypoxemia in healthy humans remains a mystery.

Throughout numerous studies, we are able to characterize EIAH in men with the following: i) EIAH occurs in *some* highly trained men, ii) EIAH is associated with a large gas exchange inefficiency as indicated by an alveolar to arterial oxygen gradient ($A\text{-}aDO_2$) above 20-25 mmHg, iii) mechanical ventilatory constraints can lead to, or exacerbate, EIAH in some highly trained men, iv) the underlying mechanism behind EIAH is attributed primarily to $\dot{V}_A/\dot{Q}$ mismatching and secondary to relative alveolar hypoventilation, however, diffusion limitations or intracardiac/intrathoracic shunts have not been conclusively excluded, v) EIAH can be reversed by inspiring slightly hyperoxic gas (F_iO_2 0.26), resulting in an increased $\dot{V}O_{2Max}$ and increased exercise performance/tolerance and vi) EIAH can occur at submaximal exercise intensities (13).

The primary goal of increasing $\dot{V}_A$ during exercise is to maintain arterial blood gases at resting levels despite increasing metabolic demand. The dynamic regulation of $\dot{V}_A$ and ultimately blood gases is complex and connects many physiological systems with multiple feed-forward and feed-back loops, yet, the pulmonary mechanics responsible for respiration can be effectively reduced for ease of understanding and studying. Specifically, the respiratory system can be simplified into a series of air filled sacs that open to ducts and drain into a common vessel. As such, the respiratory system obeys the physical laws of flow through tubes and the maximal capacity of the respiratory system is dictated by these laws. As previously alluded to, the respiratory system is relatively fixed in its capacity to generate flow and volume. The primary measured variable that defines maximal ventilatory capacity is one's maximal flow-volume (MFV) curve (Figure 1).

Figure 1- Maximal flow-volume curve with resting and maximal tidal flow-volume loops for a healthy woman during cycle exercise.



Legend: Solid line represents the maximal flow-volume curve, hashed line represents maximal exercise tidal flow-volume loops and the dotted line represents a resting flow-volume loop. Definition of abbreviations: EELV, end-expiratory lung volume; EFL, expiratory flow limitation; EILV, end-inspiratory lung volume; IFL, inspiratory flow limitation; RV, residual volume; TLC, total lung capacity.

The MFV is said to be impenetrable, that is, all combinations of flow and volume must fall inside the outer boundary. In Figure 1, a MFV curve from a healthy woman along with a resting flow-volume (FV) loop and a maximal exercise FV loop is shown. At rest, there is considerable room to increase both inspiratory and expiratory flow and volume may increase via changes in end-inspiratory lung volume (EILV) and end-expiratory lung volume (EELV). However, at maximal exercise, the subject's tidal FV loop intersects the MFV curve on both the inspiratory and expiratory aspect, which is referred to as inspiratory flow limitation (IFL) and expiratory flow limitation (EFL); respectively. When a subject is flow limited, they are unable

to increase flow at a given volume. When flow limitation occurs, a subject's ventilation is mechanically constrained. Additionally, in Figure 1, EILV is approaching total lung capacity (TLC), therefore, any increases in tidal volume (V_T), must come from decreasing EELV. However, by decreasing EELV, the subject would experience a greater degree of EFL. Experiencing flow limitation is not a benign condition; rather it is associated with negative physiological outcomes. For example, EFL can cause relative hyperinflation, forcing the respiratory musculature to contract at less than optimal lengths and hasten fatigue (42). Additionally, EFL has been shown to decrease stroke volume (80) and increase the elastic work of breathing (WOB)(27). The interaction between the MFV curve and tidal FV loops results in a dynamic balance between increasing ventilatory demand and a static ventilatory capacity.

Previously, most research with regards to respiratory physiology used male subjects and there was not thought to be any sex-related differences, independent of gross size. However, this assumption is no longer justified as several sex-based differences with regards to the respiratory system have been identified and described. Specifically, even when matched for trunk height, women have smaller lungs (4) and smaller airways (50, 54, 76) compared to men. The smaller lungs and airways results in a reduced MFV curve for the average woman, when compared to a height matched man. Consequently, women often develop mechanical ventilatory constraints and have been shown to develop EFL more often and have a higher WOB when compared men (27, 52). Subsequently, at lower relative fitness levels, women show more mechanical constraints than men and some untrained woman can show EFL (15), a finding rarely reported in men. However, despite the above mentioned mechanical constraints, women appear to be more resistant to diaphragm fatigue then men (26).

Given the aforementioned sex-differences in the respiratory system which result in greater mechanical ventilatory constraints, it was hypothesized that women may be especially prone to developing EIAH. The hypothesis was that women would develop severe flow limitation and would be mechanically unable to increase $\dot{V}_A$ to adequately meet metabolic demands. Put in other words, some women may not show a strong hyperventilatory response to intense exercise and would be relatively hypoventilating. Indeed, this was confirmed in a study by Harms et al (30) who found that 75% of women tested developed some degree of EIAH. Surprisingly, some untrained women (maximal oxygen consumption ($\dot{V}O_{2Max}$) within 15% of predicted) developed EIAH, a finding which has not been reported in men. Similar to studies in

men, the degree of EIAH in women was found to be highly associated with the extent of the gas exchange inefficiency (30) and secondary to increasing mechanical ventilatory constraints (52). Similar to men, many of the women also began to display EIAH at submaximal exercise intensities. However, shortly thereafter, a similar study was conducted in which they found that women developed EIAH similar to men, in terms of severity and prevalence (33). That is, only trained women developed EIAH and the overall prevalence was ~24%. The methods and analysis were very similar between the two studies and cohorts were remarkably similar in anthropometrics, pulmonary function and fitness. Other studies have attempted to provide additional descriptive data on EIAH in women, but unfortunately, addressed a slight variation of the main questions (59, 85) or did not use optimal methodologies (24, 68, 88). Therefore, controversy still exists in the literature regarding EIAH in women and the necessary data to characterize this phenomenon is lacking. Specifically, a detailed assessment of mechanical ventilatory constraints, as it pertains to blood gas homeostasis, has not been done in women.

As such, the purpose of this study is to more fully characterize EIAH and mechanical constraints in women. Importantly, this study assesses EIAH directly by measuring arterial blood gases and correcting them for core temperature and mechanical constraints will be aided by using an esophageal balloon catheter. Specifically, the purpose of this study is fivefold. First, to determine if EIAH occurs in women more often than is commonly reported in men. Second, to see if untrained women can develop EIAH. Third, to assess EIAH at all exercise intensities. Fourth, determine the role of mechanical ventilatory constraints in EIAH and women. Fifth, assess how relieving some mechanical ventialtory constraints with heliox gas will affect EIAH.

HYPOTHESES

1. Women will develop EIAH more often than is commonly reported in men.
2. Some untrained women will develop EIAH.
3. Women will develop EIAH at submaximal intensities.
4. Mechanical ventilatory constraints will be associated with the occurrence of EIAH in women.
5. Inspiring heliox gas will partially reverse EIAH in women who show mechanical ventilatory constraints.

Methods

SUBJECTS

Forty-two, young (19-42 years), healthy, non-smoking women were recruited for testing. There was a failure to cannulate the radial artery in nine subjects. One subject withdrew before arterial cannulation was finished and testing could not be completed in 1 subject. Subjects where cannulation failed or did not complete all testing have been excluded from all analysis. Therefore, the analyzed group was 31. The cohort included subjects from a variety of athletic disciplines including endurance trained (competitive runners, cyclists, triathletes'), mixed aerobic/anaerobic trained (rugby, soccer, rowing, roller-derby), primarily anaerobically/strength trained (hockey, baseball), active but not trained and non-obese sedentary subjects, with a large range (28-62 mL/kg/min) of $\dot{V}O_{2Max}$ values. The large range of $\dot{V}O_{2Max}$ values was desired to i) test our hypothesis regarding EIAH in untrained women ii) to better extend our findings at a population level. Subjects were free of any current or previously diagnosed cardiorespiratory illness and were excluded if they had any form of asthma or if they presently or formerly had a tumour or ulcer in their esophagus. Testing occurred at random points throughout the subject's menstrual cycle and subjects were not excluded if they were taking oral contraceptives. Testing occurred at various times of days, with the environmental conditions remaining consistent between testing days (Table 1).

Table 1- Environmental conditions for testing

	Average	Range
Barometric pressure (mmHg)	752 ± 8	734-767
Humidity (%)	37 ± 5	29-46
Temperature (°C)	21 ± 1	19-23

Values are mean ± SD

EXPERIMENTAL OVERVIEW

Upon arrival to the study area, subjects completed consent forms, physical activity and general medical questionnaires (See Appendix C) followed by spirometry and diffusion capacity measures. All protocols were approved by the Clinical Research Ethics Board (Approval number: H10-03237) at the University of British Columbia, which conforms to the *Declaration*

of Helsinki. An arterial catheter was placed in the radial artery near the subjects' wrist. An esophageal balloon catheter and an esophageal temperature thermistor were then inserted and static recoil of the lungs and chest-wall were measured. Ten min of sitting resting metabolic and blood gas measures were obtained followed by assessment of functional residual capacity (FRC) in the standing position. Subjects' then performed several maximal inspiratory pressure maneuvers followed by several forced vital capacity (FVC) and graded forced vital capacity (gFVC) maneuvers. A maximal test to exhaustion on a treadmill was then performed. After completion of the maximal exercise test, 24 subjects completed a secondary exercise bout whereby they ran at a sub-maximal intensity while breathing heliox gas to reduce mechanical ventilatory constraints (see *Additional exercise bout* below).

MEASUREMENTS AND PROCEDURES

Spirometry and pulmonary diffusion

General pulmonary function measures (Spirolab II, Medical International Research) were performed according to ATS standards (4), including: FVC, forced expiratory volume in 1 second (FEV_1), % of FVC first second; forced expiratory flow at 25-75 % of expiration and peak expiratory flow (PEF). Subjects also practiced performing the inspiratory capacity (IC) and gFVC maneuvers with visual feedback. Pulmonary diffusing capacity for carbon monoxide (Collins DSI) was measured according to ATS standards (4). All values were compared to standardized reference values (4)

Arterial catheterization and blood sampling

Under sterile conditions, a physician inserted a 20-gauge arterial catheter (Radial Artery Catheter, Arrow International, Reading, PA) into the radial artery (approximately 3 cm proximal to the wrist) by percutaneous cannulation (Sledenger technique) after administering local anaesthesia (1% Xylocaine). The catheter was connected to a commercially available arterial blood sampling kit (VP1, Edwards Lifescience, Irvine CA) allowing for repeated blood samples and flushing of the sample line with 0.9% saline, the dead space between the catheter and sampling port was 3 mL. Subjects had a total of 100-250 mL of saline infused during all

flushing of the sample line. Before sampling, an excess of the dead space volume (~5 mL) was withdrawn into a non-heparinized syringe and discarded. Immediately thereafter, arterial blood samples (~3 mL) were collected in commercially available pre-heparinized syringes (Portex® Pro-Vent®, Smiths Medical, Keene NH) containing 23 I.U. per mL of dry lithium heparin. Pre-heparinized syringes were utilized to prevent clotting in the sampled blood. Additionally, care was taken to ensure adequate blood was sampled to prevent excessive heparin from compromising blood gas values. Blood samples had all air immediately evacuated and were repeatedly inverted manually to ensure the blood was fully mixed and there was homogeneity throughout the sample. Samples were analyzed within 2 min of sampling (most analyzed within 30 sec) with a calibrated blood gas analyzer (ABL Flex80 CO-OX, Radiometer, Copenhagen, Demark). Analyzed variables included: pH, P_aO_2, P_aCO_2, S_aO_2, Na^+, K^+, Cl^-, Ca^{2+}, [Hb], Hct, FO_2Hb, FCOHb, FMetHb, FHHb and $cHCO_3$. Total blood loss was estimated at 30-60 mL per subject, with none exceeding 100 mL. If $P_aO_2 < 85$ mmHg at rest, the sample was ran in duplicate or another sample was immediately obtained. All samples ran in duplicate were in close agreement.

Pressure measurement and esophageal temperature thermistor placement

A topical anaesthetic (Xylocaine ®, 2% Lidocaine Hydrochloride) was applied to the subjects' nares and nasal conchae before passing a balloon tipped latex catheter (no. 47–9005; Ackrad Laboratory, Cranford, NJ) through the nose. The balloon was positioned in the lower third of the esophagus to measure esophageal pressure and estimate pleural pressure. Subjects performed a brief Valsalva manoeuvre while the catheter was open to the atmosphere to empty the balloon, thereafter 1 mL of air was injected into the balloon using a glass syringe (56). The validity of the esophageal balloon position was assessed using a dynamic occlusion test before being secured in place with tape. The balloon catheter was connected to a piezoelectric pressure transducer (±100 cmH_2O; Raytech Instruments, Vancouver, BC, Canada). Mouth pressure was measured through a port in the mouth piece and connected to the same piezoelectric pressure transducer. The pressure transducer was calibrated at baseline and before and after each test using a digital manometer (2021P, Digitron, Torquay UK). Transpulmonary pressure was taken as the difference between mouth and esophageal pressure. An esophageal temperature thermistor (Ret-1, Physitemp Instruments, Clinton, NJ) was placed in the esophagus to the same

depth as the esophageal balloon catheter and connected to a temperature sensor (Thermalert TH-5, Physitemp Instruments, Clinton, NJ). Prior to placement, the thermistor and sensor was calibrated using in several water baths within a physiologically relevant temperature range (35-42 °C).

Static recoil

Static recoil at 50% FVC was determined using previously accepted methods (83). While standing, the subjects breathed through a mouth piece connected to a volume displacement spirometer (Ohio 822, Houston, Texas). The subjects were instructed to inhale to total lung capacity several times in order to gather an accurate volume history. The subjects then again inhale to total lung capacity and were asked to exhale passively; without the use of respiratory muscles. The expired tube was occluded during the expiration, for ~1 sec, and the subjects were told to relax during the occlusion. The occlusion occurred at 50% of FVC, as determined by the spirometer; volume was corrected to reflect inspiration under ATPS conditions and expiration of BTPS conditions. Static transpulmonary pressure was read during the middle of the cardiac oscillations (83).

Ventilatory and metabolic parameters

Subjects breathed through a low-resistance, two-way non-rebreathing valve (model 2700B, Hans Rudolph, Kansas City, MO) attached to large bore tubing. Inspired and expired flow was measured by separate, independently calibrated pneumotachographs (model 3813, Hans Rudolph, Kansas City, MO). Average resistance of the breathing circuit was 0.68 $cmH_2O/L/sec$ and ranged from 0.57-0.89 $cmH_2O/L/sec$ over a physiological range of flows (0.5-8 L/sec). Ventilatory and mixed expired metabolic parameters were gathered using a customized metabolic cart consisting of expired and inspired pneumotachographs and calibrated O_2 and CO_2 analyzers (Model S-3-A/I and Model CD-3A, respectively, Applied Electrochemistry, Pittsburgh, PA). Expired gas was collected in a 5 L mixing chamber and sampled via port near the rear of the chamber. Inspired and expired ventilation was measured directly with the pneumotachograph, additionally, inspired ventilation was calculated using the *Haldane* conversion. Before expired gas was analysed, the sample was drawn through bi-permeable *Nafion* tubing contained within an air-tight de-humidification chamber containing *Drierite*

(Anhydrous Calcium Sulfate) ensuring the gas was analysed dry; the gas remained in the sample line throughout drying and was not directly exposed to drying salts or subject to further mixing. All volumes were corrected using the *Gay-Lussac* ideal gas laws and are expressed in STPD.

Functional residual capacity, maximal inspiratory pressure and forced vital capacities

Functional residual capacity will differ depending on body position (i.e., standing vs. sitting) as the chest and abdominal wall's compliance changes slightly. Therefore, FRC measurements were performed in the standing position as it best represents a running stance. After standing, the subjects' were instructed to breath quietly for several min. Throughout the quiet breathing the subjects' were prompted to perform several inspiratory capacity (IC) maneuvers. The exact instructions given were "at the end of a normal breath out, take a maximal breath all the way in till you fill up your lungs." Next, subjects performed several maximal inspiratory pressure maneuvers (MIP) at FRC by inspiring through a mouth piece with a pin-hole opening. While standing, several FVC and gFVC were performed in order to construct the MEFV curve. FVCs were performed according to ATS standards (4). To perform gFVCs the subject were instructed to inspire maximally, but expire with a submaximal effort, but ensure all air is expired. Submaximal efforts ranged from 70-95% of maximum, as instructed by the experimenter. Both FVC and gFVC were performed immediately before and after the exercise bout. Post-exercise maneuvers account for any exercise related bronchodilation while the graded maneuvers are intended to minimize the effect of thoracic gas compression; both of which ensure EFL is not overestimated (25).

Maximal exercise test

During the exercise test, all subjects' wore a chest harness attached to a support structure around the treadmill (model TMX425C, Full Vision Inc, Newton, KA). The support structure was also used to keep the pneumotachographs, pressure transducer, pnuemotach heater, pneumotach amplifier and temperature sensor close to the subject and minimize any motion artefacts associated with running exercise. The test was a staged maximal test to exhaustion and consisted of between 3-9 stages. The starting workload was be determined during the self-selected warm-up and was between 3.5-5.5 mph at 0% grade. Every 2.5 min, the speed of the treadmill increased by 1 mph until a comfortable speed or 10 mph is reached. At this point the

grade of the treadmill was increased by 1% every 2.5 min until volitional fatigue. Heart rate and ratings of dyspnea and leg discomfort (according to Borg scale ((8)) were assessed every min. At approximately the 2 and 2.5 min mark of each stage the subjects were instructed to perform an IC maneuver. Immediately after the first IC maneuver a blood sample was drawn and analyzed. At maximal exercise, repeated blood samples were drawn without an associated IC maneuver. Several subjects had another blood sample taken immediately (<1 min) after exercise while sitting on a chair on the treadmill.

Constant load exercise bout

After performing the maximal exercise test, 24 subjects sat and rested until their esophageal temperature and ventilation returned to resting or near resting levels (15-20 min). All subjects were to eligible to participate in the constant load exercise bout, however, some could not due to either: time constraints, mental/physical fatigue or self-reported poor tolerance of instrumentation (esohageal balloon). After the initial 15-20 min, subjects continued to rest for an additional 5 min while ventilatory and metabolic parameters were gathered. Near the end of the final 5 min of rest, a blood sample was drawn and analyzed. Subjects then performed a bout of constant load exercise, with the intensity being 1 or 2 stages less than their maximal. The constant load exercise bout consisted of three phases where different inspirates were used. For the 1^{st} and 3^{rd} phase, the subject breathed room air, during the 2^{nd} phase the subject inspired heliox (20.93-21.17% O_2: balance He%) gas. The subjects were aware they would breathe a compressed gas, but were blinded to the gas composition or the intended effects. After testing, subjects were queried on any difference in breathing sensations during stage 2, after which, they were informed of the gas concentration and the desired effect. The heliox gas was humidified in a re-humidification chamber to achieve ~50% humidity. Each stage lasted between 2.5 and 3 min. During the final 30 sec of each stage, an IC maneuver was performed and a blood sample was drawn. Immediately after the 3^{rd} stage, the subject was switched back to breathing heliox gas and performed several FVC and gFVC maneuvers. The pneumotachographs were then recalibrated using heliox gas. The average resistance of the breathing circuit with heliox was 0.34 $cmH_2O/L/sec$ and ranged from 0.3-0.5 $cmH_2O/L/sec$ over a physiological range of flows (1.5-9.5 L/sec). Offline, data was segmented and ventilatory and metabolic were adjusted for the heliox gas containing a slightly different O_2 concentration and different humidity.

Repeated testing

Two subjects (AC and SW) were tested over multiple days in attempt to better understand underlying mechanisms behind their observed EIAH. Subject AC was tested a total of 4 times. The first two testing days occurred 4.5 months apart and were identical to the above outlined procedures. On the second testing day, a mildly hyperoxic hypercapnic inspirate (F_iO_2 0.22, F_iCO_2 0.035) was utilized rather than heliox for the constant load exercise bout. The mild hyperoxia was due to a gas supplier error. The hypercapnic gas was used to increase the drive to breath and determine if the subject mechanically could not breathe more (due to EFL) or they chose not to (chemosensitivity). During the third and fourth visit, the subject performed an identical maximal exercise test except without an arterial catheter or esophageal balloon catheter; therefore S_aO_2 was estimated via pulse oximetry and some respiratory mechanics were not assessed. For the third visit, the subject inspired a slightly hyperoxic gas (F_iO_2 0.26) for the entire test and on the fourth visit they inspired compressed room air; the subject was blinded to the condition. The hyperoxic gas was used for two reasons: 1) to eliminate the EIAH and to keep the S_aO_2 at resting levels, 2) test whether shunts were the primary mechanism behind the EIAH.

Subject SW was tested twice, 5 months apart, with identical procedures as outlined above. During the first test, the subject had recently recovered from an injury and was "relatively" untrained. For the second testing day, the subject had increased their $\dot{V}O_{2Max}$ and considered themselves fully trained while competing in middle distance running. For subject SW, we aimed to assess the effect of increased aerobic training on EIAH.

Data collection and processing

Raw data (flow, volume, pressure, ventilatory and mixed expired metabolic parameters) were recorded continuously at 200 Hz using a 16-channel analog-to-digital data acquisition system (PowerLab/16SP model ML 795, ADI, Colorado Springs, CO) and stored on a computer for subsequent analysis (LabChart v7.1.3, ADInstrument, Colorado Springs, CO). Blood gas values were extracted from the blood gas analyzer and stored on a computer for analysis and temperature correction.

DATA ANALYSIS

Maximal expiratory flow volume curve and operational lung volumes

MEFV curves were defined as the highest flow at any given volume. This was determined by aligning pre and post exercise FVC and gFVC maneuvers to the highest volume, which represent the subjects' forced vital capacity. With all maneuvers superimposed upon each other, the highest expiratory flow in 10 mL volume segments were taken as the outer boundary of the MEFV curve. End-expired lung volume was estimated by subtracting the IC volume from the subject's FVC. End-inspired lung volume was determined by adding the tidal volume to end-expired lung volume. Volumes were corrected for any pneumotachograph drift using customized software (IC of DOOM, LabVIEW software V6.1; National Instruments, Austin, TX). Additionally, peak esophageal pressure during the IC maneuver was used to ensure the subject attained similar peak pressures.

Flow-volume and pressure-volume loops and expiratory flow limitation

Composite average flow-volume and pressure-volume loops were generated using customized software (BIBO, LabVIEW software V6.1; National Instruments, Austin, TX). Between 8 and 15 breaths were used for the construction of the averaged loop and were taken immediately before the IC maneuver. The flow-volume loops were aligned on the MEFV curve according to end-expiratory lung volume. Expiratory flow limitation was determined by dividing the part of the tidal flow-volume loop that intersects with the MEFV curve by the tidal volume. Expiratory flow limitation was only considered if > 5% of the tidal volume intersected the MEFV curve (14).

Work of breathing

The energetic work of breathing was estimated by construction of modified Campbell diagrams (71) and integration of transpulmonary pressure-volume (PV) loops. For modified Campbell diagrams, a tidal volume-esophageal pressure loop from the previous analysis was graphed and the zero flow points at end-inspiratory and end-expiratory lung volume were connected with a line representing the dynamic compliance of the lungs, the compliance of the

chest-wall was estimated using data from previously published work (19). The functional residual capacity was set as the intersection of the chest-wall and lung compliance lines. The area enclosed by the volume-pressure loop was split into its four constituent parts: inspiratory resistive work, expiratory resistive work, expiratory elastic work and inspiratory elastic work; with the latter two having an additional component added that falls outside the enclosed loop. The four components were summed and multiplied by breathing frequency, and expressed in J/min. The PV loops were constructed from similar breaths as outlined above, except transpulmonary pressure was utilized. This form of analysis is able to discern between inspiratory elastic work, inspiratory resistive work and total expiratory work. The distinction is accomplished by first connecting EELV and EILV with a straight line, representing the total system compliance. A right angle triangle was created by connecting an iso-pressure line from EELV to an iso-volume line from EILV. The area bound by the triangle represents the inspiratory elastic component and needs to include the portion falling outside the PV curve to include all appreciable work. Inspiratory elastic work is needed to overcome the lungs tendency to recoil inwards and is a function of the specific compliance at which the ventilation occurs at. The area bound by the total compliance line and the lower part of the PV curve from EELV to EILV represents the inspiratory resistive work. The three components were summed and multiplied by breathing frequency, and expressed in J/min.

To facilitate comparisons between individuals and groups, each individual had a regression equations fitted to relationship between WOB and $\dot{V}_E$. The equation used is similar to that described by Otis (60) and employed by others (27) and is described by

$$WOB = a \cdot \dot{V}_E^{\,3} + b \cdot \dot{V}_E^{\,2}$$

where WOB is the work of breathing in J/min, *a* is the constant for the resistive component, *b* is the component for the viscous component and $\dot{V}_E$ is expired minute ventilation. The resistive component of the WOB is to overcome the resistance to airflow and is linked to airway size and geometry. The viscous component of the WOB is to deform elastic and non-elastic lung tissue and is similar between most healthy individuals.

To determine the mechanical efficiency of breathing, we utilized equations described by Otis et al (61). These equations determine the optimal *f*, which minimizes work, for a given $\dot{V}_A$ and deadspace. Frequencies above the nadir result in increased viscous and turbulent work (due to higher flows and deadspace ventilating), while *f* below result in significantly greater elastic

work (due to large tidal volume). Each subject's optimal *f* for every $\dot{V}_A$ and the associated minimal work was compared to the measured *f* and estimated work. For every stage we obtained an absolute inefficiency in work described by the following equation

$$W_{Ineff} = \frac{\sum \Delta W}{n}$$

where W_{Ineff} is the average absolute inefficient work, ΔW is the absolute deviation of work from the minimal and n is the number of V_A used. However, as $\dot{V}_A$ increase, the work increased exponentially, therefore, the inefficient work was also calculated relative to minimal work; as described by the following equations

$$W_{Ineff(\%)} = \frac{\sum ((\frac{\Delta W}{W_{Min}}) * 100)}{n}$$

where $W_{Ineff(\%)}$ is the average relative inefficient work, ΔW is the absolute deviation of work from the minimal, W_{Min} is the minimal work at the given $\dot{V}_A$ and n is the number of $\dot{V}_A$ used in the calculation

Dynamic compliance

Dynamic compliance was determined by adapting the technique described by Mead and Whittenberger (55). This technique relies on the transpulmonary pressure-volume and flow-volume loops created from the previous analysis (*see Flow-volume and pressure-volume loops above)*. Dynamic compliance was determined by dividing the transpulmonary pressure difference between the two zero flow points (end-inspiration and end-expiration) by the volume change and expressed in mL/cmH_2O.

Ventilatory capacity

The method used to estimate ventilatory capacity ($\dot{V}_{ECap}$) is similar to that described by Johnson *et al.* (55) and Jensen *et al*. (40, 43). This method determines the theoretical ventilation if the subject breathed exclusively along their MEFV curve for a given tidal volume and end-expiratory lung volume. The flow-volume loop used were the same as determined from the previous analysis (*see Flow-volume and pressure-volume loops above)*. The volume of the tidal breath was divided into volume equal segments; ranging from 30-40 mL. Each volume segment

is then divided by the corresponding maximal expiratory flow to give an estimated minimal expiratory time. All equal volume segments are summed to give a minimal expiratory time for the tidal breath. Inspiratory time will be determined using the inspiratory-to-total breathing cycle time ratio. Maximal breathing frequency is determined after the minimal tidal breath time is calculated. Measured tidal volume and calculated maximal breathing frequency are multiplied to give the $\dot{V}_{ECap}$ for each stage. Ventilatory reserve is the difference between ventilatory capacity and measured minute ventilation.

Dysanapsis

The degree of dysanapsis was determined using the ratio originally proposed by Mead (75): a measurement sensitive to lung size versus a measurement sensitive to airway size. This estimate was used to assess differences in relative airway size by minimizing the confounding effect of absolute lung volume. Lung size was determined using the FVC, and airway size was estimated using the following equation;

$$AS = \frac{FEF_{50}}{FVC \cdot Pst_{50}}$$

where AS is airway size, FEF_{50} is forced expired flow at 50% forced vital capacity, FVC is forced vital capacity and Pst_{50} is static recoil of the lungs and chest-wall at 50% forced vital capacity.

Calculations and corrections for environmental conditions

Water vapour pressure was calculated using the following formula;

$$P_{H_2 0} = \%Hu \cdot (13.955 - (0.6584 \cdot T) + (0.0419 \cdot T^2))$$

where P_{H2O} is the water vapour pressure, % Hu is the percent humidity and T is ambient temperature. Water vapour pressure was used to correct gas concentrations for different ambient environmental conditions. Physiological deadspace was calculated using the standard equation;

$$V_D = V_T \cdot \frac{P_a CO_2 - P_{\overline{ET}} CO_2}{P_a CO_2} - V_{DV}$$

where V_D is physiological deadspace, V_T is tidal volume, P_aCO_2 is temperature corrected arterial carbon dioxide tension, $P_{ET}CO_2$ is mixed end-tidal carbon dioxide tension and V_{DV} is the

breathing valve deadspace (105mL). Blood gases were corrected for any temperature and pH changes associated with exercise according to standard formulas (75). Alveolar PO_2 was estimated using a modification of the alveolar gas equation;

$$P_AO_2 = F_iO_2 \cdot (P_B - P_{H_20}) - \frac{P_aCO_2}{RER} \cdot (1 - F_iO_2(1 - RER))$$

where P_AO_2 is ideal alveolar O_2, F_iO_2 is the fraction of inspired oxygen (room air 20.93 or heliox oxygen content), P_B is daily barometric pressure, P_{H2O} is the saturated water vapour pressure at *esophageal temperature*, P_aCO_2 is temperature corrected arterial carbon dioxide tension and RER is respiratory exchange ratio. The A-aDO_2 was derived by subtracting P_aO_2 from P_AO_2. Oxyhemoglobin saturation was measured directly by the blood gas analyzer and S_aO_2 was also calculated if pH, temperature and P_aCO_2 remained unchanged from ideal resting conditions (7.4, 37°C, 40 mmHg; respectively) (indicating what percent of the desaturation was due solely to changes in P_aO_2) and if P_aO_2 remained at resting levels, but with pH, temperature and P_aCO_2 at their respective levels. Arterial oxygen content was determined using the equations;

$$C_aO_2 = (1.39 \cdot Hb - \frac{S_aO_2}{100}) + 0.003 \cdot P_aO_2$$

where C_aO_2 is arterial oxygen content, Hb is hemoglobin concentration (g/dL), S_aO_2 is oxyhemoglobin saturation and P_aO_2 is arterial oxygen tension. Arterial oxygen content was calculated using: directly measured values obtained by blood gas analysis, S_aO_2 and P_aO_2 at resting levels (indicating an ideal situation), S_aO_2 due to only P_aO_2 decrease and S_aO_2 due to temperature, pH and P_aCO_2 changes. The latter two intended to identify which aspect influenced C_aO_2 the most. Alveolar ventilation was calculated using the alveolar ventilation equation;

$$\dot{V}_A = (\frac{\dot{V}CO_2}{P_aCO_2}) \cdot K$$

where $\dot{V}_A$ is alveolar ventilation, $\dot{V}CO_2$ is carbon dioxide production, P_aCO_2 is arterial tension of carbon dioxide and K is a constant (0.863). For all subjects at maximal and near maximal intensities, we determined the theoretical $\dot{V}_A$ and $\dot{V}_E$ needed to maintain P_aO_2 at resting levels. This was accomplished by determining the P_AO_2 needed to return P_aO_2 to resting levels, using the concurrent A-aDO_2 for every stage, as it is not possible to accurately estimate any changes A-aDO_2 for a given increase in ventilation. After P_AO_2 was determined, the alveolar gas

equation was resolved to indicate what the P_aCO_2 would be for this increased ventilation. The estimated P_aCO_2 was then used in the alveolar ventilation equation (along with concurrent $\dot{V}CO_2$) to predict the needed $\dot{V}_A$. Measured dead-space space ventilation for each workload was used to predict $\dot{V}_E$. Bicarbonate content was calculated using temperature corrected pH and P_aCO_2 values according to the following equations;

$$HCO_3^{-1} = 0.23 \cdot P_aCO_2 \cdot 10^{(pH - pKp)}$$

where HCO_3^{-1} is bicarbonate (mmol/L), P_aCO_2 is arterial tension of carbon dioxide, pH is the negative base of hydrogen ions in solution and pKp is negative log base of the acid dissociation constant calculated with the following equations;

$$pKp = 6.125 - \log(1 + 10^{(pH - 8.7)})$$

Statistical analysis

Pearson product moment correlations were used to determine relationships between selected variables. All subjects were pooled together and compared at different percentages of their $\dot{V}O_{2Max}$ (Rest (~8%), 60, 80, 90, 100%) using a repeated measures analysis of variance. When significant F ratios were detected, Tukey's post-hoc test was used. Subjects were also partitioned into groups based on the appearance of EIAH (EIAH and NEIAH group) and any EFL (EFL and NEFL). We utilized the common definition of EIAH, which is a 10 mmHg decrease in P_aO_2 during exercise, compared to rest (13). The EIAH group was compared to the NEIAH group at rest and at different percentages of their $\dot{V}O_{2Max}$ using unpaired t-tests with bonferroni corrections. Independently, EFL and NEFL groups were comparing using similar methods. For the heliox trial, only subjects who previously showed EIAH were included. Using a repeated measures analysis of variance, rest, air breathing and heliox time points were compared. When significant F ratios were detected, Tukey's post-hoc test was used. The group that completed the constant load exercise test were subdivided based on the appearance of EFL. The EFL and NEFL groups for the heliox trail were at rest, air breathing and heliox breathing compared using unpaired t-tests with bonferroni corrections. Before any bonferroni corrections, alpha was set at 0.05.

Results

DESCRIPTIVE DATA

Anthropometric and resting pulmonary function values for the cohort as a whole are shown in Table 2. Pulmonary function was similar to predicted values, however, there was considerable variation, where values ranged from 80-120% of predicted. No subjects were excluded for pulmonary function <80% of predicted. Descriptive characteristics based upon the appearance EIAH (n=20, 65%) are shown in Table 2. The EIAH and NEIAH groups were similar with respect to all variables except diffusion capacity. Based on criteria used by others (30), 10 subjects showed mild EIAH (P_aO_2 decrease 10-15 mmHg from rest), 5 showed moderate EIAH (P_aO_2 decrease 15-20 mmHg from rest) and 5 showed severe EIAH (P_aO_2 decrease +20 mmHg from rest). Eighteen subjects showed EIAH at submaximal intensities, defined as intensities at least 1 exercise stage below the maximal. One subject (CM) displayed EIAH at submaximal intensities, but not at maximal intensity, while all other EIAH subjects maintained a P_aO_2 10 mmHg below rest at maximal exercise. Six subjects with a $\dot{V}O_{2Max}$ < 50 mL/kg/min showed EIAH, with three having a $\dot{V}O_{2Max}$ < 45 mL/kg/min. Table 3 displays descriptive characteristics for subjects split into groups based on the appearance of EFL. The NEFL groups had superior lung function, while the groups were similar anthropometrically (Table 3). The average severity of EFL was 39% of V_T, ranging from 14-69%. Six subjects showed EFL at exercise intensities other than maximum.

Table 2- Descriptive variables for thirty-one subjects based on the appearance of any EIAH

	All		EIAH (n=20)		NEIAH (n=11)	
	Value	Range	Value	Range	Value	Range
Age (yrs)	26 ± 1	19-42	27 ± 2	19-42	25 ± 2	19-34
Height (cm)	168 ± 1	157-188	169 ±1	161-179	167 ± 3	157-188
Weight (kg)	62 ± 1	48-81	62 ± 1	51-72	65 ± 3	48-81
BMI (kg/m^2)	22.4 ± 0.4	18-29.4	21.9 ± 0.5	18.0-25.7	23.3 ± 0.9	18.5-29.4
BSA (m^2)	1.72 ± 0.02	1.47-2.05	1.71 ± 0.02	1.50-1.88	1.74 ± 0.05	1.47-2.05
Hb (g/dL)	12.1 ± 0.1	10.1-13.4	12.7 ± 0.2	11.3-13.7	12.0 ± 0.3	10.1-13.2
Hct (%)	37 ± 1	31-42	37 ± 1	35-42	37 ± 1	31-41
FVC (L)	4.0 ± 0.1	2.9-4.8	4.0 ± 0.1	2.9-4.8	4.0 ± 0.1	3.7-4.7
% Pred	104 ± 2	82-120	103 ± 2	82-118	105 ± 2	95-120
FEV_1 (L)	3.4 ± 0.1	2.7-4	3.4 ± 0.1	2.7-4.0	3.4 ± 0.1	3.0-3.9
% Pred	101 ± 2	84-116	101 ± 2	84-116	100 ± 2	84-112
FEV_1/FVC (%)	85 ± 1	69-95	86 ± 1	69-95	85 ± 2	73-93
% Pred	102 ± 1	81-122	102 ± 2	81-122	100 ± 2	88-112
PEF (L/sec)	7.9 ± 0.2	4.5-10.1	8.1 ± 0.3	4.5-10.1	7.4 ± 0.3	6.2-8.9
FEF_{75} (L/sec)	6.6 ± 0.2	4.5-8.9	6.8 ± 0.3	4.5-8.9	6.3 ± 0.2	5.5-7.2
FEF_{50} (L/sec)	4.6 ± 0.2	2.9-7.5	4.7 ± 0.3	2.9-7.5	4.5 ± 0.2	3.1-5.3
FEF_{25} (L/sec)	2.4 ± 0.2	0.8-4.9	2.4 ± 0.2	0.8-4.9	2.2 ± 0.2	1.3-3.5
DLCO (mmHg/ml/min)	27.2 ± 0.9	20.3-37.3	28.2 ± 1.0	22.1-37.2	24.7 ± 1.5	20.6-32.8
% Pred	103 ± 4	81-144	109 ± 4	85-144	91 ± 5*	81-116
MIP (cmH_2O)	97 ± 4	41-134	97 ± 5	62-134	98 ± 7	41-13
% Pred	123 ± 5	50-173	122 ± 7	69-173	123 ± 9	50-157

All values are mean ± SE. EIAH, exercise induced arterial hypoxemia; NEIAH, no exercise induced arterial hypoxemia; yrs, years; BMI, body mass index; BSA, body surface area; Hb, hemoglobin; Hct, hematocrit; FVC, forced vital capacity; Pred, predicted; FEV_1, forced expired volume in 1 sec; PEF, peak expiratory flow; FEF_{75}, forced expiratory flow at 75% FVC; FEF_{50}, forced expiratory flow at 50% FVC; FEF_{25}, forced expiratory flow at 25% FVC; DLCO, carbon monoxide diffusion capacity of the lung; MIP, maximal inspiratory pressure. * significantly different from EIAH group ($P < 0.05$).

Table 3- Descriptive variables for thirty-one subjects based on the appearance of any EFL

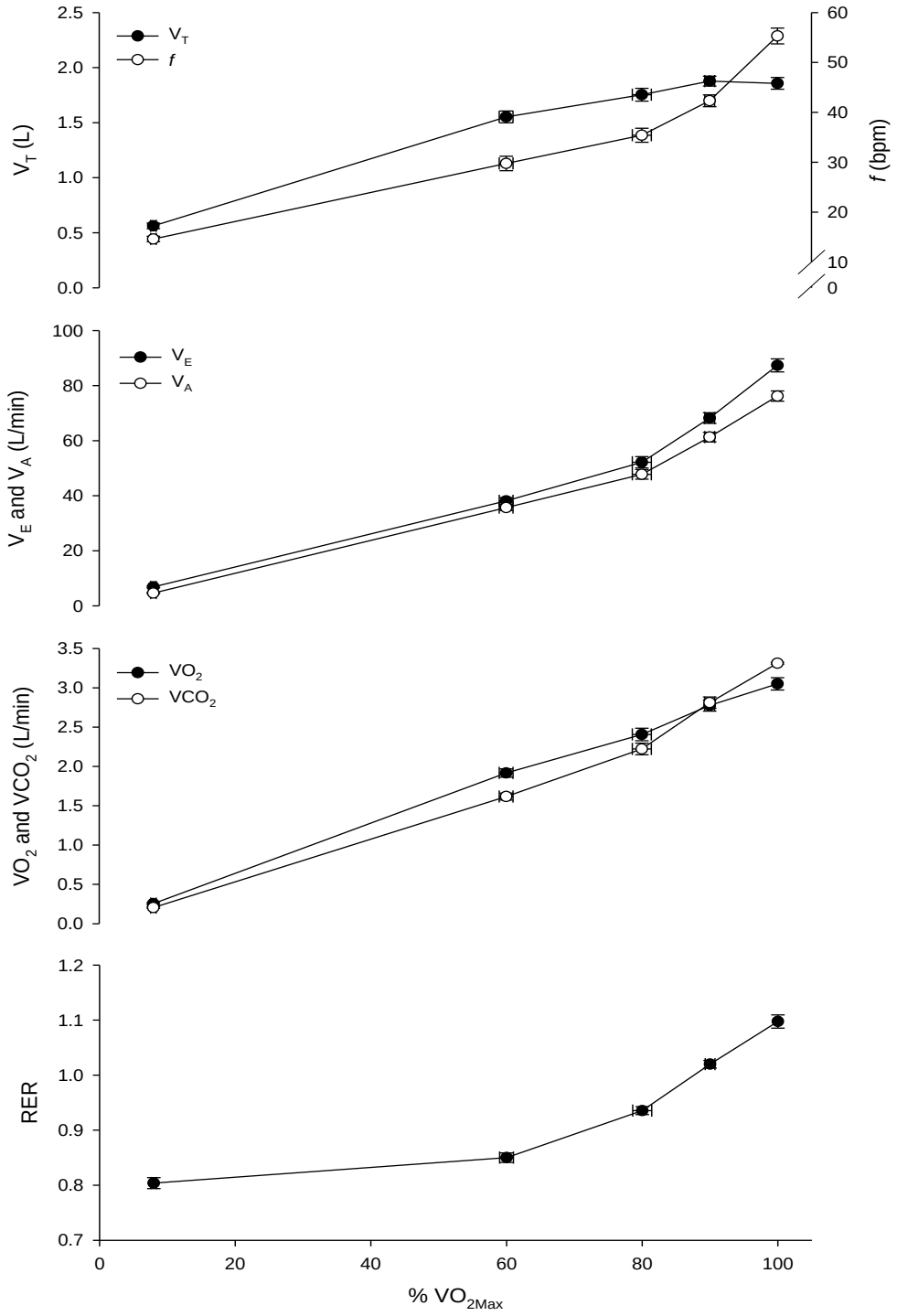
	EFL (n=14)		NEFL (n=17)	
	Value	Range	Value	Range
Age (yrs)	26 ± 2	19-38	26 ± 2	19-42
Height (cm)	168 ± 1	161-177	169 ± 2	157-188
Weight (kg)	64 ± 2	51-74	63 ± 2	48-81
BMI (kg/m^2)	22.8 ± 0.6	19.5-26.9	22.0 ± 0.7	18-29.4
BSA (m^2)	1.7 ± 0.03	1.5-1.9	1.7 ± 0.03	1.5-2.1
Hb (g/dL)	11.8 ± 0.2	10.1-12.8	12.3 ± 0.2*	11.1-13.7
Hct (%)	36 ± 0.6	31-39	38 ± 0.5*	34-44
FVC (L)	4.0 ± 0.1	2.9-4.8	4.1 ± 0.1	3.5-4.7
% Pred	101 ± 2	82-114	105 ± 2	95-120
FEV_1 (L)	3.3 ± 0.1	2.7-3.9	3.5 ± 0.1*	3.1-4
% Pred	97 ± 2	84-112	104 ± 2*	84-116
FEV_1/FVC (%)	84 ± 2	69-95	86 ± 1	73-95
% Pred	101 ± 3	81-122	102 ± 2	88-112
PEF (L/sec)	7.8 ± 0.4	4.5-10.1	8.0 ± 0.2	6.6-9.8
FEF_{75} (L/sec)	6.4 ± 0.4	4.5-8.7	6.8 ± 0.2	5.5-8.9
FEF_{50} (L/sec)	4.6 ± 0.3	2.9-6.6	5.0 ± 0.2*	3.1-7.5
FEF_{25} (L/sec)	1.9 ± 0.2	0.8-4.5	2.7 ± 0.2*	1.3-4.9
DLCO (mmHg/ml/min)	27.8 ± 1.5	22.1-35.6	26.8 ± 1.2	20.6-37.3
% Pred	106 ± 6	89-138	102 ± 5	81-144
MIP (cmH_2O)	100 ± 6	62-134	95 ± 5	41-123
% Pred	126 ± 9	69-173	120 ± 7	50-160

All values are mean ± SE. EFL, expiratory flow limited; NEFL, no expiratory flow limitation; yrs, years; BMI, body mass index; BSA, body surface area; Hb, hemoglobin; Hct, hematocrit; FVC, forced vital capacity; Pred, predicted; FEV_1, forced expired volume in 1 sec; PEF, peak expiratory flow; FEF_{75}, forced expiratory flow at 75% FVC; FEF_{50}, forced expiratory flow at 50% FVC; FEF_{25}, forced expiratory flow at 25% FVC; DLCO, carbon monoxide diffusion capacity of the lung; MIP, maximal inspiratory pressure. * significantly different from EFL group ($P < 0.05$).

EXERCISE RESPONSE FOR ALL SUBJECTS

Figure 2 shows ventilatory and metabolic measures during incremental treadmill exercise test. The subjects, as a whole, demonstrated the expected response with respect to all variables.

Figure 2- Metabolic and ventilatory variables during maximal exercise test



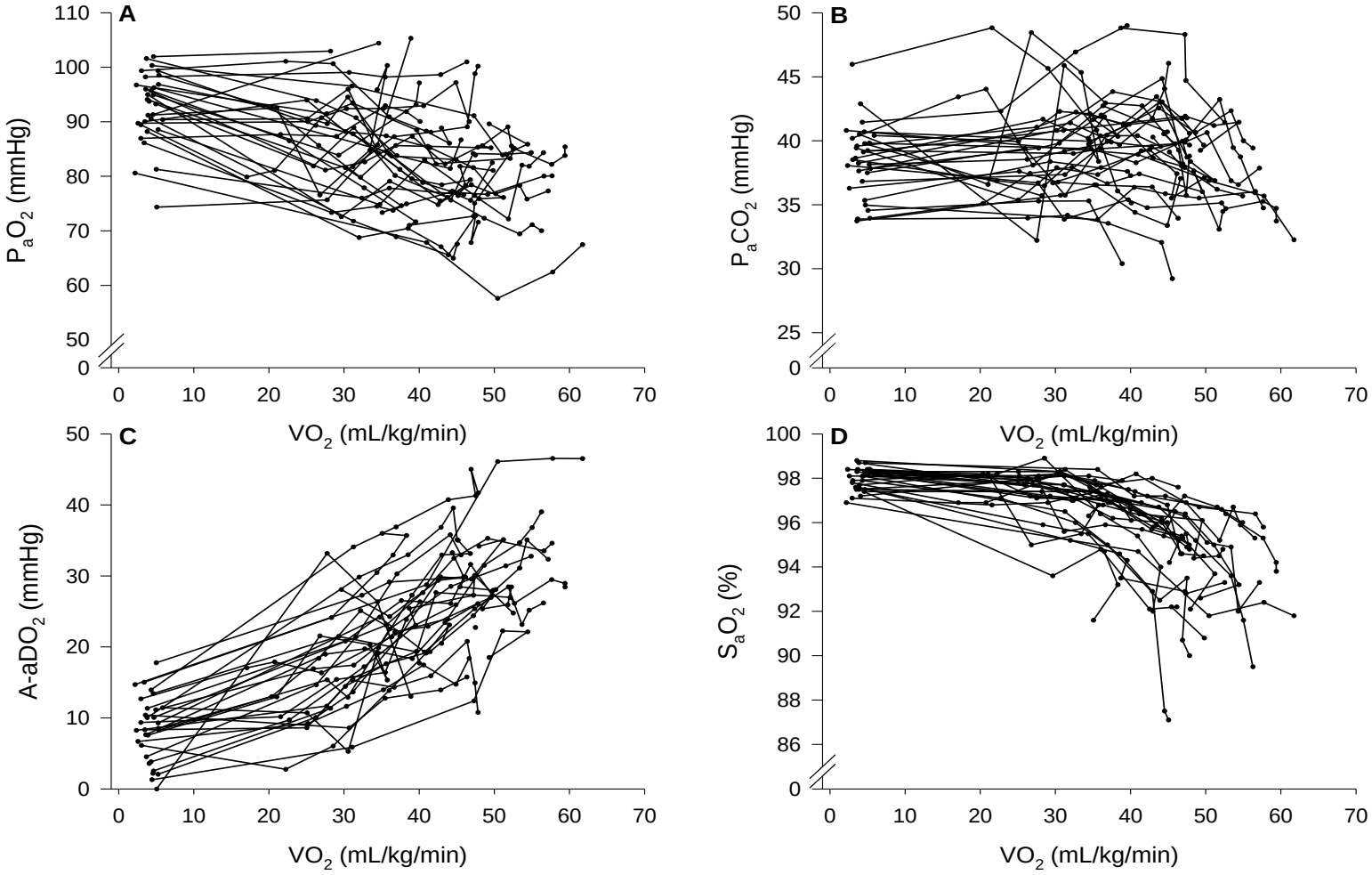
Legend: For each variable, each time point is different from preceding point, except V_T, where the 60, 80 and 100% $\dot{V}O_{2Max}$ are similar ($P < 0.05$). V_T, tidal volume, *f*, breathing frequency; $\dot{V}_E$, minute ventilation; $\dot{V}_A$, alveolar ventilation; $\dot{V}O_2$, oxygen consumption; $\dot{V}CO_2$, carbon dioxide production; RER, respiratory exchange ratio. Error bars are ± SE, n=30.

Blood gases

In Figure 3, the blood gas response for each subject is shown. The three subjects in Panel A with resting P_aO_2 values at or below 80 mmHg had an additional resting sample taken to ensure the values were not erroneous. The samples were in close agreement (1-2 mmHg) and the three subjects with low resting P_aO_2 had $S_aO_2 > 98\%$. There was high variability amongst P_aO_2 and P_aCO_2 at all exercise intensities, while S_aO_2 and A-aDO_2 became more variable at higher intensities. Figure 4 shows relationships between blood gas variables at $\dot{V}O_{2Max}$ for all subjects. The degree of P_aO_2 change was weakly related to P_aCO_2 levels and highly related to the degree of gas exchange inefficiency (Panel A and B). Higher fitness levels were associated with greater hypoxemia (Panel C) and greater gas exchange impairments (Panel D), however, there are notable outliers in both. The grouped blood gas response to progressive exercise is shown in Figure 5. On average, subjects met the criteria for EIAH between 60 and 80% of $\dot{V}O_{2Max}$, indicating, that on average our subjects became hypoxemia at submaximal intensities (Panel A). Indeed, the lowest P_aO_2 was achieved at 80% of $\dot{V}O_{2Max}$ and then showed some increase toward resting values. The rise in P_aO_2 near maximal exercise was concurrent with a hyperventilatory response (Figure 5, Panel C) and a plateauing of A-aDO_2 (Figure 5, Panel D.

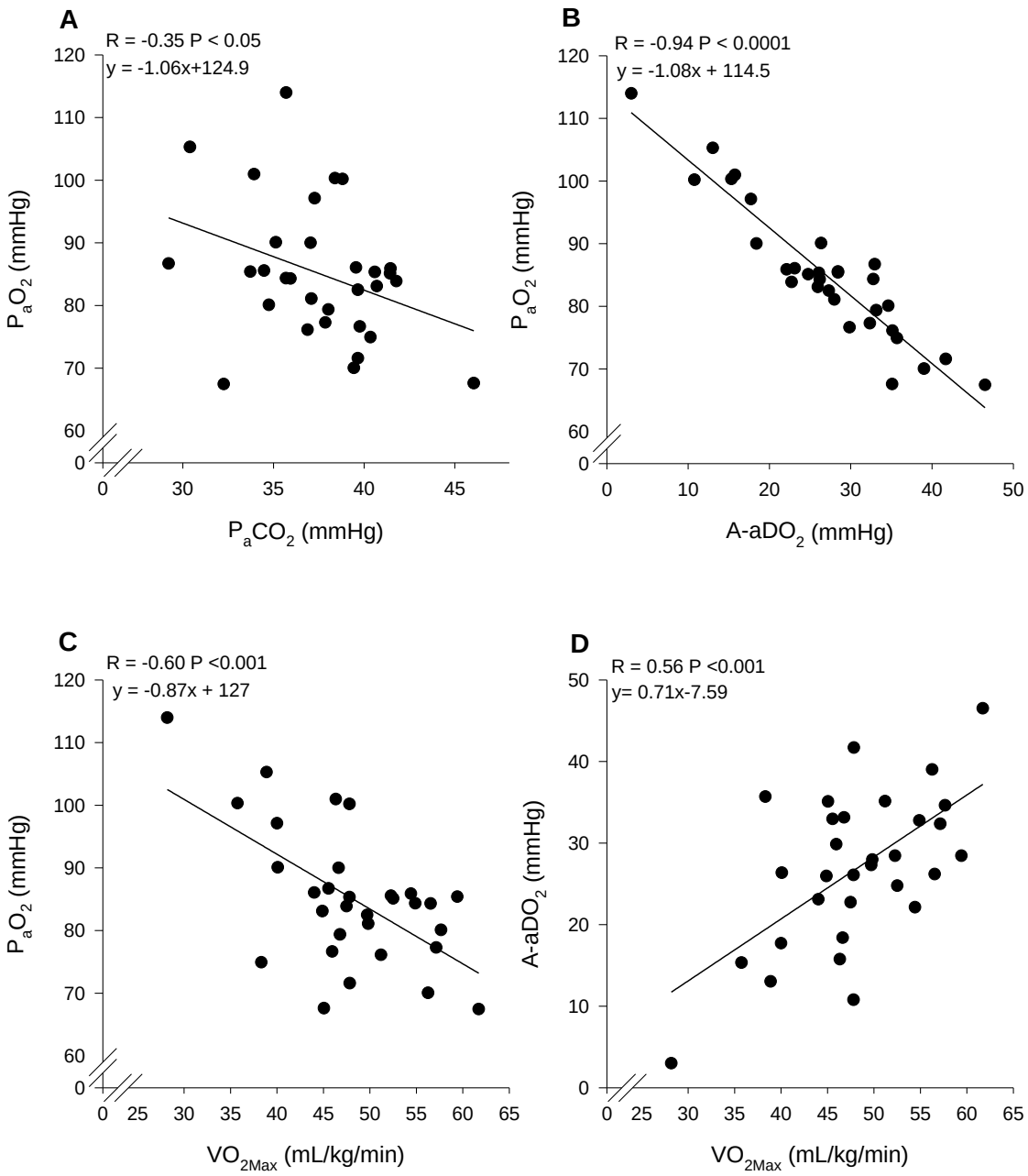
Oxyhemoglobin saturation fell progressively throughout exercise and ended below the cited threshold for decrements in $\dot{V}O_{2Max}$ ($S_aO_2 > 95\%$ and/or 3% decrease from rest) (29). The decrease in S_aO_2 was due to both P_aO_2 changes and shifting of the oxygen dissociation curve due to blood acidity, hyperthermia and P_aCO_2 changes (Figure 6,7). Despite S_aO_2 decreasing, the C_aO_2 rose throughout exercise, but not to the extent it *could* have if EIAH was not present (Figure 6, Panel B). The rise in C_aO_2 was due to a progressive increase in hemoglobin concentration (Figure 6, Panel C). Figure 7 demonstrates the extent of the exercise related acidity and hyperthermia. While arterial pH was relatively maintained until 90% $\dot{V}O_{2Max}$, thereafter, it declined sharply (Figure 7, Panel A). Circulating plasma K^+ rose progressively during exercise but was slightly below other reported values (30, 52) (Figure 7, Panel C). Esophgeal temperature increased exponentially as exercise progressed (Figure 7, Panel D). We obtained a blood sample immediately after exercise in some subjects (within 1 min of exercise cessation) and P_aO_2 and S_aO_2 had already returned to pre-exercise levels.

Figure 3- Individual blood gas response to maximal exercise test.



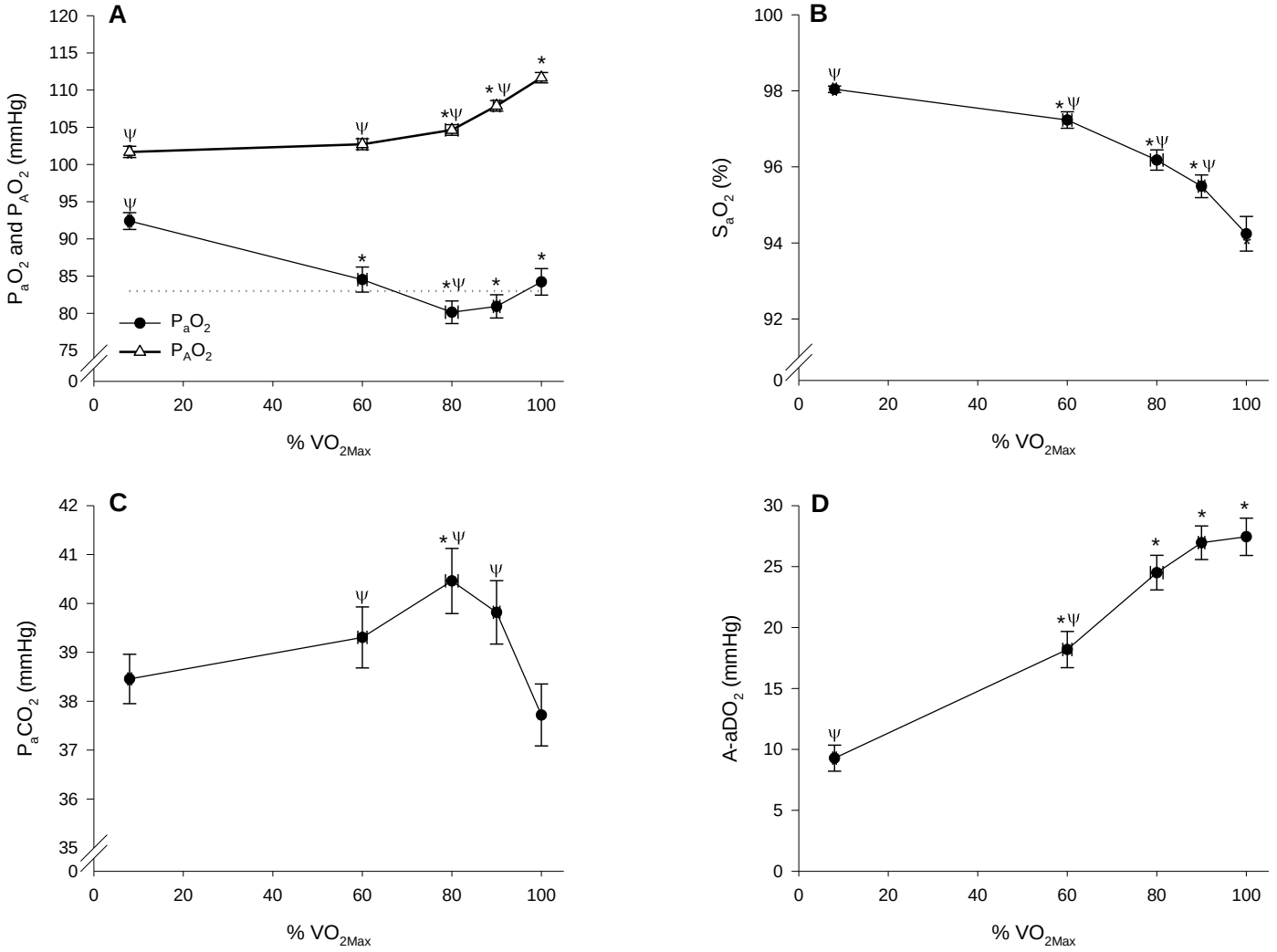
Legend: P_aO_2, arterial oxygen tension; P_aCO_2, arterial carbon dioxide tension; A-aDO_2, alveolar to arterial oxygen difference; S_aO_2, oxyhemoglobin saturation. n=31

Figure 4- Relationships between blood gas variables at $\dot{V}O_{2MAX}$.



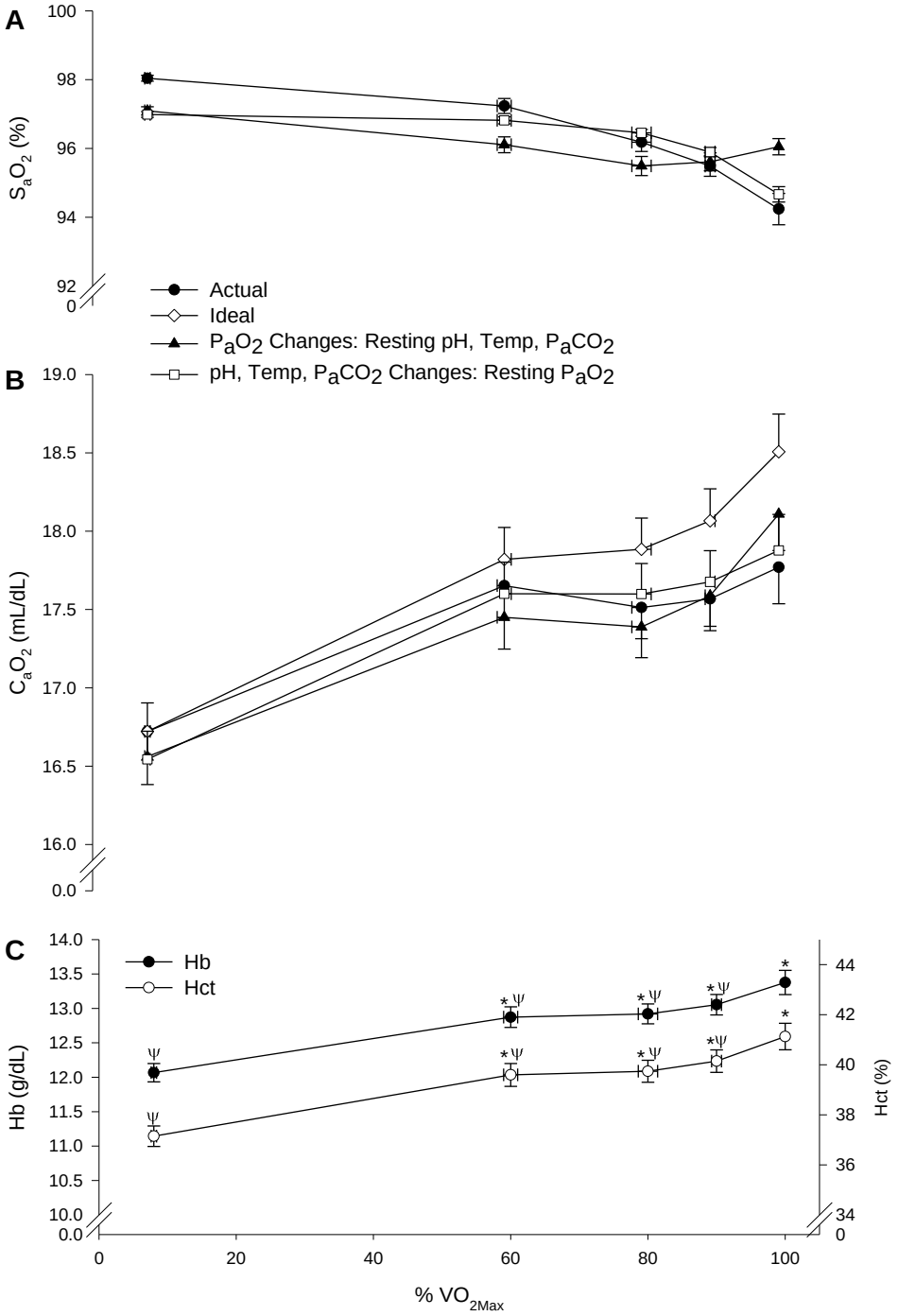
Legend: P_aO_2, arterial oxygen tension; P_aCO_2, arterial carbon dioxide tension; A-aDO_2, alveolar to arterial oxygen difference. n=31.

Figure 5- Grouped blood gas response during maximal exercise test.



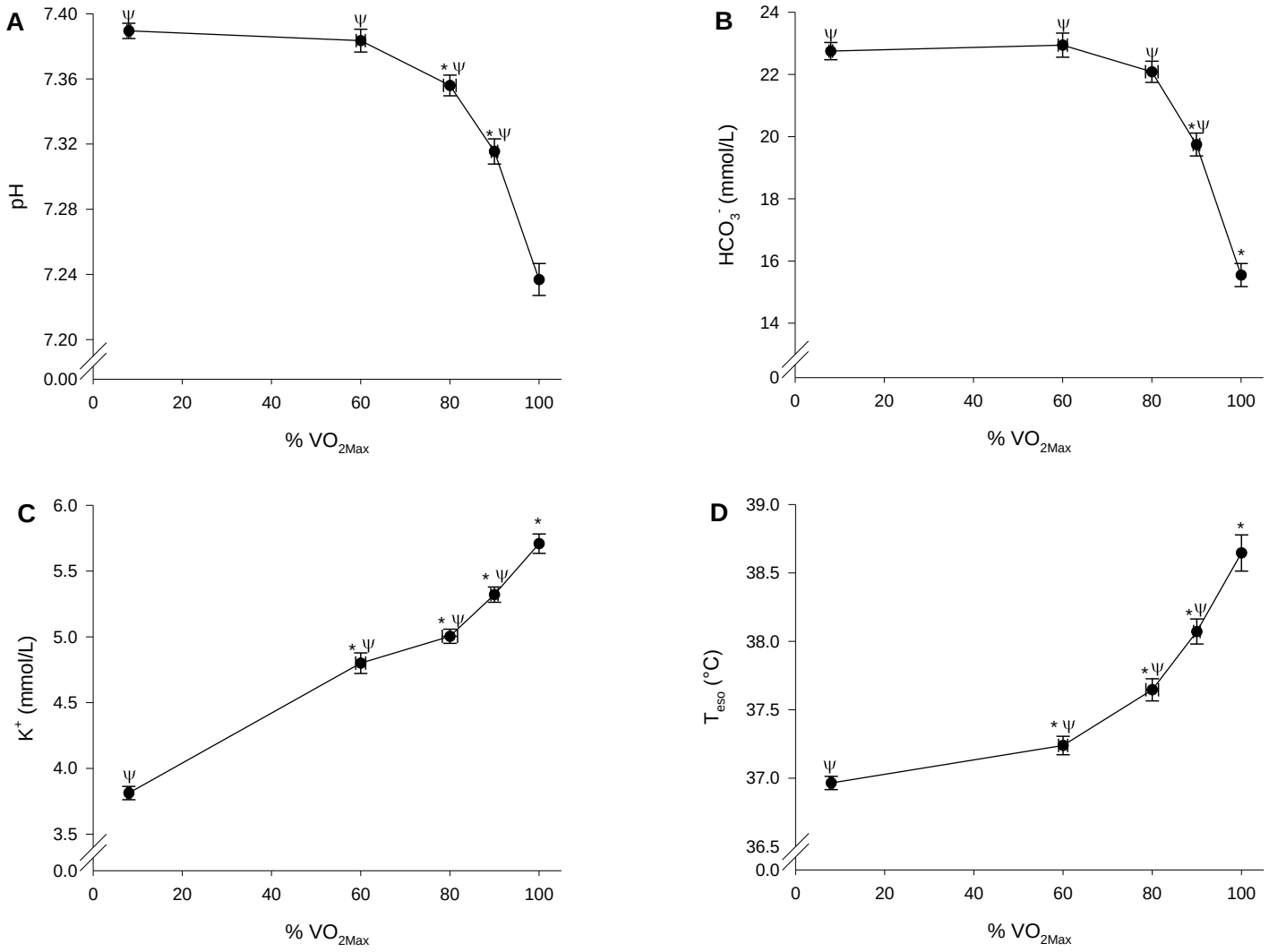
Legend: The dotted line in Panel A represent the 10 mmHg decrement in P_aO_2 from rest. P_AO_2, alveolar oxygen tension; P_aO_2, arterial oxygen tension; S_aO_2, oxyhemoglobin saturation P_aCO_2, arterial carbon dioxide tension; A-aDO_2, alveolar to arterial oxygen difference. * significantly different from rest, $^{\Psi}$, significantly different from maximal exercise ($P<0.05$). n=30.

Figure 6- The relative contribution to changes in hemoglobin saturation and oxygen content during the maximal exercise test.



Legend: Ideal oxygen content is derived using resting saturation and with concurrent hemoglobin concentration. Resting pH, temperature and P_aCO_2 was defined as 7.40, 37°C and 40 mmHg; respectively. S_aO_2, oxyhemoglobin saturation; P_aO_2, arterial oxygen tension; P_aCO_2, arterial carbon dioxide tension; C_aO_2, arterial oxygen content; Hb, hemoglobin concentration; Hct, hematocrit. * significantly different from rest, $^{\Psi}$, significantly different from maximal exercise ($P<0.05$). n=30.

Figure 7- Acid-base, potassium and esophageal temperature changes during maximal exercise test.

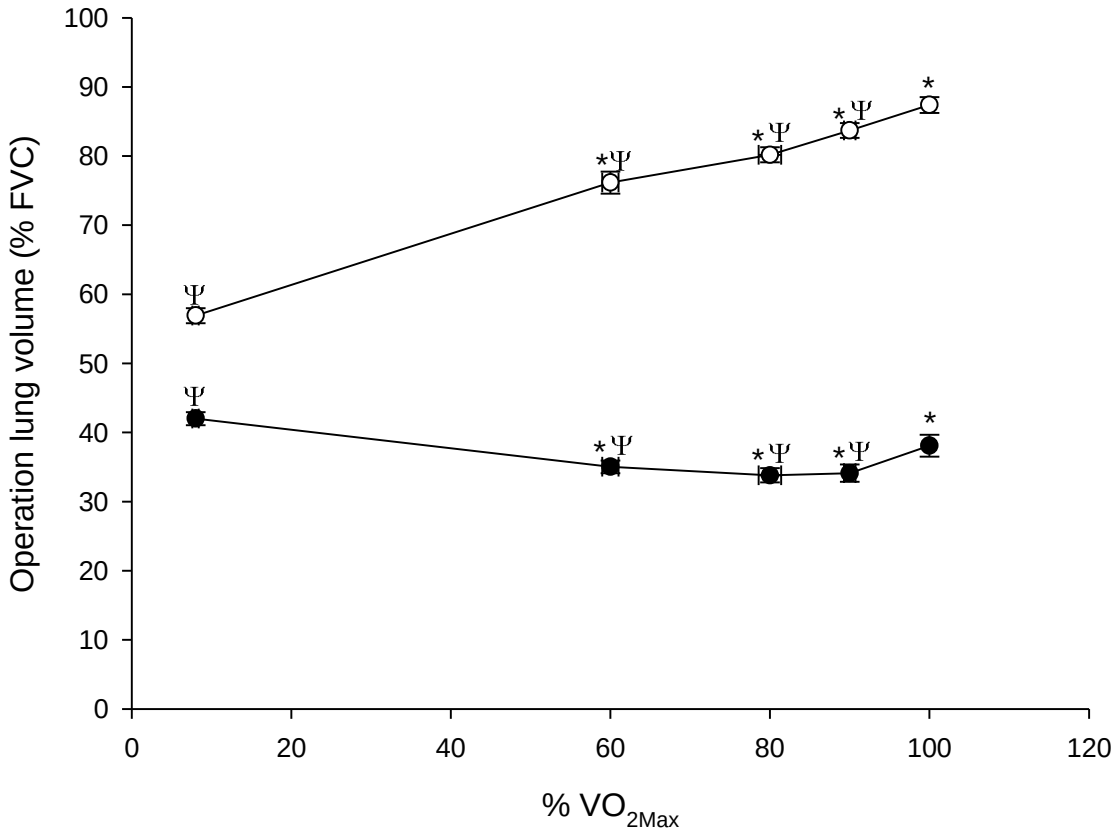


Legend: T_{eso}, esophageal temperature.* significantly different from rest, $^{\Psi}$, significantly different from maximal exercise ($P<0.05$). n=30 except Panel C which is n=24.

Respiratory mechanics

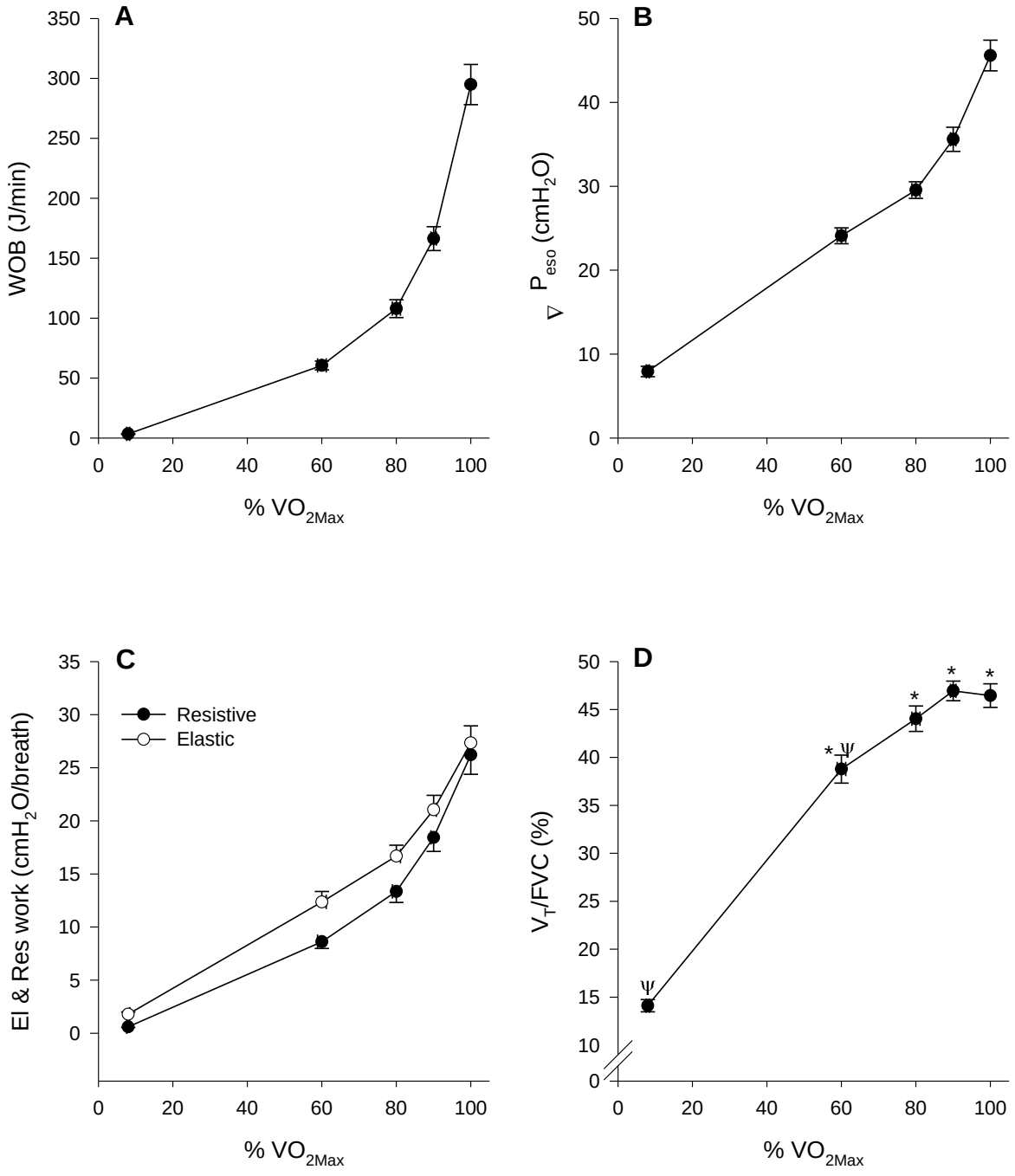
In two subjects, the esophageal balloon was suspected of being displaced near the end of exercise, therefore some groups only include 28 subjects. We suspect the balloon to have been displaced because the tidal ΔP_{eso} had become unphysiologically low (<8 cmH_2O for 2 L V_T) and during extraction had moved significantly higher in the subjects(s) esophagus (<20cm from nares). Figure 8 shows the changes in operational lung volumes during the maximal exercise test. As expected, EILV rose consistently throughout exercise (Figure 8) and in some subjects approached TLC (>90% FVC). End-expiratory lung volume progressively decreased during exercise, but, increased back toward FRC at maximal intensities (Figure 8). Figure 9 (Panel A, B) displays both WOB and esophageal pressure swing exponential increase throughout exercise. When broken into constituent components, elastic WOB (WOB_{El}) was a greater contributor to total WOB then the resistive component; however, at maximal intensities the difference between the two was negligible (Figure 9, Panel C). Individual plots for WOB are shown in Figure 10, with little difference between EIAH and NEIAH subjects (Panel A, B, D). However, despite having similar ventilations, the WOB appears to be associated with a decreasing P_aO_2 in the EIAH group, indicating their exercise hyperpnea is relatively ineffective (Figure 10, Panel C). Figure 11 displays the relationship between $\dot{V}_E$, $\dot{V}_{ECAP}$ and the theoretical ventilation needed to completely offset the hypoxemia and bring P_aO_2 back to resting levels along with the accompanying P_aCO_2 changes. Figure 11, Panel A demonstrated that the theoretical P_aCO_2 that would result from offsetting EIAH would be significantly lower than the actual P_aCO_2 and low in absolute values. Figure 11, Panel B shows that $\dot{V}_{ECAP}$ remains stable during exercise, yet $\dot{V}_E$ and the theoretical $\dot{V}_E$ necessary to offset EIAH continue to increase and approach $\dot{V}_{ECAP}$.

Figure 8- Operational lung volumes during maximal exercise test.



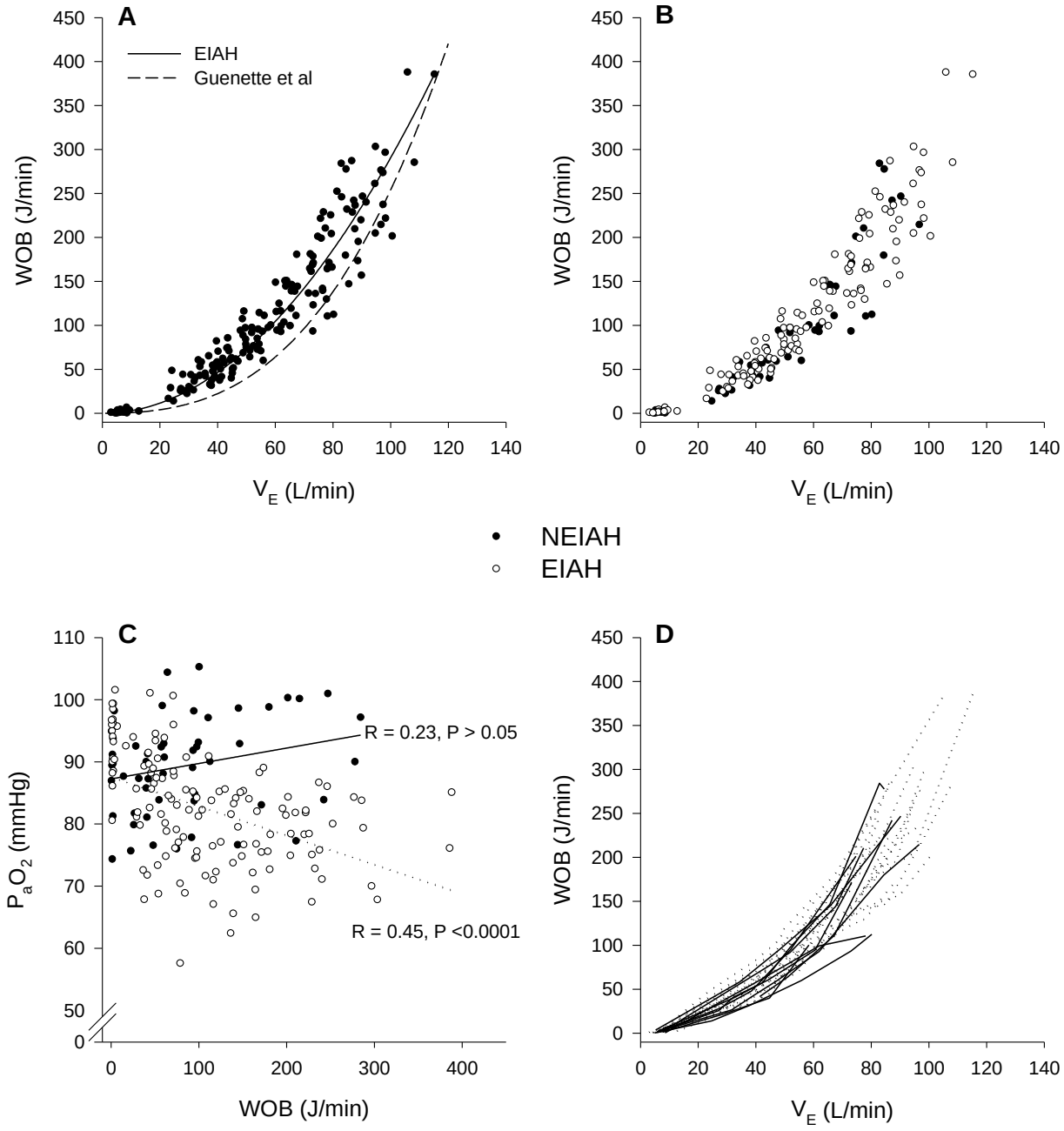
Legend: Open circles represent end-inspiratory lung volume while filled circles represent end-expiratory lung volume. FVC, forced vital capacity; $\dot{V}O_{2Max}$, maximal oxygen consumption. * significantly different from rest, $^{\Psi}$, significantly different from maximal exercise ($P<0.05$). n=30

Figure 9- Respiratory mechanics during maximal exercise test.



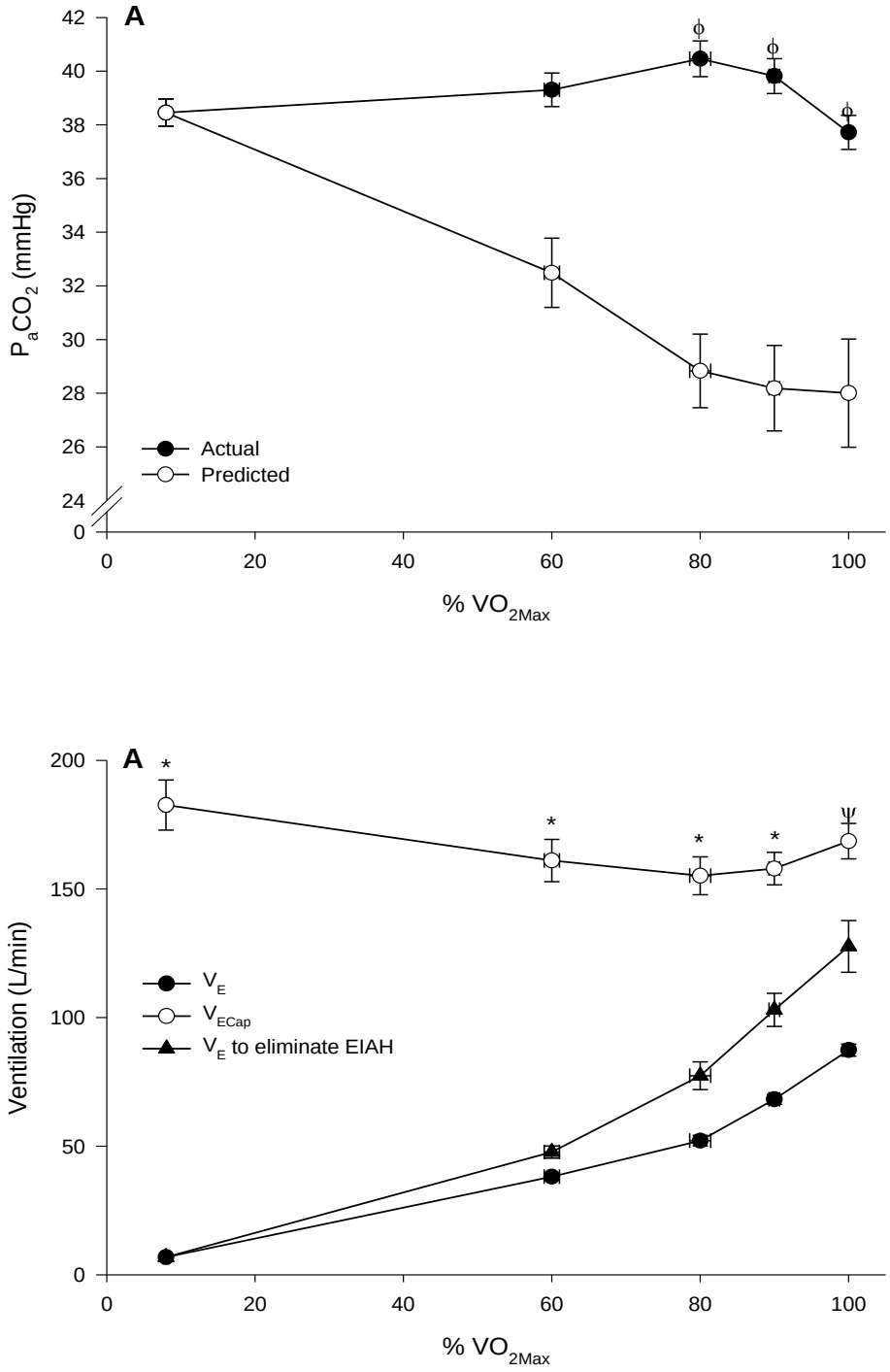
Legend: In Panel A,B,C all time points are statistically different from each other. WOB, work of breathing; ΔP_{eso} esophageal pressure swings; El, elastic; Res, resistive; V_T, tidal volume; FVC, forced vital capacity; $\dot{V}O_{2Max,}$ maximal oxygen consumption. * significantly different from rest, $^{\Psi}$, significantly different from maximal exercise ($P<0.05$). Panel A and C n=28, Panel B n=29, Panel D n=30.

Figure 10- Work of breathing for all subjects at all time points for the maximal exercise test.



Legend: Regression in Panel A is from Guenette et al. J Physiol 2007 with 10 trained cyclists. WOB, work of breathing; $\dot{V}_E$, minute ventilation; P_aO_2, arterial oxygen tension. n=31.

Figure 11- Minute ventilation, maximal ventilatory capacity, theoretical ventilation to offset EIAH and the associated arterial carbon dioxide tension during maximal exercise test.

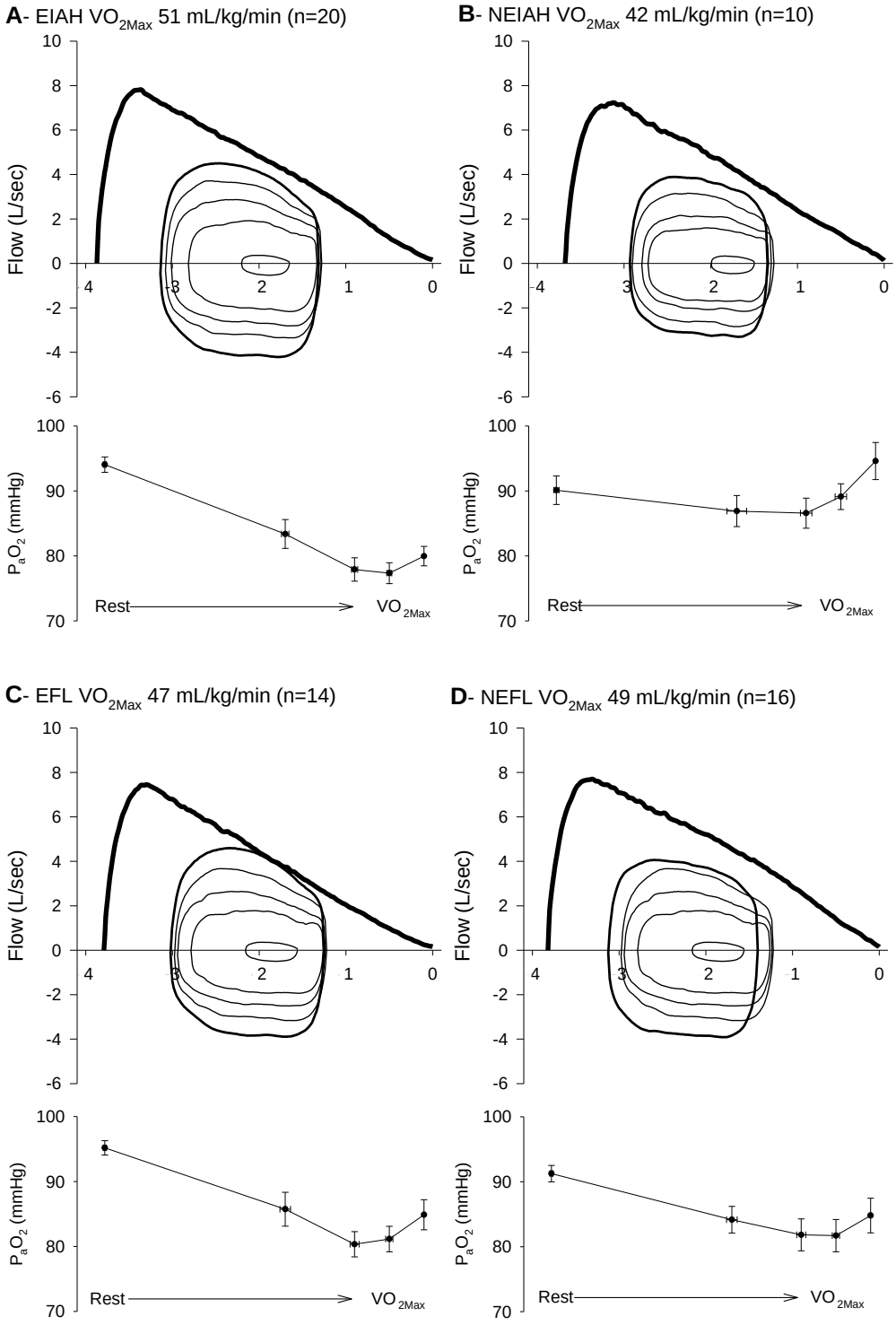


Legend: Predicted P_aCO_2 is calculated using alveolar gas equation and the minute ventilation needed to eliminate the EIAH. P_aCO_2, arterial carbon dioxide tension; $\dot{V}_E$, minute ventilation, $\dot{V}_{ECap}$, ventilatory capacity; $\dot{V}O_{2Max}$, maximal oxygen consumption. * significantly different from $\dot{V}_E$ and $\dot{V}_E$Cap, $^{\psi}$, significantly different from $\dot{V}_E$, ϕ, different from P_aCO_2 predicted. ($P<0.05$). n=30

EXERCISE RESPONSE SPLIT INTO EIAH/NEIAH AND EFL/NEFL

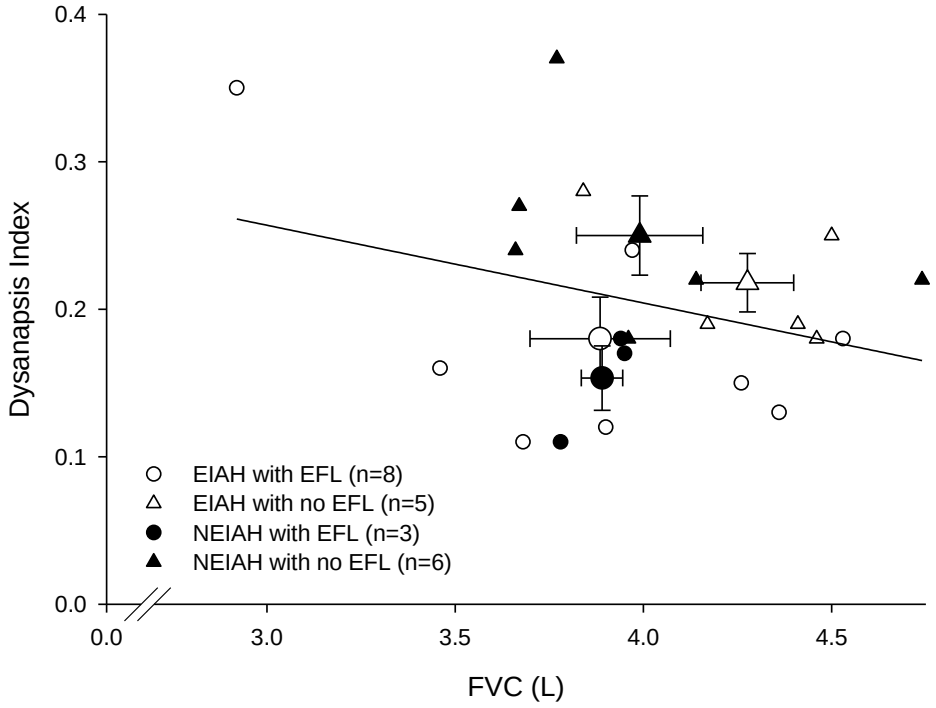
Figure 12 shows the MEFV curves and tidal FV loops for the subjects split independently into EIAH/NEIAH and EFL/NEFL groups. The EIAH group shows the most dramatic drop in P_aO_2 (Panel A) and does not display any EFL. The NEIAH group maintains and increases P_aO_2 and also does not show any EFL. The EFL group becomes flow limited during maximal intensities, but still increases P_aO_2. The NEFL group maintains considerable ventilatory reserve and shows little to no EIAH. The EFL and NEFL groups had similar $\dot{V}O_{2Max}$ values ($P > 0.05$). Subjects who show any EFL appear to show more dysanapsis than those who do not show any EFL (Figure 13), while the appearance of EIAH appears to be less related to dysanapsis (Figure 13).

Figure 12- Maximal flow-volume curves and tidal flow volume loops with arterial oxygen tension for subjects split into four groups during maximal exercise test.



Legend: Groups split based on the appearance of and EIAH or any EFL. A, EIAH; B NEIAH; C, EFL; D, NEFL. EIAH, exercise induced arterial hypoxemia; NEIAH, no exercise induced arterial hypoxemia; EFL, expiratory flow limitation; NEFL, no expiratory flow limitation.

Figure 13- Dysanapsis index for subjects split into four mutually exclusive groups.



Legend: Line is the regression for all subjects pooled. EIAH, exercise induced arterial hypoxemia; NEIAH, no exercise induced arterial hypoxemia; EFL, expiratory flow limitation; NEFL, no expiratory flow limitation. FVC, forced vital capacity. Error bars are SE.

EIAH VS. NEIAH

Tables 4, 5 and 6 compare metabolic and ventilatory, blood gas and lung mechanics variables between the EIAH and NEIAH groups at $\dot{V}O_{2Max}$. The EIAH group was significantly fitter and had larger ventilations (Table 4). The EIAH had lower P_aO_2, S_aO_2 and larger A-aDO_2 and a higher core temperature (Table 5). The difference in S_aO_2 between groups was due to changes in P_aO_2 and not temperature, pH or P_aCO_2. Consequently, the EIAH groups C_aO_2 did not rise as much as the NEIAH group (Table 5). Operational lung volumes were similar between groups. The EIAH group had a greater WOB_{Res}, leading to a greater total WOB. While the groups had similar $\dot{V}_{ECap}$, the EIAH group used a greater proportion of it.

Table 4- Metabolic and ventilatory data at maximal oxygen consumption for thirty-one subjects divided into groups based on the occurrence of any EIAH.

	All		EIAH (n=20)		NEIAH (n=11)	
	Value	Range	Value	Range	Value	Range
$\dot{V}O_2$ (L/min)	3.0 ± 0.1	1.9-3.7	3.2 ± 0.1	2.4-3.7	2.7 ± 0.1*	1.9-3.3
(mL/kg/min)	48 ± 1	28-62	51 ± 1	38-62	42 ± 2*	28-52
$\dot{V}CO_2$ (L/min)	3.3 ± 0.1	1.9-4.1	3.5 ± 0.1	2.7-4.1	2.9 ± 0.1*	1.9-3.6
RER	1.1 ± 0.01	0.89-1.23	1.1 ± 0.01	1-1.19	1.08 ± 0.01	0.89-1.23
$\dot{V}_E$ (L/min)	87 ± 2	58-115	91 ± 3	63-115	77 ±4*	58-96
$\dot{V}_A$ (L/min)	76 ± 2	54-93	80 ± 2	61-93	69 ± 2*	54-80
V_T (L)	1.9 ± 0.1	1.4-2.6	1.9 ±0.1	1.5-2.6	1.8 ± 0.1	1.4-2.1
f (bpm)	55 ± 2	34-71	56 ± 2	40-71	52 ± 3	34-68
V_D (L)	0.4 ± 0.03	0.08-1.1	0.3 ± 0.02	0.2-0.6	0.4 ± 0.08	0.08-1.1
V_D/V_T	0.18 ± 0.02	0.05-0.6	0.18 ± 0.01	0.09-0.27	0.2 ± 0.04	0.05-0.6
$\dot{V}_E/\dot{V}O_2$	29 ± 1	20-34	29 ± 1	25-32	29 ± 1	20-34
$\dot{V}_E/\dot{V}CO_2$	26 ± 1	21-32	26 ± 1	22-32	27 ± 1	21-31
T_i (s)	0.55 ± 0.02	0.38-0.9	0.52 ± 0.02	0.38-0.71	0.58 ± 0.04	0.43-0.76
T_e (s)	0.58 ± 0.02	0.44-0.88	0.57 ± 0.02	0.45-0.81	0.57 ± 0.03	0.44-0.70
T_{Tot} (s)	1.13 ± 0.04	0.84-1.78	1.10 ± 0.04	0.84-1.49	1.15 ± 0.06	0.89-1.45
T_i/T_{tot} (%)	49 ± 1	41-56	48 ± 1	41-56	50 ± 1*	47-54

Values are mean ± SE. $\dot{V}O_2$, oxygen consumption; $\dot{V}CO_2$, carbon dioxide production; RER, respiratory exchange ratio;$\dot{V}_E$, expired minute ventilation; $\dot{V}_A$, alveolar ventilation; V_T, tidal volume; *f*, breathing frequency; V_D, physiological deadspace; T_i, inspiratory time; T_e, expiratory time; T_{Tot}, total breathing time. * Significantly different from EIAH group, $P < 0.05$.

Table 5- Arterial blood data at maximal oxygen consumption for thirty-one subject divided into groups based on the occurrence of any EIAH.

	All		EIAH (n=20)		NEIAH (n=11)	
	Value	Range	Value	Range	Value	Range
P_aO_2 (mmHg)	85 ± 2	67-105	80 ± 2	67-89	95 ± 2*	77-105
ΔP_aO_2 rest (mmHg)	-8 ± 2	-23-+31	-14 ± 1	-23-(-4)	5 ± 3*	-6-+31
P_AO_2 (mmHg)	112 ± 1	103-119	111 ± 1	103-119	113 ±1	106-118
A-aDO_2 (mmHg)	27 ± 2	11-45	31 ± 1	21-45	17 ± 1*	11-26
P_aCO_2 (mmHg)	38 ± 1	30-46	38 ± 1	30-46	37 ± 1.0	30-42
pH	7.24 ± 0.01	7.14-7.36	7.23 ± 0.01	7.14-7.31	7.25 ± 0.02	7.16-7.36
HCO_3^- (mmol/L)	16 ± 0.4	11-22	15 ± 0.3	11-17	16 ± 0.8	13-22
K^+ (mmol/L)	5.7 ± 0.1	4.9-6.3	5.7 ± 0.1	4.9-6.2	5.7 ± 0.1	5.2-6.3
T_{eso} (°C)	38.6 ± 0.1	37.2-40	38.9 ± 0.2	37.5-40.0	38.1 ± 0.2*	37.3-39.3
S_aO_2 (%)	94.3 ± 0.5	87.1-97.9	93.2 ± 0.5	87.1-96.0	96.3 ± 0.3*	94.6-97.9
P_aO_2 changes	96.1 ± 0.3	93.1-98.1	95.6 ± 0.3	93.1-96.8	97.1 ± 0.3*	95.2-98.1
pH,T_{eso},P_aCO_2	94.7 ± 0.2	91.4-97.0	94.5 ± 0.3	91.4-96.5	95.1 ± 0.4	93.0-97.0
Hb (g/dL)	13.4 ± 0.2	11.4-15.7	13.4 ± 0.2	12.2-15.7	13.3 ± 0.4	11.4-15.2
Hct (%)	41 ± 1	35-48	41 ± 1	38-48	41 ± 1	35-47
C_aO_2 (ml/dL)	17.8 ± 0.2	15.5-20.7	17.6 0.2	16-19.7	18.1 ± 0.5	15.5-20.7
P_aO_2 changes	18.1 ± 0.2	15.8-20.9	18.1 ± 0.2	16.4-20.7	18.2 ± 0.5	15.8-20.9
pH,T_{eso}, P_aCO_2	17.9 ± 0.2	15.1-20.7	17.9 ± 0.2	16.4-20.7	17.8 ± 0.5	15.1-20.4
Ideal	18.5 ± 0.2	15.8-21.8	18.6 ± 0.3	17.0-21.8	18.3 ± 0.2	15.8-21.8
ΔC_aO_2 rest (mL/dL)	+1.0 ± 0.2	-0.8-3.2	+0.75 ± 0.2	-0.8-2.5	+1.5 ± 0.3*	0.1-3.2

Values are mean ± SE. P_aO_2, arterial oxygen tension; ΔP_aO_2 rest, change in arterial oxygen tension from rest; P_AO_2, alveolar oxygen tension; A-aDO_2, alveolar to arterial oxygen difference; P_aCO_2, arterial carbon dioxide production; T_{eso}, esophageal temperature; S_aO_2, arterial oxyhemoglobin saturation; Hb, hemoglobin concentration; Hct, hematocrit; C_aO_2, arterial oxygen content; ΔC_aO_2 rest, change in arterial oxygen content from rest. * Significantly different from EIAH group, $P < 0.05$.

Table 6- Respiratory mechanics data at maximal oxygen consumption for thirty-one subject divided into groups based on the occurrence of any EIAH.

	All		EIAH (n=20)		NEIAH (n=11)	
	Value	Range	Value	Range	Value	Range
EELV (% FVC)	38 ± 2	21-63	36 ± 2	21-49	40 ± 3	23-63
EILV (% FVC)	87 ± 1	73-96	87 ± 2	73-96	88 ± 2	74-96
WOB_c (J/min)	289 ± 17	124-507	324 ± 19	158-507	224 ± 24*	124-330
WOB_{pv} (J/min)	223 ± 13	100-386	253 ± 14	151-386	170 ± 17*	100-247
WOB_{El} (cmH_2O/br)	27 ± 2	14-50	29 ± 2	16-50	24 ± 3	14-37
% tot	51 ± 2	32-74	49 ± 2	32-74	55 ± 2	45-64
WOB_{Res} (cmH_2O/br)	26 ± 2	14-49	30 ± 2	15-49	19 ± 1*	14-24
% tot	49 ± 2	26-68	51 ± 2	26-68	45 ± 2	36-55
ΔP_{eso} (cmH_2O)	45 ± 2	26-66	49 ± 2	33-66	39 ± 3*	23-50
Comp (mL/cmH_2O)	72 ± 4	46-145	68 ± 3	46-95	80 ± 10	48-145
$\dot{V}_{ECap}$ (L/min)	167 ± 6	103-246	167 ± 9	103-246	168 ± 10	130-229
$\dot{V}_E/\dot{V}_{ECap}$ (%)	54 ± 2	32-77	57 ± 2	36-77	48 ± 3*	32-66
$\dot{V}_E$ offset EIAH (L/min)	125 ± 10	59-283	153 ± 11	89-283	75 ± 3*	59-88
% $\dot{V}_{ECap}$	76 ± 6	17-149	93 ± 6	52-149	44 ± 4*	17-59
EFL (%)	16 ± 3.5	0-58	19 ± 5	0-58	9 ± 5	0-37

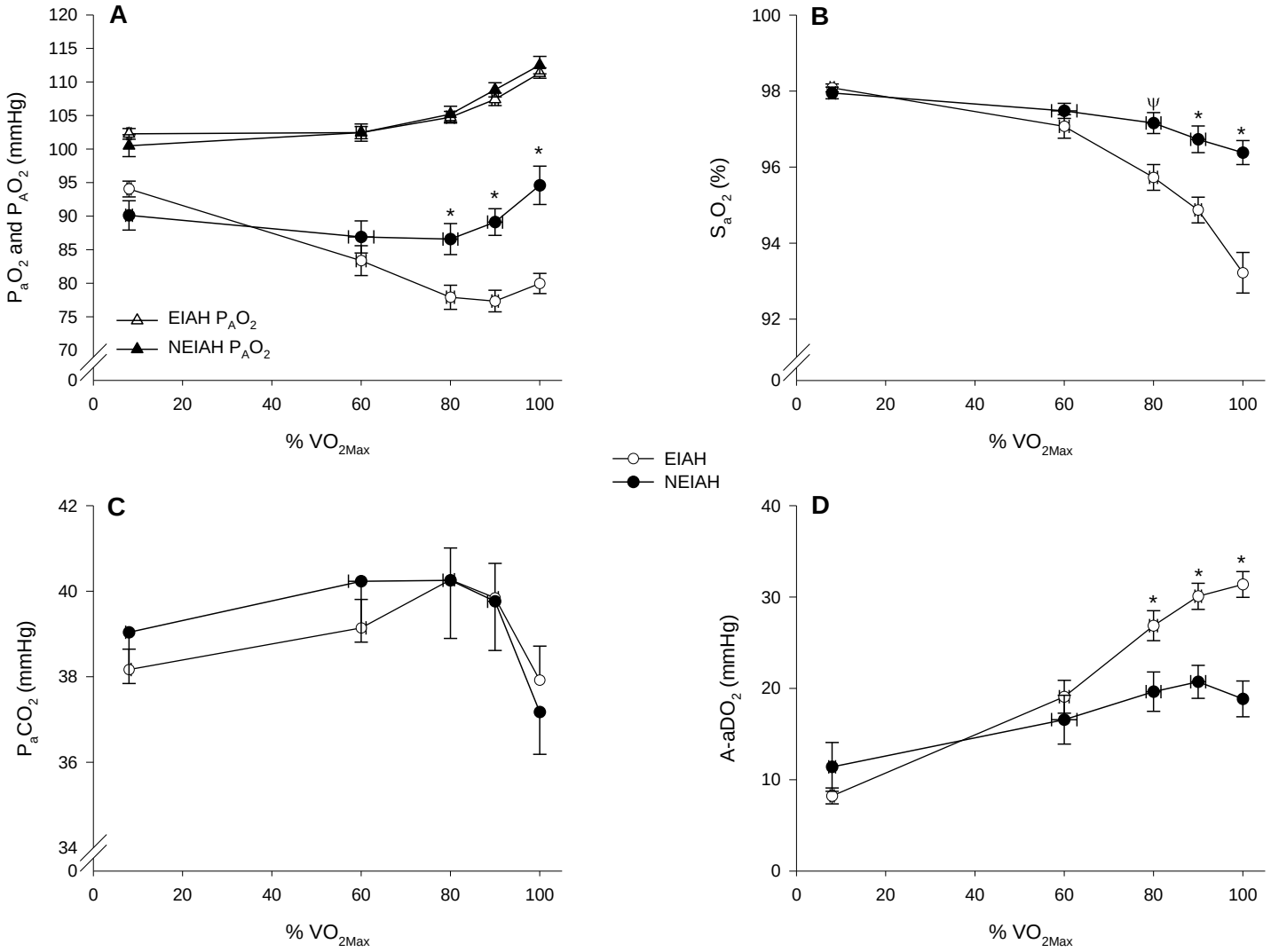
Values are mean ± SE. EELV, end expiratory lung volume; FVC, forced vital capacity; EILV, end inspiratory lung volume; WOB_c, work of breathing using Campbell diagrams; WOB_{pv}, work of breathing using pressure-volume loops; WOB_{El}, elastic work of breathing; WOB_{Res}, resistive work of breathing; ΔP_{eso}, esophageal pressure swings per breath; Comp, compliance; $\dot{V}_{ECap}$, maximal ventilatory capacity; $\dot{V}_E$, minute ventilation; EIAH, exercise induced arterial hypoxemia; EFL, expiratory flow limitation. * Significantly different from EIAH group, $P < 0.05$.

Blood gases for EIAH vs. NEAIH

Figure 14 shows the arterial blood gas variable during the maximal exercise test for the EIAH and NEIAH groups. The groups had similar P_AO_2 at all time points, while the EIAH group had significantly lower P_aO_2 from 80% $\dot{V}O_{2Max}$ onward, due to a greater A-aDO_2 (Panel A,C). Both groups displayed a rise in P_aO_2 at maximal exercise, but the NEIAH groups was greater and resulted in a maximal exercise P_aO_2 > Resting levels. Similarly, the EIAH groups

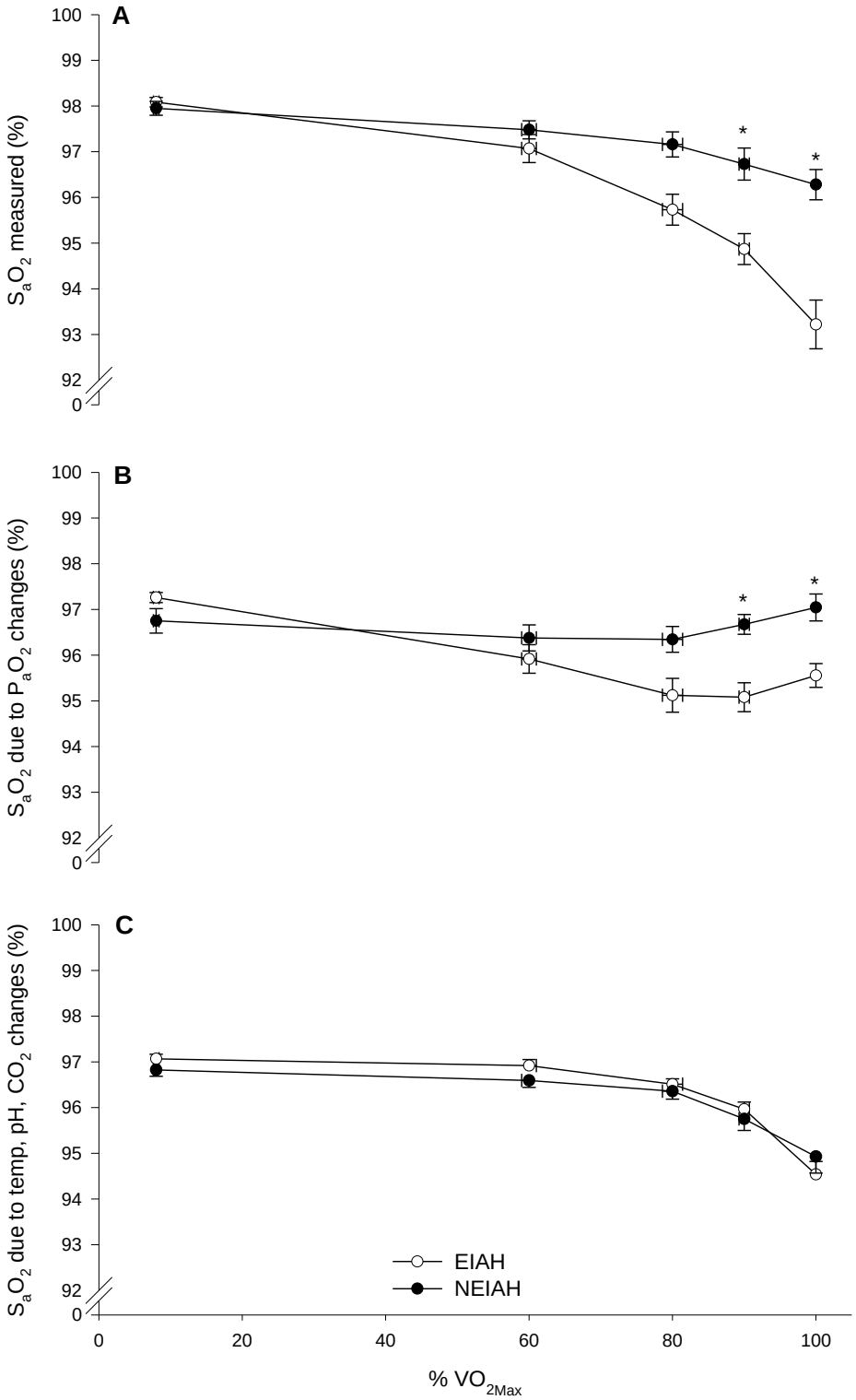
had lower S_aO_2 from 80% $\dot{V}O_{2Max}$ onward, which was due to decreased P_aO_2 and not a rightward shifting of the oxygen disassociation curve ODC (Figure 14, Panel B; Figure 15). As such, the EIAH and NEIAH groups had similar changes in acid-base balance (Figure 16, Panel A,B) and had similar T_{eso} except for maximal exercise.

Figure 14- Blood gas variables for the EIAH and NEIAH groups during maximal exercise test.



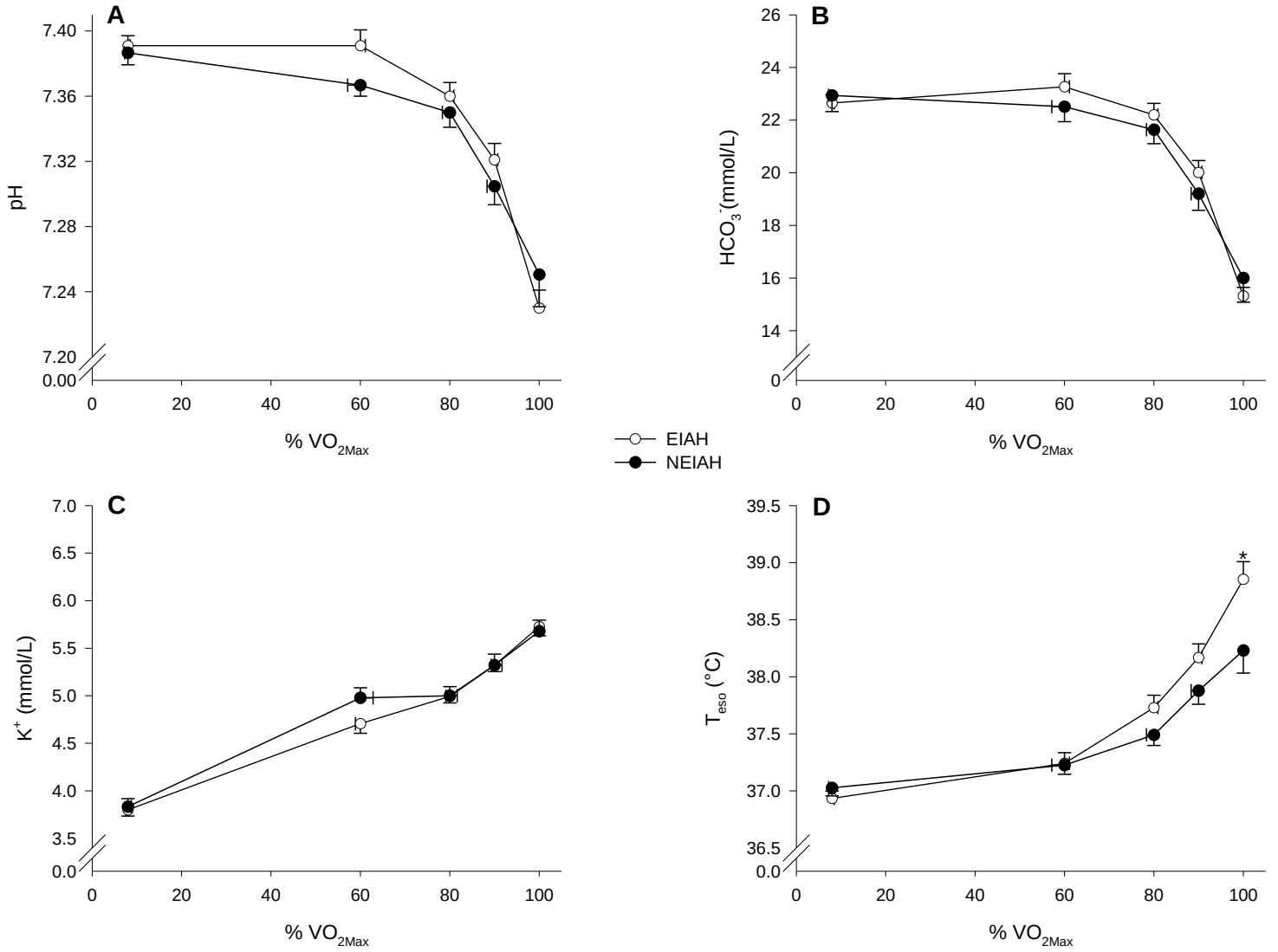
Legend: P_AO_2, alveolar oxygen tension; P_aO_2; S_aO_2, arterial oxyhemoglobin saturation; P_aCO_2, arterial carbon dioxide tension; A-aDO_2, alveolar to arterial oxygen difference, $\dot{V}O_{2Max}$, maximal oxygen consumption. *, $P < 0.01$; ψ, $P < 0.05$. n=30.

Figure 15- Arterial oxyhemoglobin saturation for the EIAH and NEIAH groups during the maximal exercise test.



Legend: Panel A is directly measured while Panel B and C represent calculated values. S_aO_2, arterial oxyhemoglobin saturation, $\dot{V}O_{2Max}$, maximal oxygen consumption. *, significantly different from EIAH. $P < 0.01$. n=30.

Figure 16- Acid-base, potassium and esophageal temperature changes during maximal exercise test for EIAH and NEIAH groups.



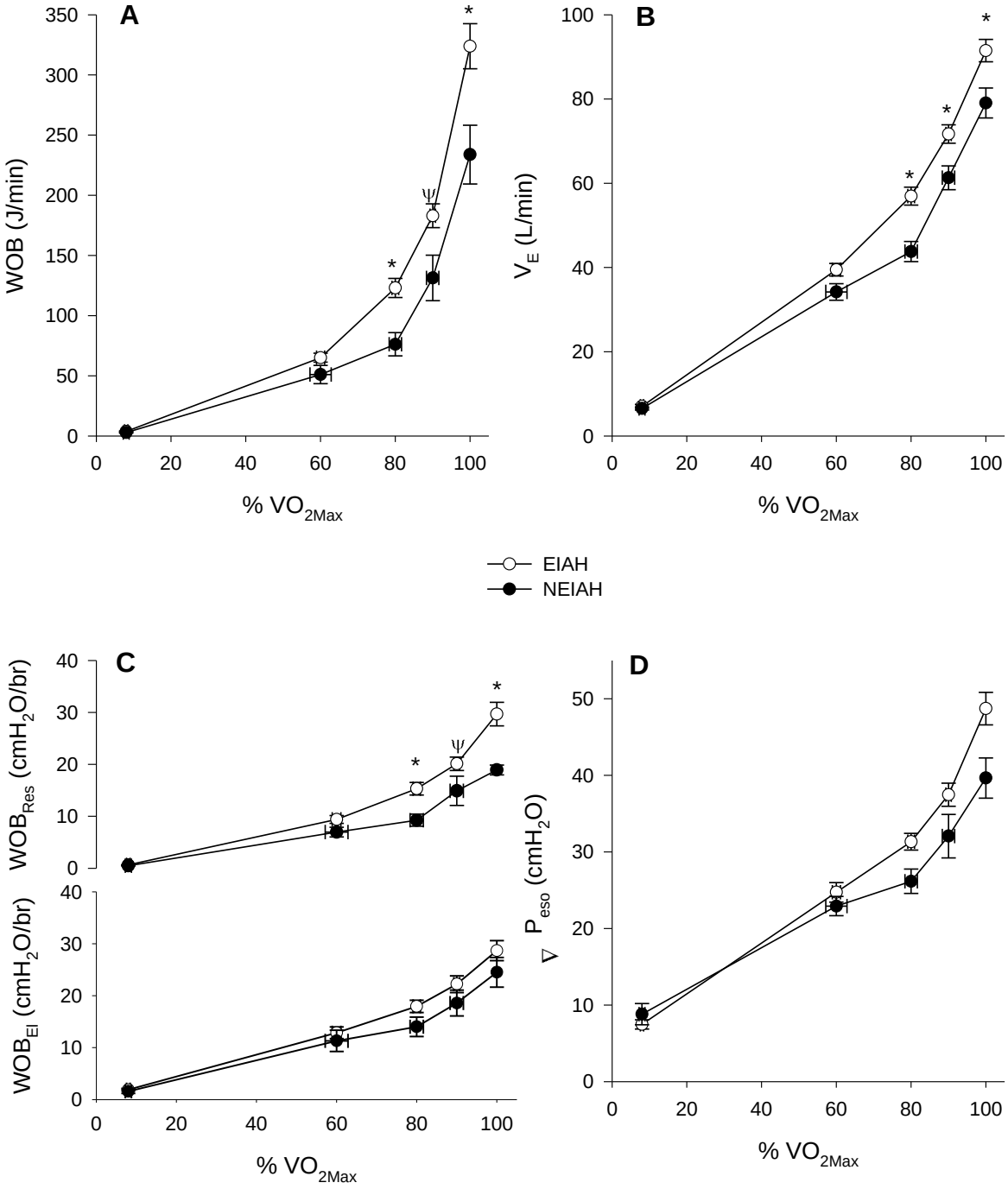
Legend: T_{eso}, esophageal temperature, $\dot{V}O_{2Max}$, maximal oxygen consumption. * P <0.01. n=30 except Panel C which is n=24

Respiratory mechanics for EIAH and NEIAH groups

Figure 17 show the WOB and its constituent components for the EIAH and NEIAH groups. The EIAH groups had a higher WOB at the same percent of $\dot{V}O_{2Max}$ (Panel A), this is attributed to the higher $\dot{V}_E$ (Panel B) as the two groups have similar WOB when compared at iso-volumes (Figure 10). The higher WOB in the EIAH group was the result of a higher WOB_{Res}, as the groups had similar WOB_{El} (Panel C). There was no difference in tidal esophageal pressure swings. The groups also had similar changes in operational lung volumes. Eleven of the 20 EIAH subjects showed some form of EFL, while only 3/10 of the NEIAH subjects showed any EFL. In Figure 18 Panel A, the EIAH group's predicted P_aCO_2 is extremely low as they increased their $\dot{V}_E$ to completely offset the hypoxemia. The EIAH and NEIAH groups have similar $\dot{V}_{ECap}$, yet if the EIAH group increased their $\dot{V}_E$ to offset the hypoxemia, they would be required to ventilate very near their $\dot{V}_{ECap}$ (Figure 18 Panel B). Table 7 shows each subject's constants for the equation described in the methods above (See *Work of Breathing*). There was no difference between EIAH and NEIAH groups. There was no difference in the mechanical breathing efficiency between the EIAH and NEIAH groups with the subject average being 1.6% of ideal *f*. However, some subjects during maximal intensity were up to 19% and incurred substantial WOB due to excessively high *f*. Figure 19 displays the MEF curve, tidal FV loops and P_aO_2 for the EIAH group split into 6 distinct patterns of hypoxemia. Subjects in Panel A display a gradual decrease in P_aO_2 with the capacity to increase ventilation, a response that is typically seen in trained men. Subjects in Panel B demonstrate an immediate fall in P_aO_2 upon exercise onset, at ~90% $\dot{V}O_{2Max}$, the group increases $\dot{V}_E$ and raises their P_aO_2 back towards resting levels and does not show any EFL. The "U shaped" response in P_aO_2 has not been reported in men. In Panel C, the subjects again show an immediate decrease in P_aO_2, however as exercise intensity increases, P_aO_2 remain stable despite an apparent ability to increase $\dot{V}_E$. In Panel D, P_aO_2 is maintained until the onset of EFL (80% $\dot{V}O_{2Max}$) at which point they sharply decrease and remain stable. Decreases in P_aO_2, due to EFL, have been reported in highly trained men, but is not seen in men with unremarkable fitness, which is in contrast to the women represented in Panel D. Panel E also shows an immediate drop in P_aO_2 upon exercise onset and a slight rebound near maximal intensities. However, unlike Panel B, subjects in Panel E are unable to substantially increase their P_aO_2 due to the onset of EFL. Finally, Panel F shows a nearly

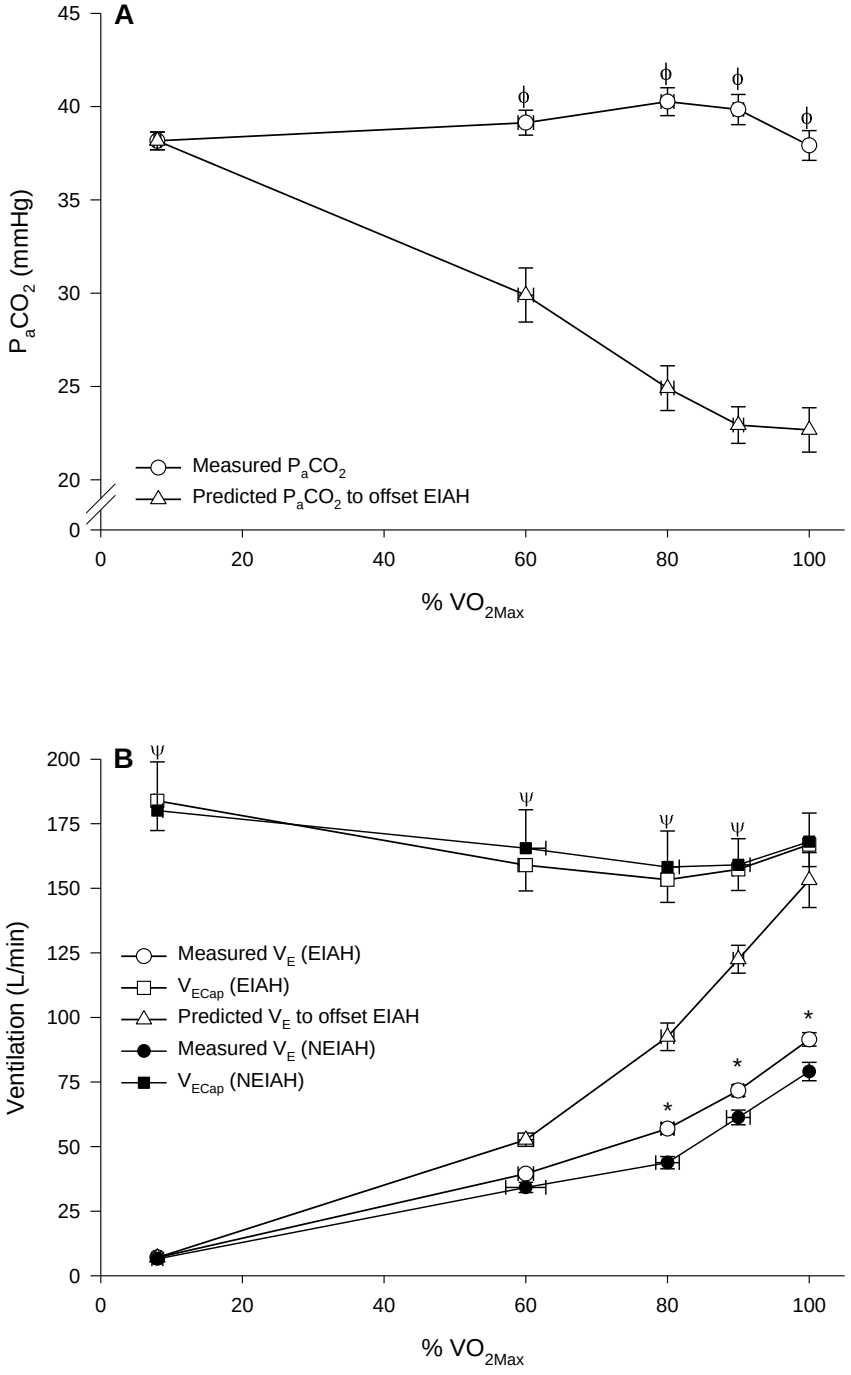
identical response as Panel C (immediate P_aO_2 drop followed by a plateauing), except, at maximal exercise they display some EFL, which may have prevented any increase in P_aO_2.

Figure 17- Respiratory mechanics for the EIAH and NEIAH groups during maximal exercise test.



Legend: WOB, work of breathing; $\dot{V}_E$, minute ventilation; WOB_{Res}, resistive work of breathing; WOB_{El}, elastic work of breathing; ΔP_{eso}, tidal esophageal swing. $\dot{V}O_{2Max}$, maximal oxygen consumption. * $P < 0.01$, ψ $P < 0.05$. Panel A and C n=28, Panel B n=29, Panel D n=30.

Figure 18- Minute ventilation, maximal ventilatory capacity, theoretical ventilation to offset EIAH and the associated arterial carbon dioxide tension during maximal exercise test for EIAH and NEIAH groups.



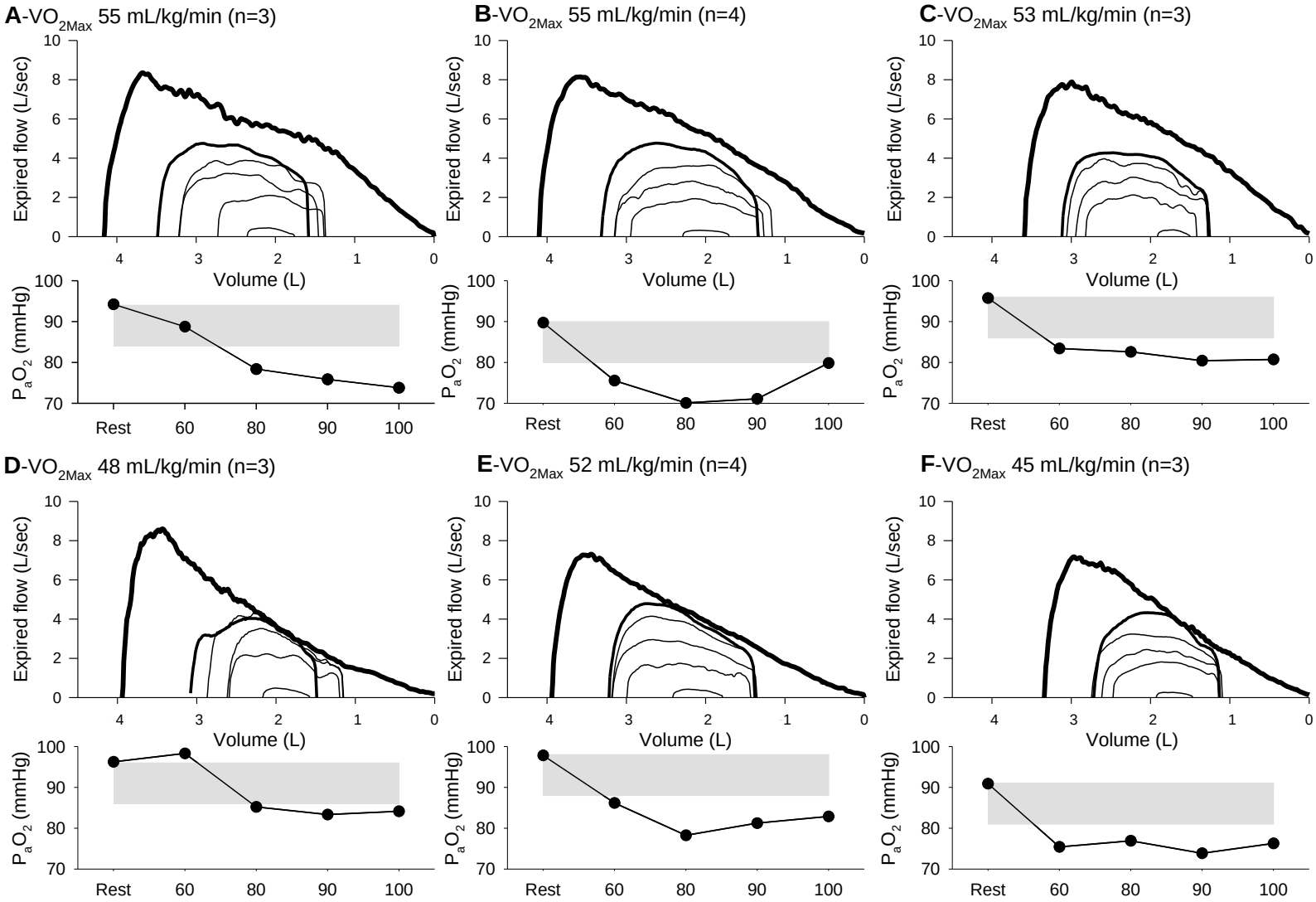
Legend: In Panel B, the $\dot{V}_E$ to offset EIAH is 60, 78 and 92% of $\dot{V}_{ECap}$ at 60, 80 and 100% $\dot{V}O_{2Max}$; respectively. P_aCO_2, arterial carbon dioxide tension; $\dot{V}_E$, minute ventilation; $\dot{V}_{ECap}$, ventilatory capacity; EIAH, exercise induced arterial hypoxemia; $\dot{V}O_{2Max}$, maximal oxygen consumption. Φ, significantly different from predicted P_aCO_2; ψ, significantly different from $\dot{V}_E$ and $\dot{V}_E$ to offset EIAH; *, significantly different from NEIAH $\dot{V}_E$. $P < 0.01$. n=30.

Table 7- Work of breathing constants for the EIAH and NEIAH groups

Subject	Constant A	Constant B
AC	3.97E-06	3.18E-02
AH	2.33E-04	1.11E-02
AM	4.52E-13	2.40E-02
AS	4.71E-05	2.90E-02
BS	2.06E-12	3.34E-02
CM	5.55E-13	2.86E-02
CR	1.56E-12	3.19E-02
EM	8.35E-13	3.78E-02
GLY	3.22E-12	3.48E-02
JB	1.24E-13	3.42E-02
JBarc	1.28E-12	3.02E-02
JC	1.86E-05	1.80E-02
JL	8.36E-13	1.79E-02
JShep	1.33E-12	2.13E-02
JS	1.27E-04	2.76E-02
KM	1.07E-12	3.80E-02
MB	1.52E-04	1.63E-02
MF	1.34E-12	2.92E-02
MG	3.91E-04	5.97E-03
MM	3.13E-05	2.83E-02
NN	1.95E-13	3.15E-02
NW	7.32E-13	2.65E-02
PH	8.59E-13	3.48E-02
RB	7.02E-05	2.30E-02
SD	2.74E-05	3.51E-02
SL	2.84E-12	2.10E-02
SS	6.83E-13	2.27E-02
SW	3.45E-06	2.31E-02
VW	1.08E-04	3.87E-02
All mean	4.18E-05	2.71E-02
EIAH mean	2.37E-05	2.86E-02
NEIAH mean	7.63E-05	2.43E-02

Legend: Constant A and B are from the WOB equation described in the methods. EIAH, exercise induced arterial hypoxemia; NEAIH, no exercise induced arterial hypoxemia.

Figure 19- Patterns of hypoxemia for the EIAH group during the maximal exercise test.

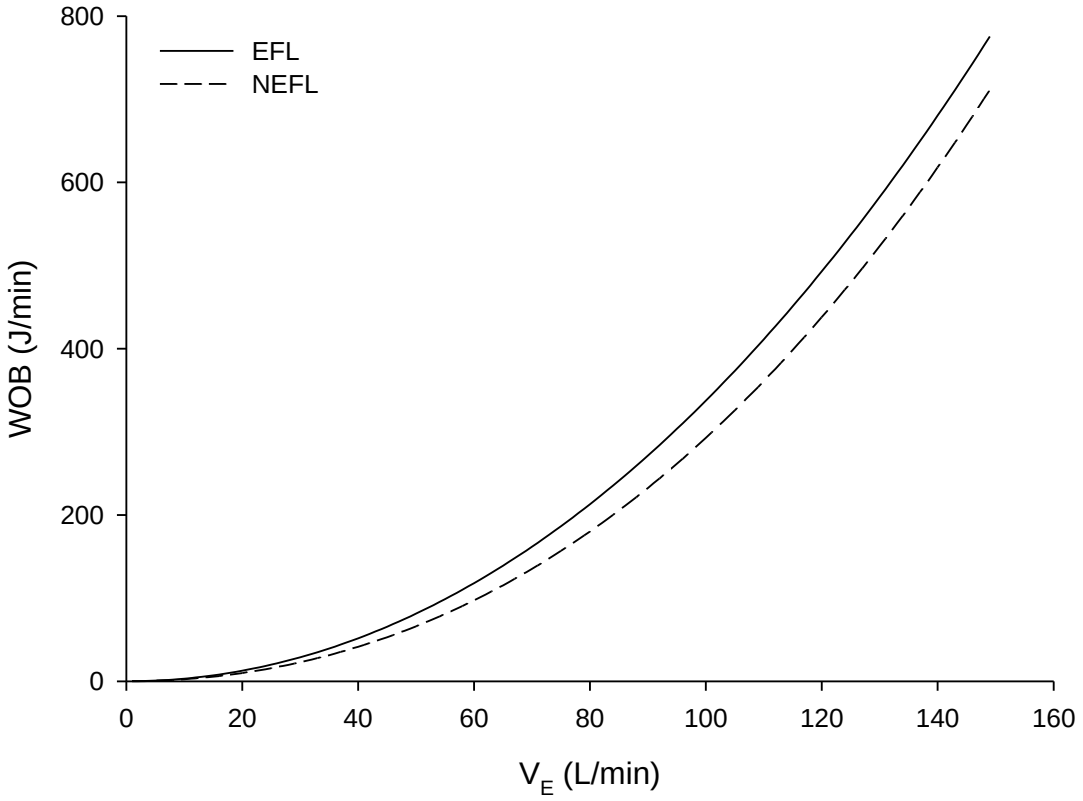


Legend: The grey area represents a P_aO_2 within 10 mmHg of rest. Rest, 60, 80, 90 and 100 are percent of $\dot{V}O_{2Max}$. P_aO_2, arterial oxygen tension, $\dot{V}O_{2Max}$, maximal oxygen consumption.

EFL VS. NEFL

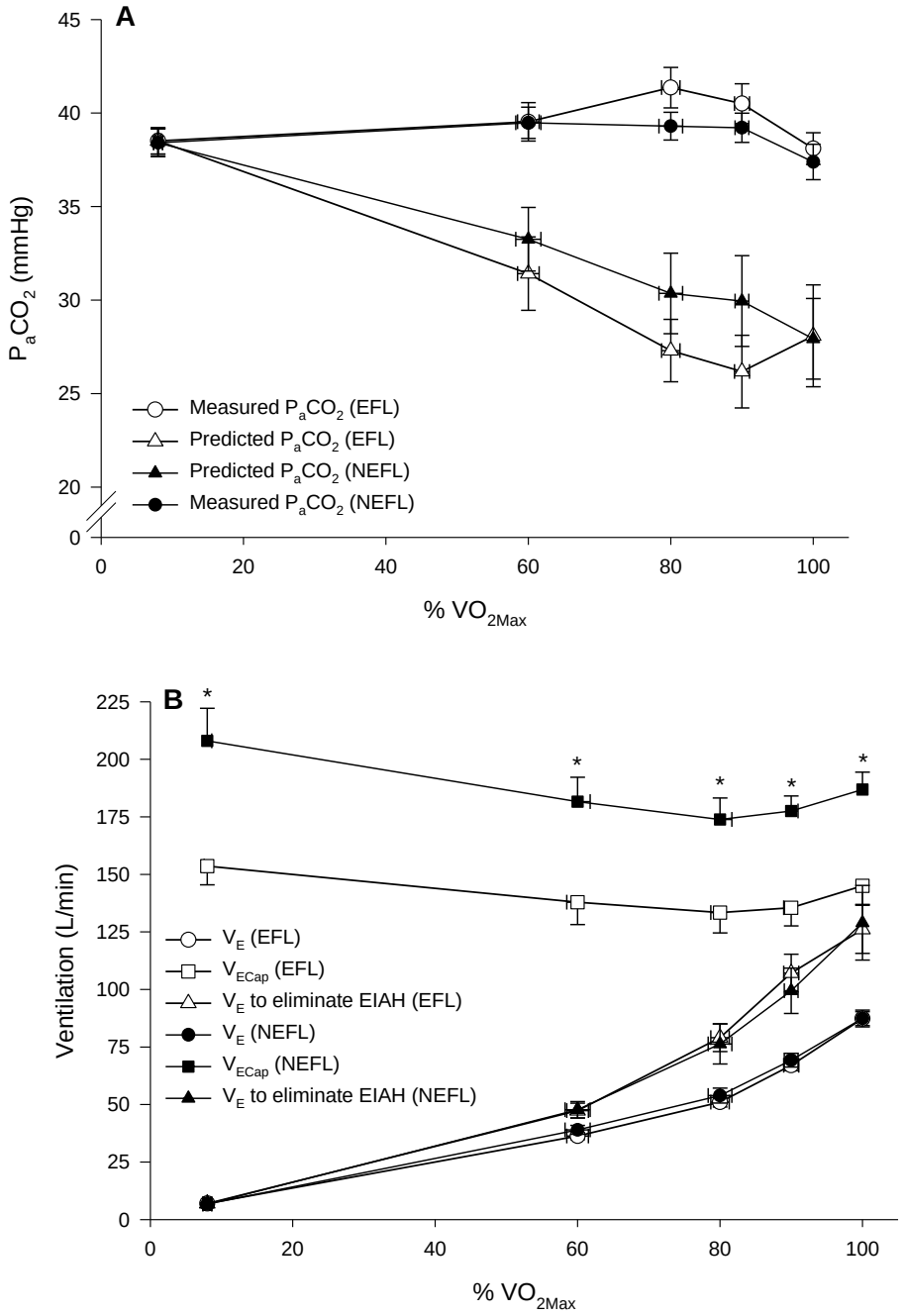
Eleven of the 14 subjects in the EFL groups also demonstrated some EIAH, while 9/16 subjects in the NEFL group showed some degree of EIAH. The EFL/NEFL groups were similar with respect to $\dot{V}O_2$ and $\dot{V}_E$ at maximal exercise. Furthermore, both groups showed had similar changes in P_aO_2, A-aDO_2, S_aO_2 and acid-base balance. However, above 40 L/min, the EFL group had a significantly higher WOB (Figure 20). Figure 21 shows the relationship between $\dot{V}_{ECap}$, $\dot{V}_E$ and the theoretical $\dot{V}_E$ required to offset any EIAH. The EFL and NEFL groups have similar $\dot{V}_E$ and $\dot{V}_E$ to offset EIAH at all intensities, however, the EFL group has a significantly lower $\dot{V}_{ECap}$ at all intensities (Panel B). This results in the $\dot{V}_E$ to offset EIAH approaching and nearly meeting $\dot{V}_{ECap}$ in the EFL group. At $\dot{V}O_{2Max}$, the $\dot{V}_E$ required to eliminate EIAH would be 87% of $\dot{V}_{ECap}$ in the EFL group and 68% of $\dot{V}_{ECap}$ in the NEFL group.

Figure 20- The work of breathing for the EFL and NEFL groups during the maximal exercise test.



Legend: At 40 L/min, the EFL group's WOB is significantly greater than the NEFL group's. WOB, work of breathing; $\dot{V}_E$, minute ventilation. $P < 0.05$.

Figure 21- Minute ventilation, maximal ventilatory capacity, theoretical ventilation to offset EIAH and the associated arterial carbon dioxide tension during maximal exercise test for EFL and NEFL groups.

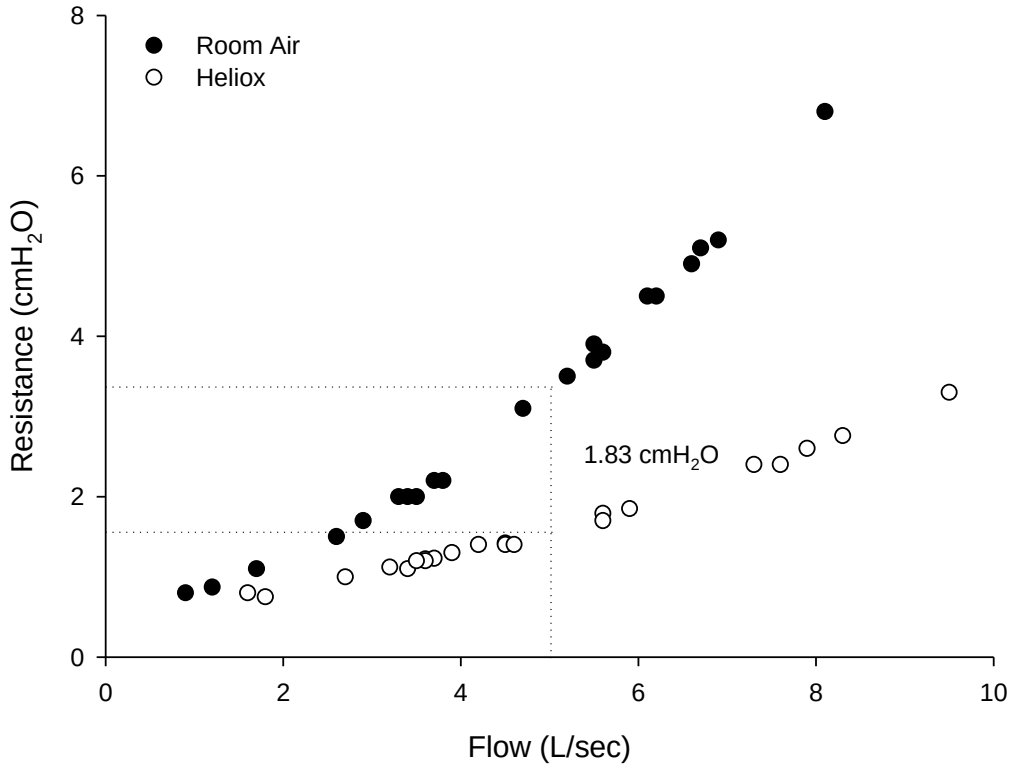


Legend: P_aCO_2, arterial carbon dioxide tension; $\dot{V}_E$, minute ventilation; $\dot{V}_{ECap}$, ventilatory capacity; EFL, expiratory flow limited; NEFL, no expiratory flow limitation; EIAH, exercise induced arterial hypoxemia. $\dot{V}O_{2Max}$, maximal oxygen consumption. *, significantly different from EFL $\dot{V}_{ECap}$. $P < 0.01$. n=30.

CONSTANT LOAD HELIOX TRIAL

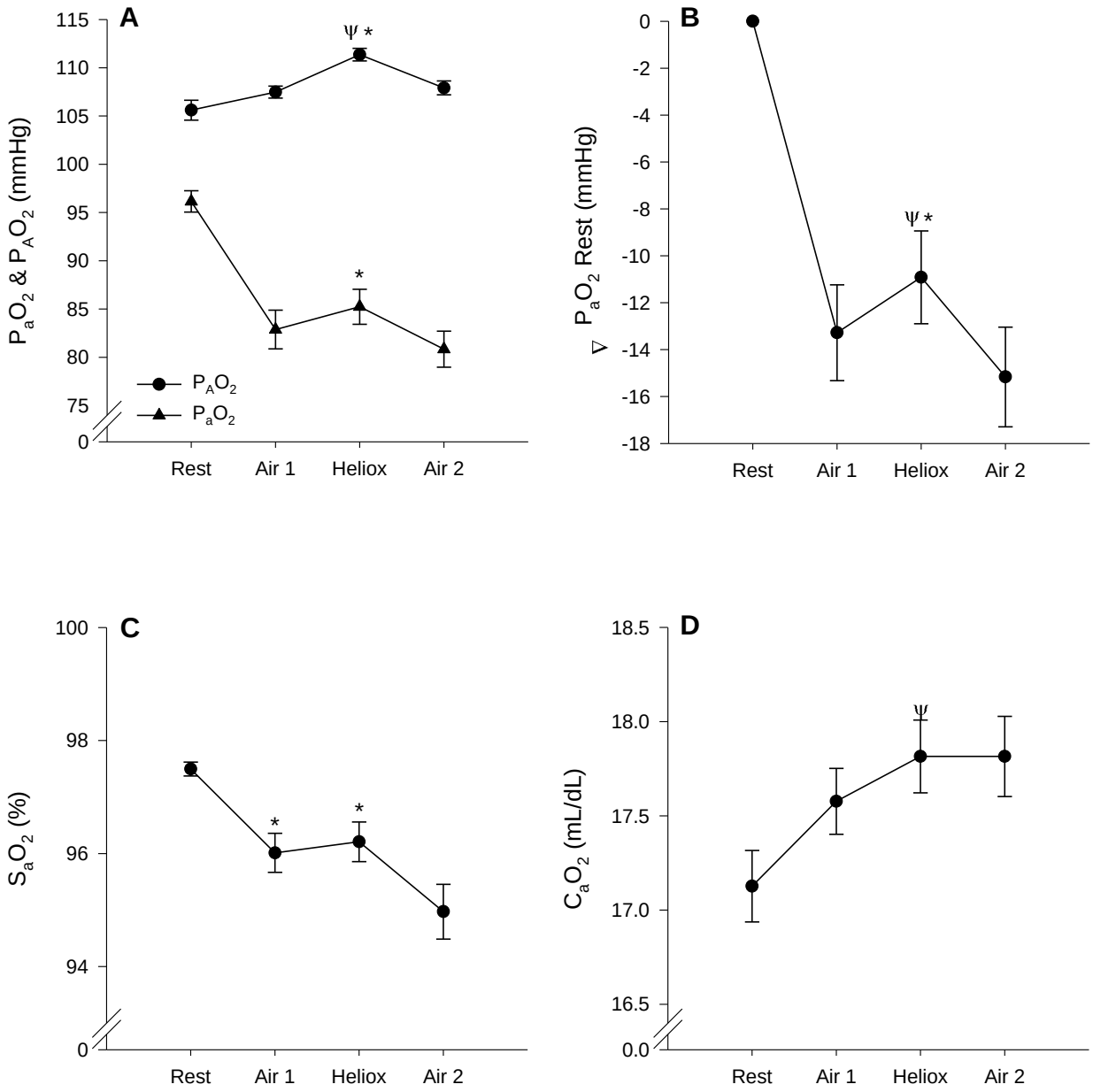
Twenty-four of the 31 subjects were able to complete the constant load heliox trial. Eighteen of the 24 showed some degree of EIAH during the maximal exercise test and 11 showed some EFL. Figure 22 shows the resistance in the external breathing apparatus for room air and heliox gas. As expected, the heliox gas decreased resistance at all flows and the difference was more pronounced at higher flows where turbulent flow starts to predominate. Figure 23 shows arterial blood gas variables for all subjects pooled during the constant load heliox trial. Arterial oxygen tension and S_aO_2 had returned to pre-exercise levels in all subjects. Subjects displaying EIAH during the $\dot{V}O_{2Max}$ test presented a similar degree of hypoxemia during the constant load exercise bout. Inspiring heliox gas increased P_aO_2, primarily through an increase in P_AO_2 (Figure 23, Panel A,B). Breathing heliox resulted in S_aO_2 remaining similar to the first air breathing condition before falling again when switched back to room air (Panel C). Figure 24 shows the composite MEFV curve for room air and heliox. The heliox MEFV curve is identical to the air MEFV in terms of FVC (3.8 vs. 3.81 L for heliox and air; respectively) however, expiratory flows are greater at given volumes, resulting in an increased the $\dot{V}_{ECap}$ for the heliox MEFV. If subjects ventilated on air with rates observed during heliox breathing, they would be very close to developing EFL. During heliox breathing, subjects increased $\dot{V}_E$, yet had a lower total WOB (Figure 25, Panel A,C) and lower tidal ΔP_{eso} swings (Panel B). Furthermore, the decreased WOB appears to be primarily though decreases in WOB_{Res} (Panel D). Figure 26 shows the regression line for air breathing WOB along with individual points for all the subjects during the heliox phase. The average $\dot{V}_E$ during heliox breathing was 77 L/min with a corresponding WOB of 110 J/min, which is a 32% reduction in WOB compared to air at a similar $\dot{V}_E$. To facilitate better comparisons, the 18 subjects who showed EIAH during the maximal exercise test were partitioned in groups depending on the appearance of EFL during the maximal exercise test. Subjects who had EFL demonstrated greater improvement in P_aO_2 and S_aO_2 compared to the NEFL group (Figure 27, Panel A, B, C), but had little effect on C_aO_2.

Figure 22- External breathing circuit resistance with air and heliox.



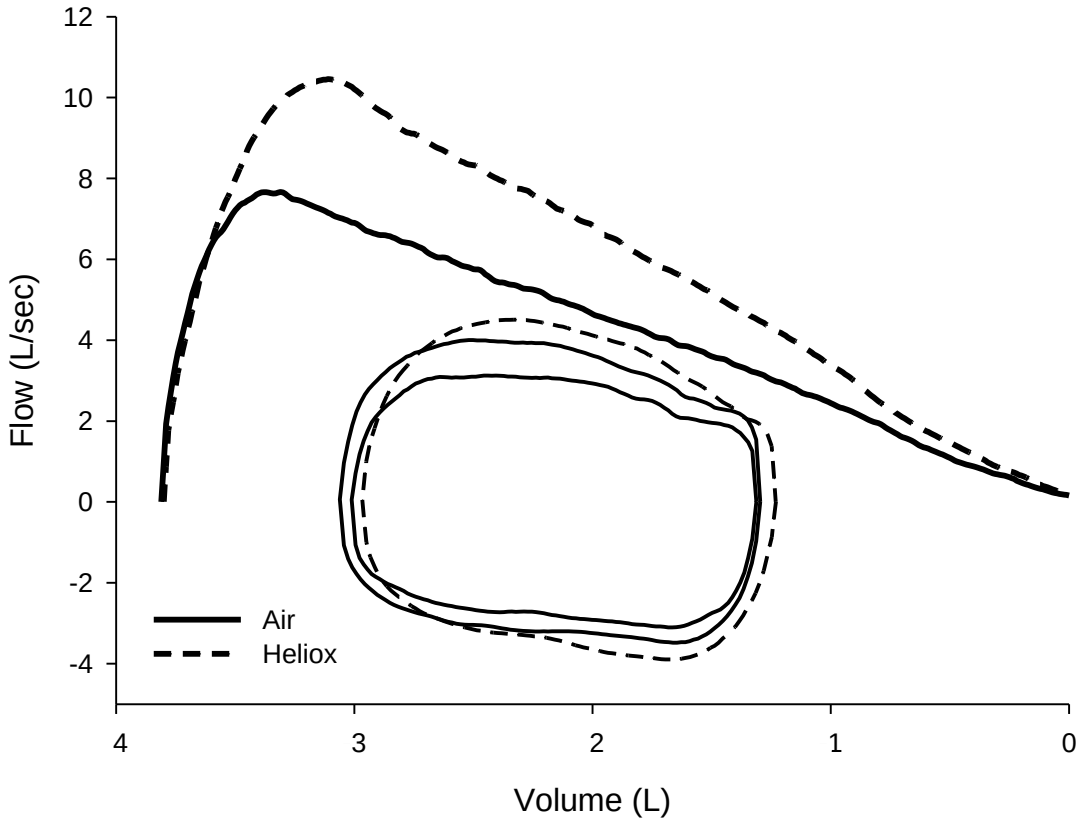
Legend: Resistance of the external breathing circuit measured by the measured pressure drop from mouth piece to pneumotachograph. At a flow of 5 L/sec the resistance was 1.83 cmH_2O less when using heliox. Average resistance was 0.68 cmH_2O/L/sec for air and 0.34 cmH_2O/L/sec on heliox

Figure 23- Blood gas variables during the constant load exercise test for all subjects.



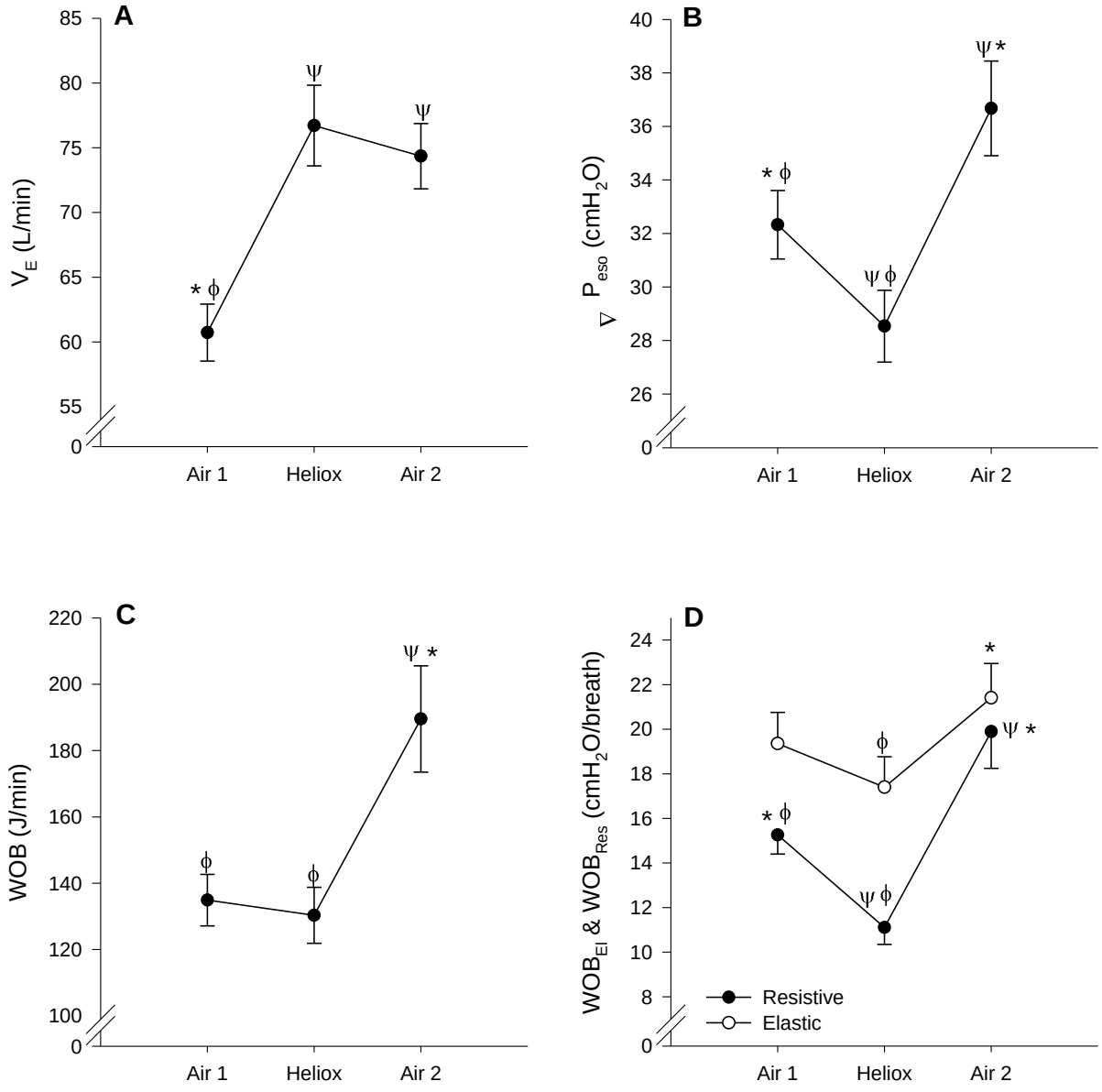
Legend: P_AO_2, alveolar oxygen tension; P_aO_2, arterial oxygen tension; ΔP_aO_2,change in arterial oxygen tension from rest; S_aO_2, oxyhemoglobin saturation; C_aO_2, oxygen content of arterial blood. Ψ, significantly different from Air 1; *, significantly different from Air 2. $P < 0.0125$. n=24.

Figure 24- Maximal expiratory flow volume curve and tidal flow volume loops while breathing air and heliox.



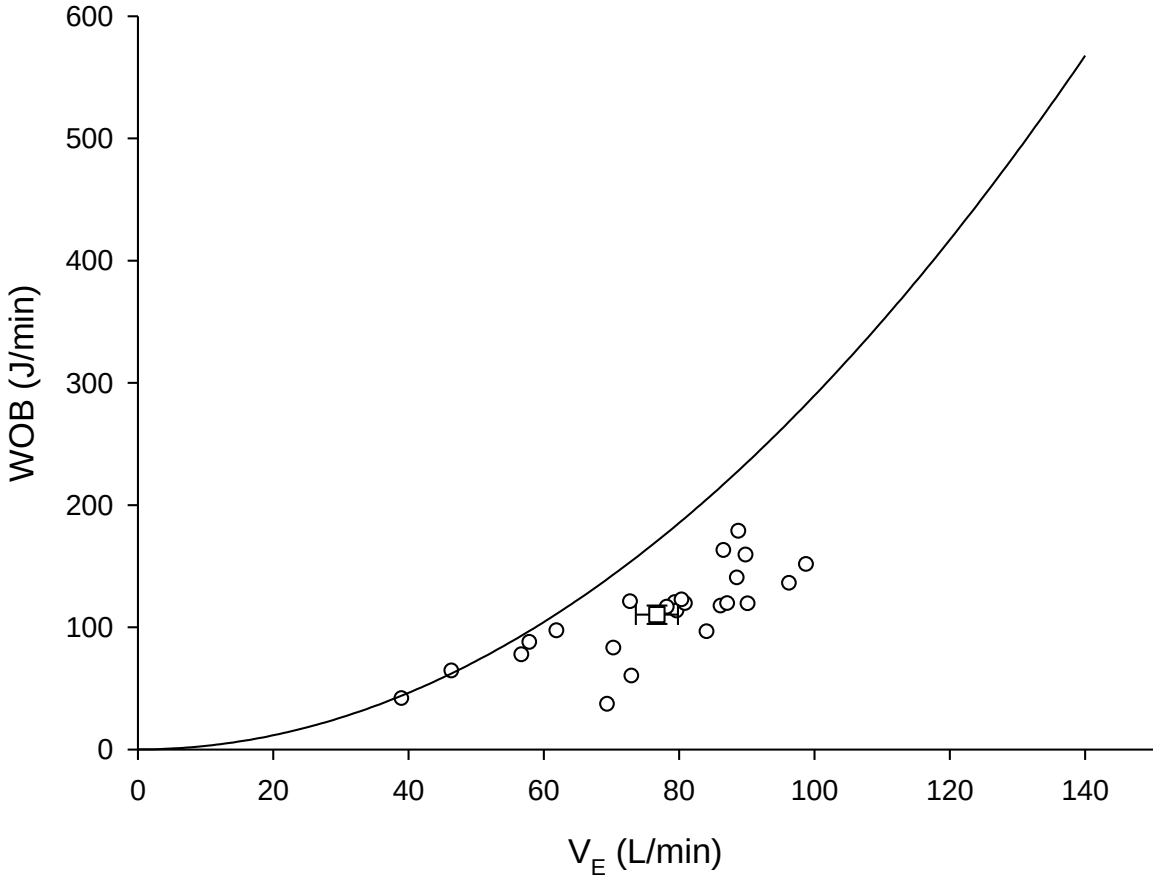
Legend: The tidal flow-volume loops are composite averages for both air breathing conditions and the heliox stage. n=24.

Figure 25- Respiratory mechanics during the constant load exercise bout for all subjects.



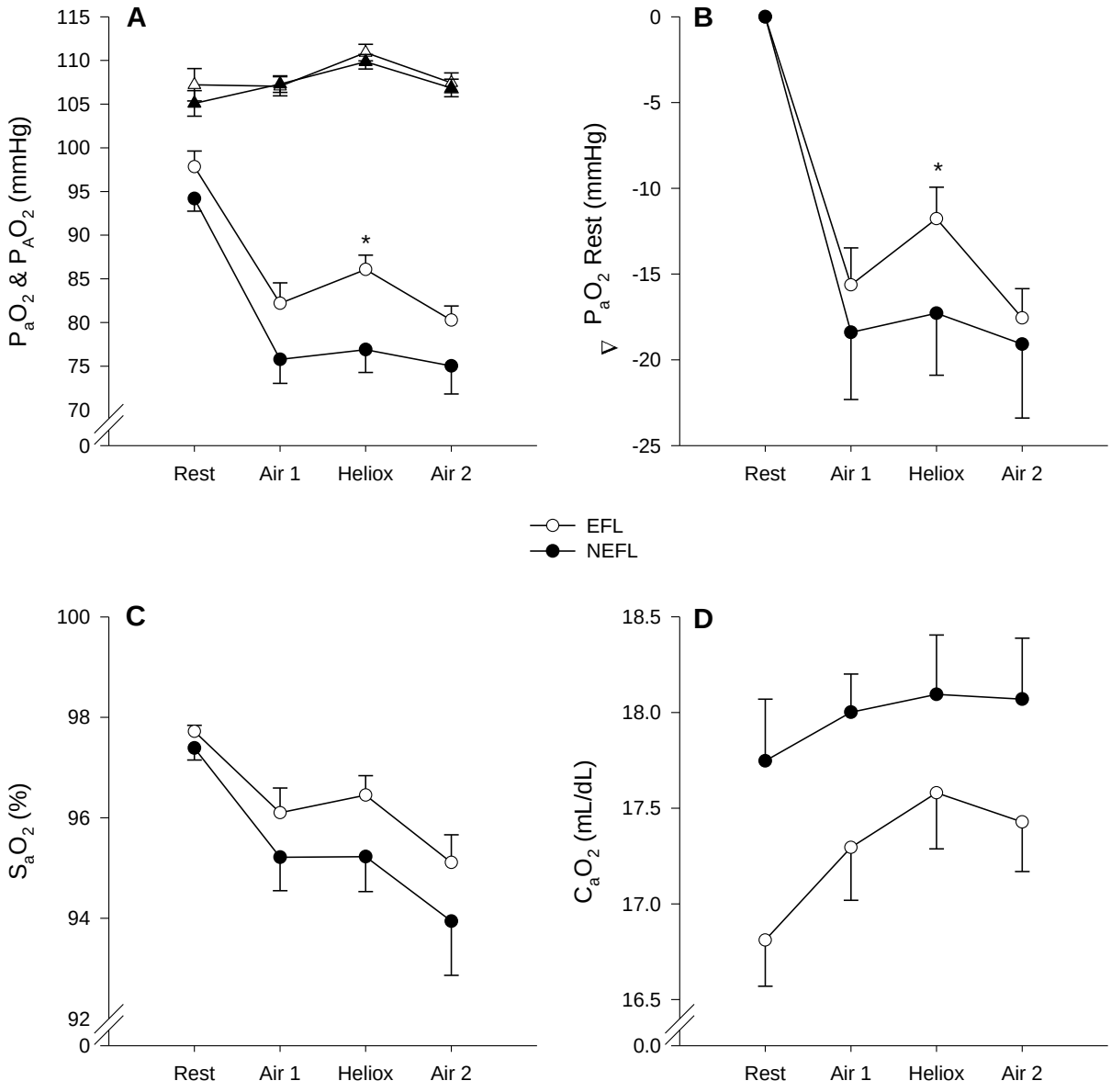
Legend: $\dot{V}_E$, minute ventilation; ΔP_{eso}, tidal esophageal pressure swing; WOB, work of breathing; WOB_{El}, elastic work of breathing; WOB_{Res}, resistive work of breathing. Ψ, significantly different from Air 1; *, significantly different from heliox; ϕ, significantly different from Air 2. $P < 0.025$. n=24,

Figure 26- Work of breathing on air and heliox during the constant load exercise trial.



Legend: Open square represent the average $\dot{V}_E$ and associated WOB during the heliox phase. At the average heliox $\dot{V}_E$ (77 L/min) the WOB is decreased by 60 J/min or 32% compared to air. Solid line represents the regression for air breathing. WOB, work of breathing; $\dot{V}_E$, minute ventilation.

Figure 27- Subjects who completed the constant load exercise bout and showed EIAH are split into EFL and NEFL groups with blood gas variables shown during the constant load exercise bout.



Legend: P_AO_2, alveolar oxygen tension; P_aO_2, arterial oxygen tension; ΔP_aO_2,change in arterial oxygen tension from rest; S_aO_2, oxyhemoglobin saturation; C_aO_2, oxygen content of arterial blood. *, significantly different from NEFL group. Open circles (○) represent the flow limited group. Filled circles (●) represent the non-flow limited group. $P < 0.0125$. n=18.

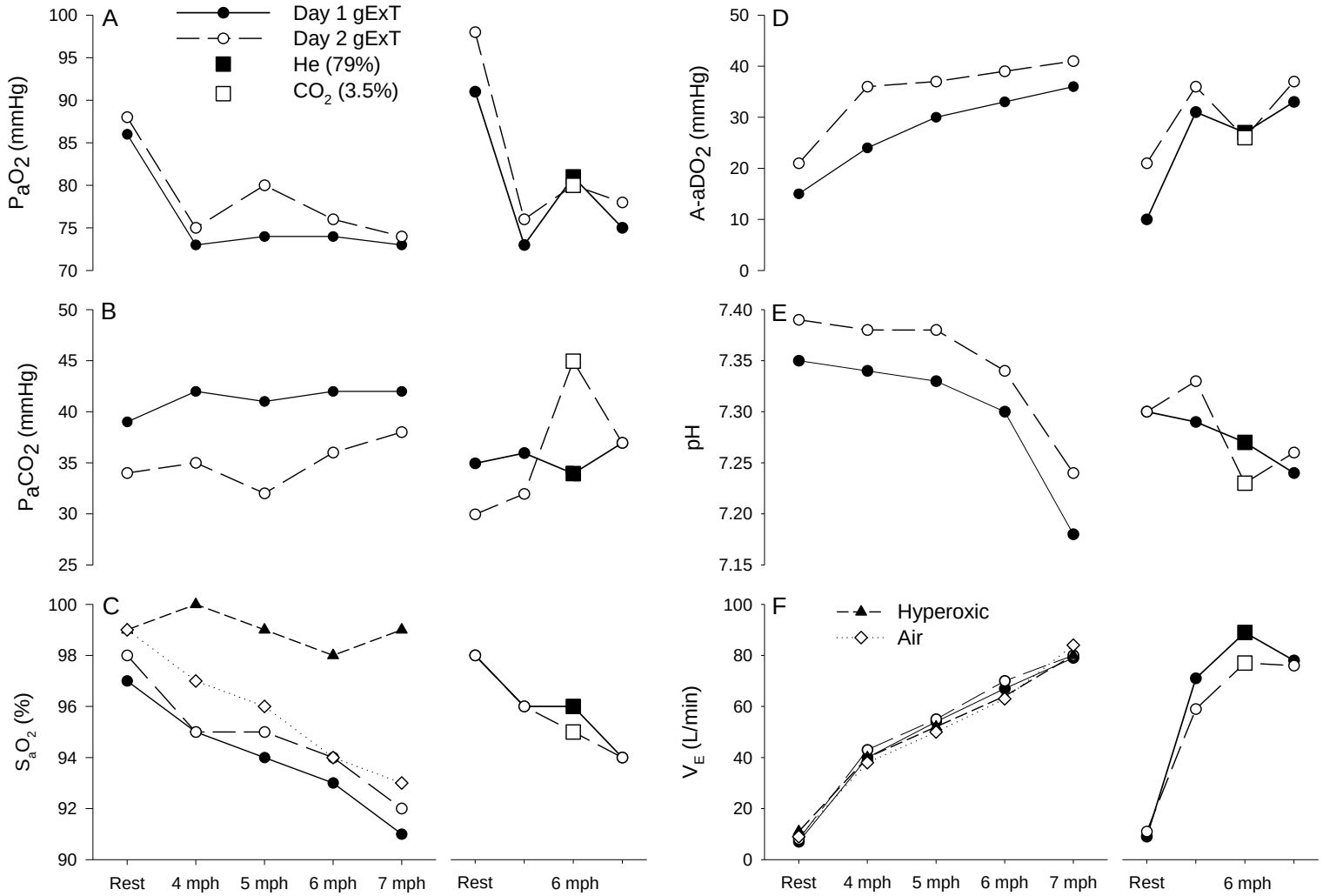
SUBJECTS WITH REPEATED TESTING

Two subjects had the maximal exercise test repeated in attempt to answer different questions. With both subjects we wanted to test the repeatability of EIAH over a relatively short time frame (4-5 months). For subject AC, we also sought to determine if $\dot{V}O_{2Max}$ would increase if EIAH was eliminated (via F_iO_2 0.26) and to test their chemosensitivity by using a F_iCO_2 of 0.035 during the constant load exercise bout. For subject SW, we wanted to determine the effect of endurance training on blood gas homeostasis. Their data will be presented individually and only their first visit has been included in any of the above results.

Repeated Subject 1- AC

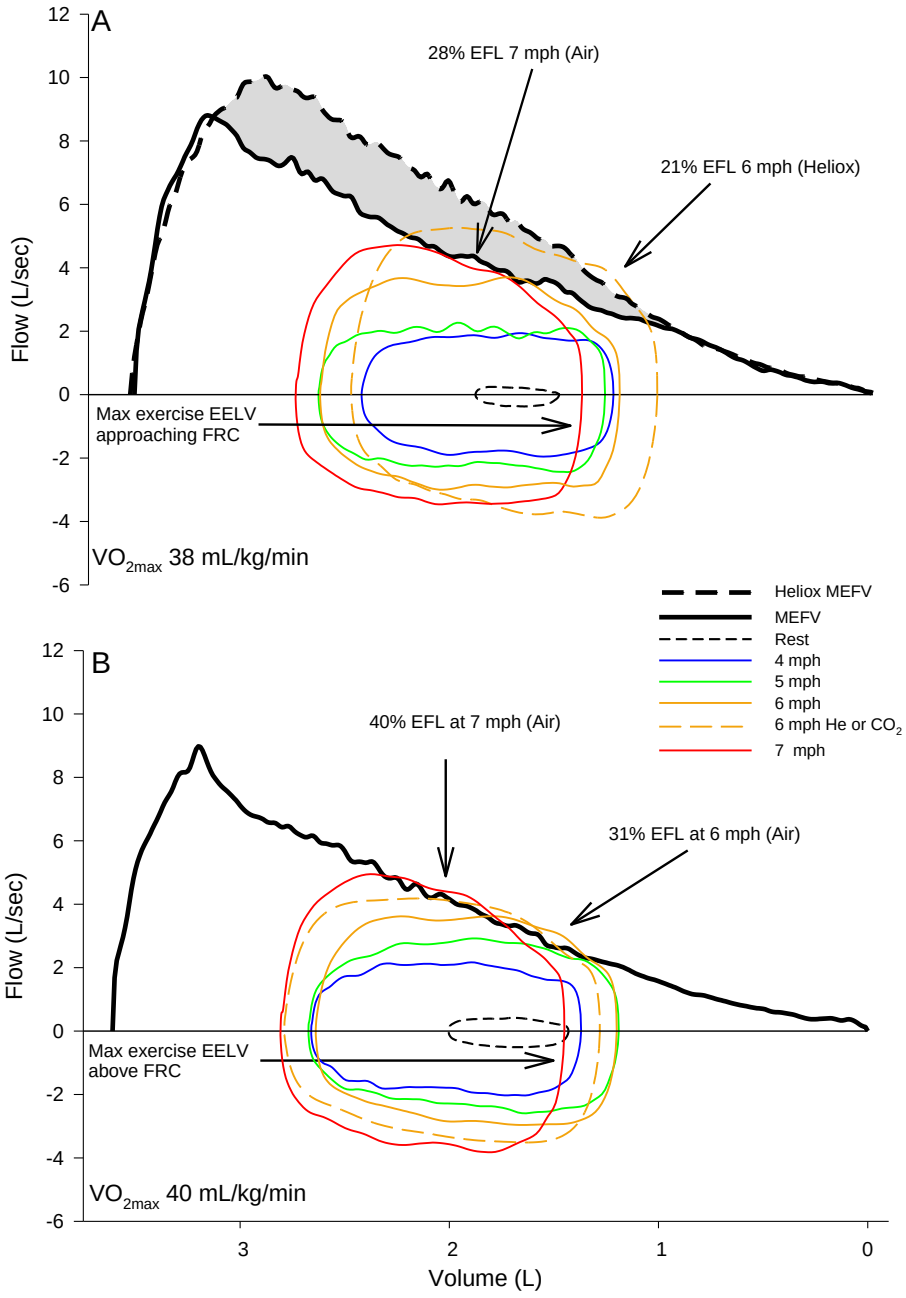
On the first visit, the subject demonstrated significant EIAH in the first stage of exercise (Figure 28, Panel A). At maximal intensities, the subject had a severe gas exchange impairment ($A\text{-}aDO_2$ > 35 mmHg), low S_aO_2 (91%) and lacked a significant hyperventilatory response (P_aCO_2 > 40 mmHg) (Figure 28, Panel B, C, D). The subject also showed EFL during the last two stages of exercise (Figure 29). During the constant load exercise bout, the heliox breathing increased $\dot{V}_E$, P_aO_2 and temporarily prevented S_aO_2 from falling (Figure 28, Panel A,C,F). During the second testing day (4.5 months later), the subject showed similar changes in blood gases, showed EFL, had similar $\dot{V}_E$ and achieved a similar $\dot{V}O_{2Max}$ for the maximal test (Figure 28). During the subsequent constant load exercise bout, the subject inspired a slightly hyperoxic hypercapnic gas (F_iO_2 0.22, F_iCO_2 0.035) rather than heliox. The hypercapnic inspirate raised P_aCO_2 levels, but did not change $\dot{V}_E$ (Figure 28, Panel B, F). All respiratory mechanics variable were similar for the first two testing days (See appendix). During the third visit, maximal exercise test inspiring F_iO_2 0.26 without arterial catheterization and esophageal balloon, the subject maintained a S_aO_2 > 98%, exercised 45 sec longer and increased their $\dot{V}O_{2Max}$ by 5 mL/kg/min with no changes in weight (Figure 28). During the fourth visit, maximal exercise test inspiring compressed room air without arterial catheterization and esophageal balloon, the subject's S_aO_2 fell to similar levels as the first and second visit and achieved a comparable $\dot{V}O_{2Max}$.

Figure 28- Selected blood gas and ventilatory variables during the first and second testing days for subject AC.



Legend: For each panel, the two series represent the graded exercise test and the constant load exercise test (left to right; respectively). gExT, graded exercise test; He, Heliox; P_aO_2, oxygen tension in arterial blood; P_aCO_2, carbon dioxide tension in arterial blood; S_aO_2, arterial oxyhemoglobin saturation; A-aDO_2, alveolar to arterial oxygen difference; $\dot{V}_E$, expired minute ventilation.

Figure 29- Maximal expiratory flow-volume curve for subject AC during the first and second testing days.

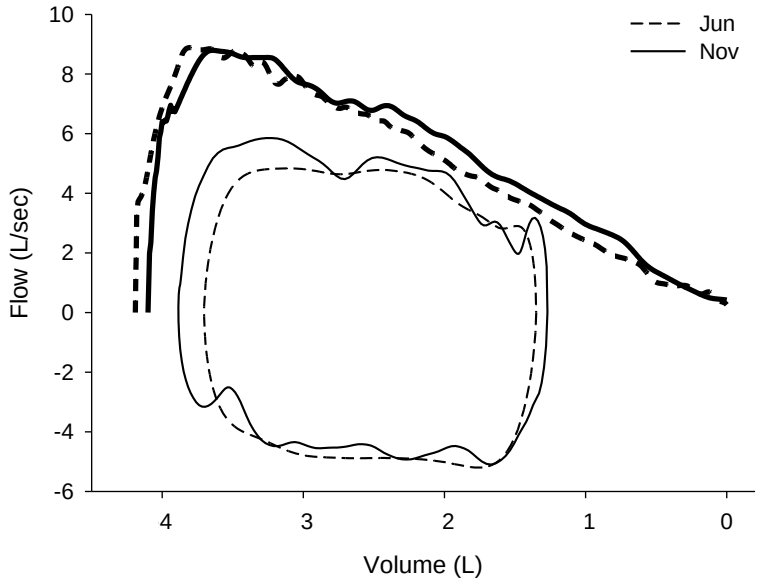


Legend: Maximal expiratory flow-volume curves, tidal flow-volume from *Days* 1 and 2 of testing. Panel A represents data from *Day1* while panel B represents data from *Day* 2; both include the graded exercise test and the altered inspirate stage of the constant load exercise test. The grey shaded area in panel A represents the increased ventilatory capacity resulting from heliox inspiration. The heliox gas was composed of 21% O_2, balance He and the hypercapnic mixture was composed of 3.5% CO_2, 21.7% O_2, balance N_2. EFL, expiratory flow limitation; EELV, end-expiratory lung volume; FRC functional residual capacity; MEFV, maximal expiratory flow-volume curve; $\dot{V}O_{2MAX}$, maximal oxygen consumption.

Repeated Subject #2- SW

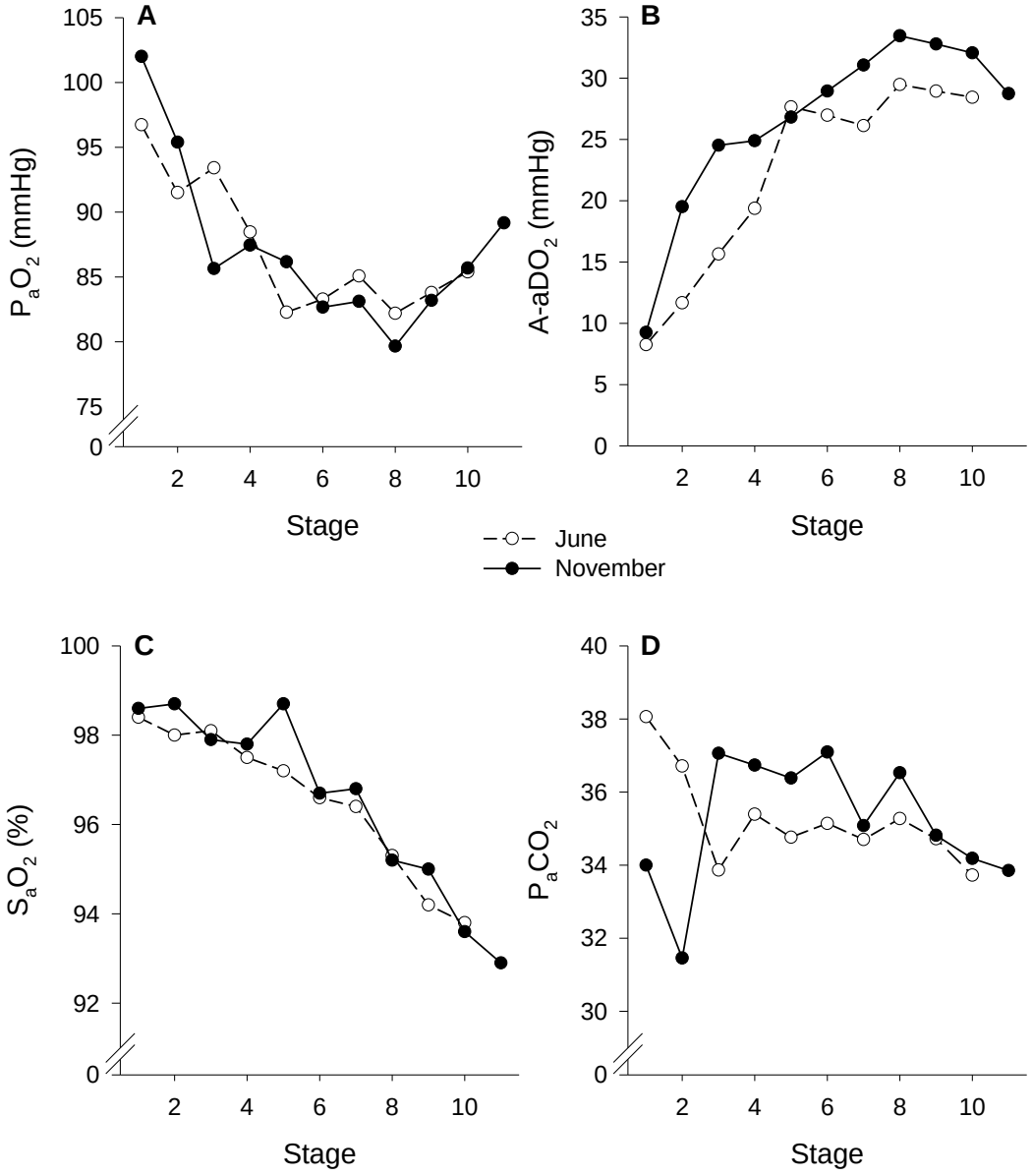
The second subject who was tested twice is a competitive middle distance runner. During the first testing session (June) SW was "relatively" untrained ($\dot{V}O_{2MAX}$ 60 mL/kg/min), as she was recovering from an injury. The second testing day (Nov) was done when the subject was back to a full training schedule and achieved a$\dot{V}O_{2MAX}$ of 68 mL/kg/min, with only minor weight change (-1 kg) and an increase in absolute $\dot{V}O_{2MAX}$ (3.43 L/min vs. 3.82 L/min for the first and second testing day). Figure 30 shows the subjects MEFV curve along with a maximal exercise FV loop; with little difference between the testing days. Figure 31 displays selected blood gases from the both training days. Despite being fitter and completing another exercise stage of exercise, there was little changes in the blood gases. The slight decrease in $S_aO_2$seen in Figure 31 Panel C is due solely to rightward shifting of the ODC (decrease pH, increase T_{eso}). The esophageal balloon catheter was displaced during the maximal exercise test for the second day, therefore, all associated data for that day is discarded as it is not known exactly when the balloon moved. The subject also demonstrated a similar response to heliox breathing during the constant load exercise test (See Appendix A).

Figure 30- Maximal expiratory flow-volume curve and maximal tidal flow volume loop for subject SW during both testing days.



Legend: Thicker lines represent the maximal expiratory flow volume curve, thinner lines are maximal flow volume loops.

Figure 31- Blood gas variables for SW during both testing days.



Footnote: P_aO_2, arterial oxygen tension; A-aDO_2, alveolar to arterial oxygen difference; S_aO_2, arterial oxyhemoglobin saturation; P_aCO_2, arterial carbon dioxide tension.

Discussion

MAJOR FINDINGS

The overarching purpose of this study was to characterize EIAH, gas exchange and respiratory mechanics during exercise in young healthy women. Secondly, we aimed to investigate the role of mechanical ventilatory constraints on EIAH in young healthy women. The major findings from this study are five-fold. First, in exercising women, there is a high degree of inter-subject variability in blood gas homeostasis and broad classifications of groups are not optimal when describing the mechanisms behind EIAH. Second, EIAH begins to develop at submaximal intensities in the majority of women (90%) in this study who display hypoxemia. Third, untrained women with unremarkable aerobic fitness levels can develop EIAH. Fourth, mechanical ventilatory constraints can lead to and/or exacerbate EIAH in women. Furthermore, mechanical ventilatory constraints could be an underlying mechanism behind EIAH in some untrained women. Fifth, relieving mechanical ventilatory constraints with heliox gas can *partially* reverse EIAH and heliox's effects appear to be greater in those that develop EFL. To date, this study is the largest assessing temperature corrected blood gases in women, the largest study on respiratory mechanics in women and the only study to make detailed blood gas measurements and respiratory mechanics measures in exercising women.

Inter-subject variability, broad classifications and patterns of EIAH

After examining Figure 2, one could determine that the subjects in the current study showed a homogenous and typical or "textbook" response to dynamic exercise. That is, $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ all increase linearly with exercise intensity until a threshold is attained whereby the latter two increase exponentially. Moreover, increasing $\dot{V}_E$ is driven by increasing V_T during low intensity exercise and increasing *f* during intense exercise. However, the primary goal of pulmonary ventilation during exercise is to maintain arterial blood gases within a narrow range despite increasing metabolic demand. Therefore, to most accurately understand dynamics of pulmonary ventilation, one should examine arterial blood gases during exercise. Figure 3 shows individual plots of arterial blood gases during the maximal exercise test and there is considerable variability with all variables. Specifically, at rest, P_aO_2 ranged from 75-~100 mmHg, yet all subjects maintained normal oxygenation (S_aO_2 > 97%) (Figure 3, Panel A). At (near) maximal

exercise, great variation in P_aO_2 was observed (range: 58-105 mmHg). Furthermore, at any given $\dot{V}O_2$ there was ~20 mmHg range in A-aDO_2 (Figure 3, Panel C). While S_aO_2 values are all ~98% at rest, upon exercise termination, there is an 11% range (87-98%), which, with all other factors being equal, would result in a 2 mL/dL difference in C_aO_2; enough to possibly elicit peripheral muscle fatigue (3, 70). However, there is a trend towards both worsening gas exchange and decreasing P_aO_2 as aerobic fitness increases (Figure 4, Panel C,D)(30), but notable exceptions exist (See *EIAH in untrained women* below).The high degree of variability is consistent with other reports in women (29, 30, 68, 85) but is not universal (33, 35).

Commonly, when studying EIAH, subjects are grouped and analyzed together, a necessary step to make statistical comparison. Unfortunately, broad grouping results in the loss of intra-subjects patterns, which could aid in describing the mechanism(s) behind EIAH. Based upon Figure 5, one could determine that the average female becomes hypoxemic during submaximal exercise until (near) maximal intensities when the corresponding increase in $\dot{V}_E$ results in increasing P_aO_2. This generalization, albeit statistically correct, provides little or no information regarding why or how the subject(s) are developing EIAH. Splitting a cohort into EIAH and NEIAH groups can offer some insight into potential mechanisms. For example, in Figure 12 Panel A, B it could be concluded that mechanical ventilatory constraints play little role in EIAH development, as both groups appear to have considerable ventilatory reserve, and the likely mechanism would be intrinsic to the pulmonary system (e.g., $\dot{V}_A/\dot{Q}$ mismatch, pulmonary diffusion impairment, arterial-venous shunt). However, this broad classification could also conceal intra-subject patterns regarding EIAH mechanisms. Rather a more instructive approach would be to partition and analyze the subjects based on the pattern of hypoxemia displayed, as illustrated in Figure 19. In this figure, the 20 subjects who showed any EIAH were split into 6 groups based on the pattern of hypoxemia throughout the maximal exercise test. While this study did not aim to test for any specific mechanism, we can make educated inferences based on MEFV curve, tidal FV loop dynamics and changes in P_aO_2.

The subjects in Figure 19, Panel A show a consistent decrease in P_aO_2 throughout exercise and do not appear to be mechanically constrained. The progressive drop in P_aO_2, due to a worsening A-aDO_2, would suggest a progressive $\dot{V}_A/\dot{Q}$ mismatch or a diffusion limitation related to increasing $\dot{Q}$ and less time for blood gas equilibrium to occur. The subjects in Panel B have a similar $\dot{V}O_{2MAX}$ and MEFV curve as Panel A, but show a dramatically different response

with respect to P_aO_2. Immediately upon starting exercise P_aO_2 decreases suggesting that pulmonary edema is not likely the primary mechanism and an acute $\dot{V}_A/\dot{Q}$ mismatch or an exercise induced shunt could be possible. However, near maximal exercise the subjects increase $\dot{V}_E$ substantially and P_aO_2 rises, giving a "U" shape to the pattern of EIAH. We suggest that this group experiences submaximal EIAH, for an unknown reason, but has a strong drive to increase ventilation near maximal intensities. In Panel C, this group of subjects show an immediate decrease in P_aO_2, however, thereafter there is little change. Mechanically, these subjects *could* increase their ventilation, but they apparently "choose" not to. Since the subjects shown in Panel B and C initially have similar patterns and both have the capacity to increase $\dot{V}_E$, it could be speculated that there is a difference in chemosensitivity between the groups that is only apparent during intense exercise. The mechanism responsible for EIAH in the subjects represented by Panel D is most noticeable; as the subjects are able to maintain P_aO_2 near resting levels until the onset of severe EFL. Thereafter, $\dot{V}_E$ is constrained and the subjects are unable to increase their ventilation to offset any EIAH. It should be emphasized that, the subjects in Panel D benefitted the most from inspiring heliox. Initially, the subjects in Panel E respond identically as Panel B with an initial drop in P_aO_2 with the onset of exercise. However, their rise in P_aO_2 is blunted by substantial EFL and they are unable to sufficiently reverse the hypoxemia. It could be suggested that the subjects in Panel B and E have a similarly strong drive to breath near the end of exercise, but the subjects in Panel E are confounded by EFL and therefore not able to increase their P_aO_2 to a similar degree as the subjects in Panel B. Finally, subjects in Panel F displays the sharp initial fall in P_aO_2, followed by the plateau, a similar response to subjects in Panel C. However, subjects in Panel F also shows EFL near the end of exercise, therefore, it would be difficult to discern whether their lack of P_aO_2 rebound is due to a mechanical constraint or blunted ventilatory drive. By analysing the pattern of EIAH, we can better appreciate the role, or lack thereof in some cases, of mechanical ventilatory constraints.

Submaximal EIAH

The majority (18/20) of subjects in the current study who developed EIAH did so at submaximal intensities (Figure 3, Panel A). Additionally, the nadir P_aO_2 in many subjects occurred at an intensities other than maximal. Submaximal EIAH has been reported by others (12, 30, 52, 66, 67, 70, 79, 85), but only a select few papers describe it in detail (30, 66). To

date, any mechanism explaining submaximal EIAH remains elusive and there is little descriptive data. However, submaximal EIAH does appear to occur more often during treadmill exercise (33) and women appear to be especially prone (30, 68). Traditional theories regarding EIAH, demand vs. capacity, cannot begin to explain submaximal EIAH, as all relevant organ systems have considerable capacity to increase output in response to increases in exercise intensity. Therefore, we must first ask, why do some individuals tolerate submaximal EIAH? Again, the current study did not test for specific mechanisms and is not able to provide any direct evidence, yet, we can speculate on some potential causes given the descriptive data. Below we present 4 theories on why some subjects would tolerate submaximal EIAH.

First, and the simplest explanation, the decrease in P_aO_2 may not be a sufficient physiological stress to elicit any response. Although P_aO_2 initially drops in many subjects, S_aO_2 remains near resting levels, therefore, C_aO_2 is largely maintained. This would suggest that submaximal EIAH has little or no effect on peripheral muscle fatigue. The main counterargument is the apparent randomness of who develops submaximal EIAH. Trained male subjects develop (submaximal) EIAH and resting chemosensitivity does not appear to be different between trained and untrained subjects (77). If submaximal EIAH has no consequences, why would unfit men not develop it or why do they prevent it by increasing $\dot{V}_E$ sufficiently? Women of all fitness levels appear to be able to develop EIAH, therefore, the same question exist, why do some tolerate submaximal EIAH and other do not? This discrepancy suggests that submaximal EIAH does negatively affect the humans response to exercise or preventing it hinders in some way.

Second, submaximal EIAH may represent a lag between pulmonary systems response to exercise. The lag could have two different origins: a lag between exercise onset and hyperpnea or a lag in the response to rapid changes in metabolism. First, the exact cause of initial exercise hyperpnea is relatively unknown, but stretch receptors that respond to the muscular contraction are implicated as a contributing factor. In dogs, it has been shown that the central and peripheral chemoreceptors are intricately linked and the stimulus in one effects the output in the other (7). In other words, there appears to be a "gain" function between the two receptors. A possibility is that the muscle receptors could modulate the relative output of the central and peripheral chemoreceptors and affect the secondary drive to breath. That is, upon exercise onset, after the initial central command related increase in output, the central and peripheral chemoreceptors

become less sensitive to the oncoming changes in blood gases. When pH is measured intra-arterially, decreases during exercise are not linear, rather an oscillating wave (5). The gain in the central and peripheral chemoreceptors may be decreased to eliminate reactions to cyclical changes and result in a more smooth output. Another distinct lag could arise from fast changes in metabolism without a coincidental increase in ventilation. Immediately upon starting exercise, RER drops from its higher pre-exercise anticipatory range. The fall in RER would reflect a fast switch from glucose metabolism to fat metabolism, resulting in a relative decrease in $\dot{V}CO_2$. Decreased $\dot{V}CO_2$ and P_aCO_2 returning to the lungs can both decrease ventilation (63, 64). Simultaneously, $\dot{V}O_2$ is unchanged, therefore, the P_vO_2 immediately returning to the lungs could be low. The low P_vO_2 coupled with a decreased ventilatory drive from CO_2 changes would result in an increased equilibrium time and possible lack of complete oxygenation at end-capillary. The lag theory could help explain why the hypoxemia appears to be fast onset and why it appears more in treadmill exercise over biking.

Third, our data suggests that submaximal EIAH is not exclusively due to relative alveolar hypoventilation ($P_aCO_2 < 38$ mmHg). Rather, submaximal EIAH is also related to gas exchange impairments as evident by the simultaneous increases in the A-aDO_2. However, we observed that while the gas exchange impairment occurs rapidly it also resolves equally as fast (See subject EM, MF and MB in appendix). We obtained post-exercise blood samples in some subjects (within 15-30 sec of exercise termination) and both P_aO_2 and the A-aDO_2 had returned to pre-exercise levels. Furthermore, the degree of EIAH experienced during the maximal test was similar to the constant load test. This suggests that there is no carry-over effect of gas-exchange impairment and the mechanism is only temporary. The lack of carry-over effect has been reported in a previous studies with female runners (79) and male cyclists (53). However, treadmill exercise is better able to elicit gas exchange impairments, when compared to cycling (33). A reasonable explanation is that the A-aDO_2 could be related to some motion disturbance caused by running, more specifically, the foot-strike. Women, due to the greater WOB, have considerable tidal ΔP_{eso} swings during exercise, which results in large changes in intrathoracic pressure. Similarly, during each foot-strike, there is a temporary change in P_{eso} that could be similar or paradoxical to the intended pressure change. However, it is not known if the foot-strikes affects all area of the lungs equally, or if the force is dispersed in proportion to chest-wall and muscular action. These large tidal changes in pressure coupled with temporary "spikes"

could result in small, temporary $\dot{V}_A/\dot{Q}$ mismatches. Specifically, the pressure swings would cause small peripheral blood vessels and airways to be temporarily occluded in a heterogeneous fashion throughout the lung. The idea of a mechanically related $\dot{V}_A/\dot{Q}$ mismatch was previously proposed by Johnson et al (42):

"*[EFL] may contribute to misdistribution of [$\dot{V}_A/\dot{Q}$] ratios during maximal exercise by causing nonuniformity in inspired $\dot{V}_E$ distribution secondary to dynamic compression of airways on expiration*".

The results of this thesis extend their idea to include blood vessels and propose that women could be especially prone to the mechanically induced $\dot{V}_A/\dot{Q}$ due to their higher WOB. Alternately, the foot-strike would cause shear mechanical forces on the blood vessels which could result in a vasospasms. The vasospasms would result in similar transient changes in blood flow. Both hypotheses require appropriate testing.

Fourth, tolerating submaximal EIAH may be a "strategy" to minimize respiratory effort and/or diaphragm and peripheral muscle fatigue. As seen in Figure 18 B, the $\dot{V}_E$ needed to offset EIAH can be considerable and would result in a substantial WOB and oxygen cost (1). Also, excessive WOB (and the ensuing fatigue of the respiratory musculature) can lead to systemic deficits in such as decreased blood flow to peripheral muscles (30). Individuals who tolerate submaximal EIAH may do so because reversing it would result in more severe consequences such as diaphragm fatigue, excessive oxygen cost of breathing and decreased leg blood flow. Finally, EIAH in men has been shown to lead to peripheral muscle fatigue (70), so presumably, submaximal EIAH would contribute to increasing fatigue. However, women appear to be more fatigue resistant compared to men in respiratory and locomotor musculature (26, 37). Therefore, women may tolerate the fatiguing effect of EIAH because they are inherently more fatigue resistant and the energetic cost to offset the hypoxemia would result in considerable energetic costs.

Untrained women

Some of the subjects in the current study who showed EIAH and were healthy but relatively untrained. Specifically, we had 6 subjects with a $\dot{V}O_{2MAX}$ under 50 ml/kg/min and 3

with a $\dot{V}O_{2MAX}$ under 45 mL/kg/min who developed EIAH. All of the untrained women who developed EIAH also had EFL, three of which developed EFL at submaximal intensities. Furthermore, 2 of the untrained subjects were able to maintain blood gas homeostasis until the onset of EFL. We believe our data along with others (30) provides evidence that untrained women can develop EIAH and that mechanical ventilatory constraints are a contributing factor to EIAH. Untrained women have previously been demonstrated to show significant mechanical ventilatory constraints (15) which could increase EIAH. The respiratory system show little or no positive adaptations to exercise training, therefore, the smaller lungs and airways in women would result in a lower ventilatory capacity that cannot be altered.

Heliox breathing

Heliox breathing appeared to have the desired effect during our constant load exercise bout where mechanical ventilatory constraints were minimized by; i) expanding the MEFV curve by reducing turbulent flow over the effort independent aspect; and ii) decreasing the mechanical WOB by reducing WOB_{Res}. The increase in MEFV is seen in Figure 24, where gains in expiratory flow are more significant over the effort independent aspect. This is important for two reasons. First, in healthy subjects, EFL occurs over the middle part of the MEFV. In this section of the MEFV maximal flow is determined by intrinsic factors rather than effort (22, 38, 62). Secondly, it implies that turbulent flow is, at some aspect of the airway tree, predominant over the effort independent aspect during air breathing. The increased MEFV allowed many subjects to increase their $\dot{V}_E$ and partially offset some of the EIAH. Partial relief of EIAH has been demonstrated by others when utilizing heliox gas (12, 52). The other effect of heliox in the present study was reductions in the total WOB (Figure 28). Theoretically, heliox should only decrease WOB_{Res}, however, we also found a slight decrease in WOB_{El} (Figure 25, D). It is possible that the decreased WOB_{El} can be attributed to small but systemic errors in the application of Campbell diagrams or pressure artefacts that alter the analysis of PV loops. Another possible explanation for the change in WOB_{El} is differences in operational lung volume during heliox breathing. While there was no statistical difference in EELV between stages, Figure 24 indicates that during heliox breathing it decreased slightly. The small change in EELV may be sufficient to change the aspect of the PV curve the subjects were breathing on, thus altering WOB_{El}. Overall, heliox appeared to decrease the WOB by ~30% compared to room air.

A 30% reduction in WOB would reduce the oxygen cost of hyperpnea (1), but, based on other research, it may not elicit changes in peripheral blood flow (28). Harms *et al*. (28) found that when the WOB was increased (50%) with a proportional assist ventilator (PAV) that leg blood flow was reduced by only 11% with considerable between-subject variation. However, as mentioned in *Submaximal EIAH* above, we speculate that high WOB and/or mechanical constraints may cause a gas exchange impairment, which heliox may partially alleviate. This theory is further confounded by heliox's effect on gas exchange, which it has been shown to improve and worsen (10, 17).

EIAH as a two-part problem

Often, EIAH is seen as a decrease in P_aO_2, which results in decreases in S_aO_2 and compromised oxygen delivery. However changes in the shape of the ODC from metabolic acidosis and hyperthermia can result in similar changes in S_aO_2. In the present study, about 50% of the reduction in S_aO_2 could be attributed to changes in the ODC, which is similar to other studies in women (30). Furthermore, the S_aO_2 from pH, T_{eso} and P_aCO_2 changes alone ranged from 91-97%, indicating that some women were not affected by ODC changes while other were. Ideally, one would keep their lung cool and alkaline, while the metabolically active tissue became hot and acidic. This situation would promote loading of oxygen at the lungs and off-loading at the muscle. However, temperature confounds this problem because as blood is heated, more oxygen can become dissolved and the P_aO_2 will increase; the opposite is true for cooling (75). Temperature related changes in P_aO_2 probably play little role during most situations because of the shape of the ODC. In the absence of EIAH, loading occurs on the upper flat part of the ODC, where large changes in P_aO_2 have little effect on S_aO_2, so hyperthermia related increases in $P_aO_2$would be irrelevant. However, the hyperthermia would shift the ODC and result in a lower S_aO_2, such is the case with most men. In women (or trained men) who develop severe EIAH, oxygen loading may start to occur on the steeper part of the ODC where small changes P_aO_2 can result in larger changes in S_aO_2. Effectively, the ODC shape change could be cancelled out by the increase in P_aO_2. Finally, women appear to have a different thermoregulatory response then men due to with a ~10% difference in fat-mass and surface area to body mass ratios (44). Women also appear to dissipate heat approximately 50% less than men during cold water submersion (82). Therefore, some of the discrepancies in EIAH observed

between men and women at intense exercise could be due to differences in regulating core temperature.

Insights into mechanisms of EIAH

The four mechanisms thought to contribute to EIAH are: relative alveolar hypoventilation, intra-cardiac or intra-pulmonary shunting, diffusion limitation and $\dot{V}_A/\dot{Q}$ mismatching. The present study is only able to provide direct evidence for relative alveolar hypoventilation, but we make insights for the others. A shunt, intracardiac or intrapulmonary, was not assessed in this study; therefore, we cannot conclusively determine its significance. However, we believe it is unlikely as the primary or exclusive mechanism. First, intracardiac shunts, in the form of patent foramen ovale (PFO) have been shown to have little effect on pulmonary gas exchange (47). Anecdotally, one of our subjects has a confirmed PFO, but, despite being the fittest subject tested ($\dot{V}O_{2Max}$= 67 mL/kg/min) she displayed relatively mild EIAH (nadir P_aO_2 = 80 mmHg). Also, some subjects (n=4) completed a hyperoxic inspirate stage during the constant load exercise bout where S_aO_2 returned to resting levels in all subjects. If the EIAH was due solely to a shunt, little benefit should be observed during slightly hyperoxic breathing. Unfortunately, it is not possible to assess shunting during running exercise and resting measures may not translate effectively to exercise. Specifically, the shunts could open in response to high pulmonary pressures and flows that occur during intense exercise and shut immediately upon exercise cessation.

All of our subjects had normal diffusion capacities at rest (Table 2). However, this does not indicate that diffusion was necessarily ideal during exercise. However, a diffusion limitation, other than extraordinary low P_vO_2, seem unlikely given EIAH began to develop immediately upon starting exercise. Diffusions limitations were often thought to be due to high $\dot{Q}$, which result in rapid red blood cell transit time (12) or excessive pulmonary artery pressure (PAP) that result in some pulmonary edema (87), both of which would not develop immediately. In some subjects, we are able demonstrate that hypoventilation was a probable mechanism behind EIAH. In these subjects, the hypoxemia coincided with the occurrence of EFL (Figure 19, D). While alveolar hypoventilation was not the primary cause of EIAH in most subjects, few would have been able to fully eliminate EIAH due to mechanical ventilatory constraints (Figure 18, B). By elimination, the primary causes appears to be $\dot{V}_A/\dot{Q}$ mismatching as postulated by others others

(13, 84). However, there is evidence suggesting no intrinsic sex-difference with respect to $\dot{V}_A/\dot{Q}$ mismatching (59), therefore, we are left with the unanswered question regarding why women appear to develop EIAH more often than men, as mechanical constraints do not appear to explain *all* of the variance.

Comparisons to men

The current study did not make any measures in men; therefore, we cannot make direct comparisons between the sexes. However, below we compare some of the results from this thesis with commonly reported findings in men. When examining the patterns of hypoxemia in the current study (Figure 19), some patterns have been previously been documented in men. Specifically, the slow progressive decline in P_aO_2 without any mechanical constraints (12) (Figure 19, Panel A) and mechanical constraints inducing a P_aO_2 drop (42) (Figure 19, Panel D) are common in men. However, the sharp initial decrease in P_aO_2 has also been reported in men (66, 70), albeit, to a lesser degree than women. To my knowledge, the "U" shape pattern of hypoxemia (Figure 19, Panel B) has not been reported in men, as such, potential mechanisms responsible for sex-difference in EIAH could be found within this group.

To date, there have not been any reports of untrained men developing EIAH, which is in contrast to our study and others (30). A possible explanation for this sex-based discrepancy could be the increased mechanical ventilatory constraints reported in women(27, 52) . Reports of untrained men experiencing mechanical constraints are rare, as the male respiratory system is generally "overbuilt" (11). That is, at $\dot{V}O_{2Max}$, the untrained male's respiratory system is capable of increasing output, whereas the cardiac and/or metabolic systems generally are not. As one engages in aerobic training, the cardiac and metabolic systems increase capacity (73), unlike the respiratory system (4). After considerable aerobic training, some highly fit men can have their respiratory system become the limiting factor in exercise (12, 42). However, this situation only occurs in highly trained men with extraordinary fitness levels ($\dot{V}O_{2Max}$ > 65-70+ mL/kg/min). Conversely, on average, women's respiratory has substantially less capacity; therefore, their respiratory system could become the limiting factor in exercise at a lower relative fitness level. All of our subjects had "normal" resting spirometry (>80% predicted), but, our untrained subjects who had EIAH had lower than predicted FVC, FEV_1 and midrange expiratory flows (no

statistics were done due to low numbers). The lower FEV_1 and midrange flows are indicative of a lower ventilatory capacity, furthermore, all of our untrained EIAH subjects developed EFL.

The prevalence of EIAH in men has been *estimated* at 50% of highly trained ($\dot{V}O_{2Max}$ 65+ mL/kg/min) subjects and it is thought not to occur in in untrained men (13). In women, the prevalence appears to be higher. Our study and others (30, 68) has found the prevalence to be 65-75% of ALL subjects tested including those with a low aerobic capacity. Furthermore, in our study, only one subject with a $\dot{V}O_{2Max}$ > 50 mL/kg/min did not develop EIAH, indicating that almost all of our trained women developed EIAH to some degree. Therefore, when comparing trained men and women ($\dot{V}O_{2Max}$ > 50 and 60 mL/kg/min; respectively) the prevalence appears to be ~93% and 50% in women and men; respectively. Adequate statistical analysis between men and women with regards to EIAH prevalence would be difficult due to the difference in cohorts, as studies in men typically only involve trained subjects. To date, the present study and two others have assessed EIAH prevalence in healthy women using temperature corrected blood gases (30, 33). Our results are similar to those of Harms *et al*. (30) although the prevalence was slightly higher (76%) compared to the present study (65%). However, the discrepancy can be easily explained by their study's higher fitness levels. Conversely, Hopkins *et al*. (33) found only 25% of women developed EIAH and only trained subjects could become hypoxemic during exercise. However, their contradictory findings could have arisen due to some problematic methodologies and results such as: arterial blood temperature correction, negative A-aDO_2 during moderate exercise, "core" temperature < 37°C during moderate exercise and peaking under 38°C, high resting P_aO_2 (108-113 mmHg) and low resting P_aCO_2 (<30 mmHg) with the latter two indicative of hyperventilation during rest.

METHODLOGICAL CONSIDERATIONS

Expiratory flow limitation

In the current study, EFL was assessed by superimposing tidal FV loops on the MEFV curves. This technique has been used extensively by others and shown to be reliable in both healthy and clinical populations (31, 41, 42, 58, 86). However, accuracy is dependent on three factors. First, the MEFV curve must be developed properly. The subjects must expire forcefully while thoracic gas compression and post-exercise bronchodilation are accounted for (25).

Subjects must also be screened for asthma of any form. Second, the IC maneuver needs to be performed properly, that is, the subject must have correct timing and inspire to TLC. Third, one must be confident that the tidal breaths used for analysis are a good representation and free of any unwanted noise artefacts. In the current study, we had subjects practice the IC maneuver at rest with visual feedback, performed gFVCs and compared the peak negative P_{eso} at rest to exercise IC maneuvers. Therefore, we are confident our assessment of EFL is accurate and reliable.

Work of breathing

Our WOB measurements must be acknowledged to be a best estimate, as there are several confounding factors, which presently cannot be accurately accounted for. First, during running, there is a considerable pressure change during the foot-strike. But, experimentally, we are unsure if the change in pressure is isolated to the esophagus (or gastric) or if it is transferred wholly or partially to the pleura space. Next, the foot-strike pressure change can be beneficial or harmful towards the intended pressure swing. For example, we can simplify the pleural pressure changes during respiration into a sine wave, with the decreasing amplitude and trough representing inspiration while increasing amplitude and crest representing expiration. If another wave (foot-strike) is added to the original, it can be in-phase and produce a constructive force OR out-of-phase and produce a destructive force on the total amplitude. If the foot-strike is destructive, it would require additional muscular effort to achieve similar amplitude. Altering and ultimately synchronizing breathing patterns in response to rhythmic exercise is referred to as entrainment. The contents of the thoracic cavity are largely tethered to the chest-wall and are held firmly in place; however, the abdominal contents are not tethered. During running, the abdominal contents represent a large mass that is constantly accelerating and decelerating in response to vertical displacement during running. During inspiration, the diaphragm moves downwards towards the abdominal cavity, if the abdominal contents are accelerating up during this inspiration, the diaphragm would have an additional opposing force to must work against. The force to overcome the abdominal contents momentum would not be reflected as a spike in gastric or esophageal pressure, but rather a temporary resistive force that decreases the overall net force created by the musculature contraction. To date, few studies have attempted to address the role of foot-strike artefacts on pulmonary mechanics. One study found the foot-strike had no

appreciable effect on volume changes, regardless of entrainment (6), however, they did not measure the pressure changes.

The second factor is the role of musculature in stabilizing the distortion of the chest-wall and/or stabilizing the abdominal wall during breathing. During rest and low intensity exercise, the chest-wall moves in a "natural" pattern, that is, in planes of least resistance. However, during strenuous breathing associated with heavy exercise, the chest-wall is distorted by accessory respiratory muscles applying unequal force and by upper body movement (20, 23). Furthermore, the abdominal wall must remain ridged to stabilize abdominal contents during rapid contractions of the diaphragm. To accurately account for both the aforementioned factors, one must first determine the natural pattern of chest and abdominal wall movements. The natural movement pattern can only be truly assessed by placing a temporarily paralysed subject inside a drinker spirometer and ventilate them via external negative pressure (similar to an iron lung) while assessing the movement of both the abdominal and chest-wall (23). Next, *during exercise* the movements of the abdominal and chest-wall needs to be accurately tracked in three planes while simultaneously measuring volume changes. Currently, making the resting measures entirely possible, but, are invasive, highly technical and prone to measurement errors. Assessing the movements during exercise is possible using optoelectronic plethysmography, but this technique is limited to biking exercise where the upper body can remain motionless. Presumably, during running the motion of the arms and torso, would at a minimum distort the chest-wall somewhat and surely abdominal muscle must contract. Third, one must determine the contribution to total volume change between the thoracic and abdominal cavity. This is necessary because any individual compartment may have a volume change in the opposite direction of the total system. Depending on whether the volume change occurred in the thorax or abdomen will change the amount of elastic work required (23). This possible underestimation of WOB is not trivial, rather the WOB has been estimated to be up to 25% lower when using just modified Campbell diagrams compared when chest-wall distortion and abdominal stabilization are not accounted for (23).

$\dot{V}O_{2MAX}$ vs. $\dot{V}O_{2Peak}$

Admittedly, not all subjects may have exercised to their true maximum; therefore, our values could be expressed as VO_{2Peak}. With naïve subjects and invasive experimental protocols,

there is a tendency for subjects to terminate exercise before their maximum. Treadmill exercise is prone to this pitfall as subjects may be hesitant about falling when fully instrumented. Despite the potential psychological limitation, all subject met most, if not all the general accepted criteria for $\dot{V}O_{2Max}$. All but two subjects attained an RER above 1.05 and all but one subject showed significant: acidification of arterial blood, decrease in bicarbonate levels, increase in esophageal temperature and a maximum HR within 10% of predicted maximum. Therefore, we are confident that our subject pool performed at or very near maximal work rates.

Arterial blood gas sampling

When measuring ABG, there are three primary sources of error. First, since the gas tension of arterial blood is substantially different from the atmosphere, blood must be drawn anaerobically and all air bubbles must be immediately evacuated. In the current study, we utilized commercially available arterial blood specific syringes, which allow air to be evacuated through a one-way membrane in the cap. The one-way membrane allowed the sample to be immediately sealed and any air bubbles removed without a second exposure to the atmosphere. Secondly, oxygen consumption and carbon dioxide production will continue in the blood after sampling, therefore, arterial blood should be analysed immediately. Ice baths can slow down metabolic activity and preserve the sample; however, quick analysis is optimal. In the present study, samples were analysed within 2 min after collection and most often within 30 sec. Therefore, there is little risk that our samples had errors from delays in analysis. Finally, an appropriate amount of heparin must be introduced into the sample to prevent the blood from clotting, yet, the amount cannot be excessive (which can alter P_aCO_2). To control the amount of heparin introduced, we utilized pre-heparinized syringes and withdrew a similar blood volume every sample. Additionally, samples were repeatedly inverted before analysis to ensure homogeneity of heparin and blood throughout the sample.

Dysanapsis/Airway size index

Our measure of airway size is not a true anatomical measure, but rather an overall index of relative airway size. The dysanapsis index has several caveats that should be considered. First, one cannot discern where along the airway tree possible differences exist. Second, all comparisons must be made at iso-lung volumes because the dysanapsis index is a relative

measure. Due to the effect of airway length (36) (mainly trachea and main bronchi) the dysanapsis index is negatively related to lung volume, therefore, the index is scaled to VC (or FVC). Technically, estimating dysanapsis requires simple measures; however, accurately performing several static recoil maneuvers requires adequate practice and is not intuitive to all subjects.

Constant load exercise bout

For our constant load exercise bout, we utilized one experimental gas (heliox) which is used to manipulate mechanical constraints. Ideally, we would have also performed trials using a mildly hypoxic mixture (F_iO_2 0.17), mildly hyperoxic mixture (F_iO_2 0.26) and a hypercapnic mixture (F_iCO_2 0.04). Utilizing these additional gases mixtures would allow a more complete analysis of EIAH mechanism (chemosensitivity and shunts). However, most (if not all) of our subjects where mentally and physically fatigued after the two exercise bouts, especially in cases where arterial catheterization took an abnormal amount of time. Therefore, we felt that results may have been compromised if subjects were asked to perform another bout and may not have given optimal effort. The stages of exercise were 2-2.5 min in length, however, we found that subjects often did not reach a steady state situation until the second stage. We aimed to keep the exercise bout as brief as possible, but acknowledge the first stage could have been extended for optimal results. Furthermore, rather than a constant load exercise bout where we manipulated one stage, we could have had each subject complete other maximal tests only breathing the altered inspirate. Thus, we would have had a full range of intensities for every gas type, unfortunately, the same fatigue issue would exist. Having subjects return on different days would eliminate the fatigue, but would have proven difficult logistically and would require multiple arterial catheterizations.

The desired property of heliox gas is its decreased density, which promotes laminar flow. The tendency toward laminar flow would be present in all circuits that the heliox flows, including the breathing circuit. Figure 22 indicates that resistance was 50% less when using air compared to heliox (0.68 vs. 0.34 $cmH_2O/L/sec$). The decrease in circuit resistance would result in a smaller driving pressure needed for a given flow rate. Our goal for using heliox was to decrease mechanical constraints, be it in the breathing circuit or intrathoracic, and use each subject as their own control. However, this method then does not allow us to make accurate

assessments of differences in airway size or geometry between subjects. For example, a subject who achieves higher flows would see a greater reduction in external circuit resistance as the two regression lines in Figure 22 are not parallel. Likewise, an individual with abnormally small airways would also see a great benefit to inspiring heliox. Partitioning the reduction in WOB between external circuit resistance and airway resistance is not possible, as we can only determine the reduction in P_{mt}, not P_{eso}. However, when the decrease in external resistance via heliox was applied to a P_{mt}-volume loop, the WOB would decrease by ~20%. Figure 26 suggest that the total WOB decreases by 32% using heliox (at a ventilation of 77 L/min). Therefore, it is possible that the significant amount of WOB changes via heliox arose from minimizing breathing circuit resistance. This problem could have been eliminated by added screens to the breathing circuit until the heliox resistance was similar to the air. However, this adds a degree of complexity that was not necessary given the goal was to minimize any mechanical constraint and not to make claims based on airway size.

Menstrual cycle

We did not attempt to control for the menstrual cycle in the present study, which has been employed in similar studies (30). Variations in circulating hormones throughout the menstrual cycle could effect chemosensitivity and alter ventilation (81). However, recent work (49) has shown that this precaution may not be necessary or practical for exercise testing. In their study, women not taking oral contraceptive and regularly menstruating, provided daily urine sample throughout an entire cycle. Several conclusions were drawn from this study: 1) Most women could not accurately self-report cycle phase. 2) There was considerable inter and intra-subject variation in hormone levels. 3) Circulating hormone levels affect resting chemosensitivity, but had no effect during exercise (49). Therefore, we believe that attempting to control for the menstrual cycle would be time consuming, impractical, expensive and ultimately futile as our primary aim was to assess the response to exercise.

Core temperature

When analyzing arterial blood samples during exercise, it is crucial that the gas tensions are corrected for core temperature. During strenuous exercise core temperature can vary from near resting levels (~37 °C) to as much as ~40 °C (Table 5). By default, blood gas analyzers

measure and express gas tension at 37 °C, however, if the subject's core temperature was 40 °C, P_aO_2 would be underestimated by over 10 mmHg. The optimal core temperature to correct blood gases would be pulmonary artery (PA) temperature, as it reflects the conditions during pulmonary gas exchange. However, PA catheterization is highly invasive and has considerable risks associated; therefore it is rarely, if ever, used for core temperature measurements in healthy exercising subjects. Several sites are commonly used as a surrogate for PA temperature, including: esophageal, rectal, peripheral arterial temperature (radial) and intramuscular. The latter two sites are not ideal because they do not accurately represent the temperature at the lungs. Peripheral arterial temperature is often lower than core temperature and is highly influenced by surrounding tissue, which is often cooler. Furthermore, intra-arterial temperature measurement is influenced by the blood flow during sampling. Intramuscular temperature is significantly lower than core temperature during rest and rises extraordinarily during exercise (74), due to the close proximity of metabolically active tissue. Therefore, intramuscular temperature would be ideal for measuring gas-exchange at the working muscle and estimated the a-vDO_2, where P_vO_2 requires correcting. However, the current study assessed pulmonary gas exchange, therefore, intramuscular temperature serves little purpose. For the current study, we chose esophageal temperature correction for several reasons. First, studies have indicated that esophageal temperature is closely related to PA temperature (~0.1 °C difference) (45, 69, 78). Secondly, when compared to other measuring sites, esophageal temperature is the most similar to PA temperature (45, 69). Finally, our esophageal thermistor was placed after the esophageal balloon catheter (which has depth markings), therefore, we are confident the thermistor tip was consistently placed in the distal esophagus in close proximity to the heart.

METHODLOGICAL IMPROVEMENTS

Full body plethysmography

To determine each subject's MFV curves, we had them perform several FVC and gFVC maneuvers and took the highest flow at any given volume. Using MFV curves is both simple, reliable and been utilized robustly in research, however, it makes no measure of pressure. Ideally, we should determine the critical pressures, for all volumes, whereby any increase in P_{pl} does not result in greater flow. To obtain these measures, a subject would need to be placed

inside a full body plethysmograph and perform several exhalations at different volume and different efforts. The plethysmograph allows for the simultaneous measurement of flow, volume and pressure. Measuring flow, volume and pressure simultaneously allows the determination of the pressure at which flow is limited, which is the most correct definition of EFL (39). The full body plethysmography technique has been used by other researchers to make detailed measured of mechanical constraints experienced during treadmill exercise (42).

Unfortunately, inspiratory flow is not limited by the same gas compressive effect as expiratory flow, therefore, the only appropriate method to determine IFL, also requires a full body plethysmograph. To determine the inspiratory aspect of a MFV curve, one must make several respiratory efforts at multiple fixed lung volume (2). Accomplishing both of the above techniques requires considerable technical expertise and a sufficiently sensitive (small) full body plethysmograph.

Inert gas dilution for operational lung volumes

An alternative method for determining operational lung volumes is to have a subject inspire inert gases during exercise. This is accomplished by breathing from a bag of known gas concentration and volume. At the end of expiration, the subject is switched from breathing room air to the bag containing the inert gas(es). Subsequently, the expired inert gas concentrations are measured for several breaths after the initial inspiration, until the inert gas(es) reach equilibrium. By knowing the initial concentrations, the bag volume and the equilibrium concentrations, one can calculate the EELV. However, inert gas dilution has several caveats and assumptions. First, while it is possible to obtain accurate timing for valve switching during low intensity exercise, this can prove difficult and often erroneous during intense exercise when f are high. Next, inert gas dilution assumes that the entire lung is equally ventilated and the gas diffuses evenly. This assumption holds true for most healthy people; however, given the high degree of gas exchange inefficiency observed in the current study, it *may* not be entirely accurate.

Blood sampling

Obtaining arterial blood in discrete samples provides an overall trend of blood gas changes, but lacks temporal sensitivity. In essence, we are sampling blood gases at 0.0067 Hz (1 sample every 2.5 min), whereas our other measures are sampled at 200 Hz and expressed in 10

sec averages. Therefore, we are "missing" 15 possible time points in between blood samples and are connecting the two data points with a straight line. However, we could utilize in-dwelling blood gas electrodes which continuously measure blood gases intra-arterially and provide valuable temporal data. Gathering on-line blood gas values would be crucial in determining the mechanism behind the initial fall in P_aO_2 upon exercise onset. In several subjects, the first sample demonstrated significant hypoxemia (P_aO_2 decreased +10 mmHg compared to rest) and subsequently P_aO_2 remained relatively stable throughout testing. By collecting on-line blood gases we could determine the pattern of initial P_aO_2 drop. An especially tantalizing possibility would be to combine on-line arterial blood gases and venous blood gases measured at (near) the right atrium *and* proximal to the main working muscle (femoral). Thus allowing for high temporal measures of gas exchange at the level of the lungs and working muscle.

End-tidal forcing during constant load exercise

In this study, subjects inspired pre-mixed gases with fixed concentrations for the constant load exercise bout. This method allowed administration of a similar "dose" of the altered inspirate. However, additional information regarding mechanism behind EIAH and EFL could have been obtained by using an end-tidal forcing system capable of high flows associated with exercise. For example, when administering the hyperoxic mixture, upon reaching steady state ventilation patterns, we could slowly raise the F_iO_2 breath-by-breath until a desired P_AO_2 was obtained. This process would allow us to determine precisely the amount of added O_2 necessary to offset the hypoxemia. Similarly, by slowing replacing nitrogen with helium, we change the mechanical work of breathing in increments, rather than a single step.

UNRESOLVED QUESTIONS AND FUTURE DIRECTION

Arterial oxygen tension

Is there a threshold for decreases in P_aO_2? This is still unknown, more precisely, how much does P_aO_2 have to decrease before $\dot{V}O_{2Max}$ and exercise performance is affected? Studies have assessed decreases in S_aO_2 (29), but we are unsure specific to P_aO_2. How does the change in P_aO_2 affect other organ systems? Is the problem in decreased oxygen delivery (C_aO_2) or does

tissue become increasingly hypoxic (P_aO_2 issue)? Is there a training effect to EIAH? Some studies have found that EIAH gets worse with training (57, 72), yet in our subject who we tested after significant fitness gains showed a similar degree of EIAH (Figure 31). Could EIAH be an innate structural and functional difference that remains relatively static in individuals? Or does an individual need to train to the point where their respiratory system becomes the limiting factor? For example, our subject that improved their aerobic fitness still has considerable capacity to increase ventilation, so their EIAH would be due to intrinsic properties. Some people may not be able to increase their aerobic capacities to a level where the pulmonary system becomes the limiting factor; such is probably the case in most men. Conversely, a subject who has relatively small lungs and airways would not have to train intensely before they began to be mechanically constrained. Finally, how does the P_aO_2 drop initially during submaximal EIAH? Is the decline linear? Curvilinear? A linear trend with oscillations? Furthermore, does the P_vO_2 drop in a similar fashion? Or does P_vO_2 drop first and then P_aO_2 lag behind?

Venous oxygen tension

Mixed venous and femoral P_vO_2 can become exceedingly low (<15 mmHg) during various forms of exercise in men (9, 21, 34). But, does the P_vO_2 in women get as low or lower and does a sex-difference exist? Others have shown a sex-difference in muscle metabolism (18), therefore, it is conceivable that for a given workload and P_aO_2, the P_vO_2 could be different in women. The most obvious answer would be to make P_vO_2 measures at multiple sites (immediately proximal to working muscle and close the right atrium) in exercising women while assessing EIAH. The P_vO_2 in exercising women could be especially valuable when determining the mechanism behind submaximal EIAH in women.

Submaximal intensity.

As outlines above, submaximal EIAH remains a mystery. Conceivable, subjects are mechanically able to eliminate it, but they don't. We believe there are 4 key questions to be answered. 1) Does submaximal EIAH have a functional consequence, such as altered blood flow and/or fatigue? 2) Why do some subjects tolerate submaximal EIAH while others don't? 3) Why do women appear to be especially prone to developing submaximal EIAH? 4) Why does running exercise elicit submaximal EIAH more often than cycling? A possible solution would be to have

a group of male and female subjects complete a cycle, treadmill and skiing maximal test. Skiing and running are both whole body exercises, while skiing eliminates much of the motion and foot-strike artefacts. Furthermore, P_aO_2 could be titrated at submaximal intensities until fatigue or $\dot{V}O_{2MAX}$ decrements are observed.

Blood flow and fatigue

In men, changes in WOB has been shown to alter limb blood flow, presumably, by preferentially supplying the respiratory muscles (28). Women, compared to men, have a higher WOB at similar ventilations (27). Are based sex-difference in WOB enough to elicit changes in limb blood flow? To date, no studies have attempted to address this question. Presumable, one would have to match men and women for fitness levels and manipulate their WOB with a PAV. Specifically, at a given ventilation, increase the men's WOB until it is similar to that of the women and vice versa. Similarly, does the onset of EIAH have any effect on limb blood flow? Localized hypoxia can cause vasodilation and increase blood flow, but is the decrement in P_aO_2 observed in EIAH sufficient? Recently, studies have assessed peripheral muscle fatigue as it related to EIAH (3, 70) using femoral nerve stimulation. Both studies were conducted in men and found that hypoxemia increased the amount of fatigue experienced. Does this relationship extent to women? Women appear to develop EIAH more often and more severely, but also appear to be more fatigue resistant in many muscles.

Foot strike

The contents of the thoracic cavity are largely tethered to the chest-wall, whereas, abdominal contents are not. Presumably, there is some motion in the abdominal viscera during running. If abdominal contents are displaced vertically, while the diaphragm is contracting, an added strain could be added to the diaphragms work. This would not be reflected in a pressure change, but rather as a temporary resistance that needs to be overcome. Also, as outlined earlier, the foot-strike may play a role in creating temporary $\dot{V}_A/\dot{Q}$ mismatches by creating more areas of the lungs where vessels are occluded. However, to the author's knowledge, it is not known experimentally if the foot-strike artefact observed in the esophagus and stomach equally affects the pleural space. If it does not, any assumption regarding the footstrike could prove to be false.

Oxygen content

In the current study, all but a few subjects increased their C_aO_2 throughout exercise, despite a decrease in S_aO_2 (Table 5). Several questions remain with regard to oxygen content and delivery. Is oxygen content manipulated by more than saturation and Hb? For example, changes in temperature, pH and CO_2 will alter the shape of the oxygen dissociation curve for a given P_aO_2. Temperature and acid-base balance is highly individualized; therefore, some subjects may prone to alterations in content due to changes in ODC shape. Furthermore, could C_aO_2 be manipulated through difference in "environment" in different parts of the body? For example, during exercise, metabolic activity causes muscles to become more acidic and increase their temperature; which promotes offloading of oxygen at the muscle. What would happen if the muscle was to remain cooler and less acidic? Would this decrease offloading and increase C_vO_2 due to a lesser utilization at the muscle? Also, what would be the effect of increased temperature at the site of oxygen loading (lungs)? Could this hinder the exchange of oxygen and decrease the C_aO_2?

Heliox

The desired property of heliox gas is decreased density, which increases the tendency towards laminar flow and minimizes turbulent flow. By keeping airflow laminar, the total WOB is decreased, due to less resistive work, and the tidal ΔP_{eso} required per breath is decreased. Additionally, heliox breathing will increase expiratory flow along the MEFV curve without changing lung volume. Therefore, heliox can partially or fully relive mechanical constraints encountered during exercise. However, is this the only effect heliox breathing has during exercise? The author believes there are several other important factors that must be acknowledged with respect to heliox breathing. First, helium, as the inert backing gas, is more efficient at diffusing then nitrogen. Gases travel primary by bulk flow in the larger conducting airways, but, once into the smaller peripheral airways, gases travel largely by diffusion. Therefore, helium may allow for quicker and more efficient gas movement deep in the lung. The improvement in gas diffusion could lead to an improvement in the A-aDO_2. Improving gas exchange with helium has been demonstrated in exercising horses (17), but refuted when using mechanically ventilated dogs as a model (10). Second, helium has a lower specific heat capacity

then nitrogen, therefore, it will transfer heat more effectively. During exercise, there is substantial heat loss in the airways due to evaporation and convection, especially during high flow associated with heavy exercise. Helium may increase heat loss and cool the airways more than nitrogen. Cooling of the airways can lead to an acute asthma attack, or a general inflammation of the airways. However, cooling of the airways could aid in central heat dissipation and could lower core temperature. A lower core temperature would be beneficial during exercise as temperature significantly shifts the ODC and hinders oxygen pick-up in the lungs. Finally, is the effect of heliox sufficient to elicit systemic changes in blood flow or peripheral muscle fatigue? By substantially reducing the WOB via a PAV, peripheral blood flow can increase (28). Also, altering C_aO_2 can change the severity of peripheral muscle fatigue and exercise performance (3).

A solution to the above problems could be addressed by a PAV with heliox and a high density gas (SF_6). The PAV would allow manipulation of the WOB and mechanical constraints while the effects of the gas density could be independently varied, thus independently altering mechanical constraints and gas density factors.

Subclinical edema

The blood-gas barrier in alveoli is both thin, yet remarkable strong. In pathological conditions, such as congestive heart failure, rises in PAP can lead to pulmonary edema. Furthermore, rises PAP is implicated the causative factor behind high-altitude pulmonary edema, which can affect previously healthy human during ascent to altitude. During acute exercise, venous return to the heart increases and the heart beat faster and more forcefully, resulting in a greater $\dot{Q}$ which increases PAP. As such, it is possible that a potential mechanism behind EIAH is pulmonary edema causing a diffusion limitation. Others have attempted to detect pulmonary edema after exercise with mixed results (16, 48, 87). An explanation for the mixed results could be the lack of sensitivity in the instruments, the time delay between end of exercise and imaging and the inability to assess edema during exercise. Therefore, it is possible that there is a very small, subclinical, amount of edema during exercise that quickly resolves, but is sufficient to contribute to gas exchange inefficiencies.

Older women

Previous studies on men have demonstrated that EIAH is more prevalent in older men compared to their younger counterparts (65). Healthy aging negatively effects pulmonary function in all individuals through a decrease in lung elasticity and stiffening of the chest-wall (19, 51, 83), both of which decrease ventilatory capacity (41). On average, women, irrespective of age, already have a decreased ventilatory capacity (52), therefore, it is possible that the effects of healthy aging could exacerbate EIAH. Due to the process of aging, some women who previously did not show any mechanical constraints or EIAH could begin to develop significant ventilatory constraints which lead to EIAH. Furthermore, our hypothesis of regarding mechanically induced $\dot{V}_A/\dot{Q}$ mismatch could be exacerbated in older women due to decreased elasticity in their airways which results in an earlier equal pressure point and greater compression of airways (and blood vessels). To date, there has not been a study to assess EIAH in healthy older women.

Conclusion

In young healthy women, there is considerable variability with respect to blood gas homeostasis during dynamic treadmill exercise. Some women experience significant and sudden gas exchange inefficiencies immediately upon starting to exercise, while others maintain their blood gases at (near) resting levels. Yet, the majority of women do develop some degree of EIAH, however, the pattern and/or mechanism(s) behind the hypoxemia is varied between subjects. Compared to trained men, trained women appear to develop EIAH more often and unlike untrained men, some untrained women can develop EIAH. In contrast to untrained men, untrained women develop mechanical ventilatory constraints during exercise, which could be a mechanism to explain EIAH in untrained women. Relieving EIAH by inspiring heliox gas will partially offset the decrease in P_aO_2, through increase ventilation, and the effect is greater in subjects who demonstrate EFL. In conclusion, the pulmonary systems response to dynamic exercise in women appears to be highly variable and unique to each subject. However, further investigation need to be completed to determine if the difference have systemic consequences such as decreased blood flow and/or increased fatigue to peripheral musculature that could negatively affect exercise tolerance or performance.

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Appendix A: Individual subject data

This appendix contains the individual subject data. Each subject has three pages, beginning with their description and MEFV curve with tidal FV for the maximal exercise test and the constant load test. Immediately following is a page dedicated to arterial blood gas variables and a page of mechanics related data. Two subjects (AC and SW) who were tested twice have both included and marked as “Day 1” and “Day 2”. The first set is an example and is NOT data collected or used for the study, rather is serves as a legend for all others.

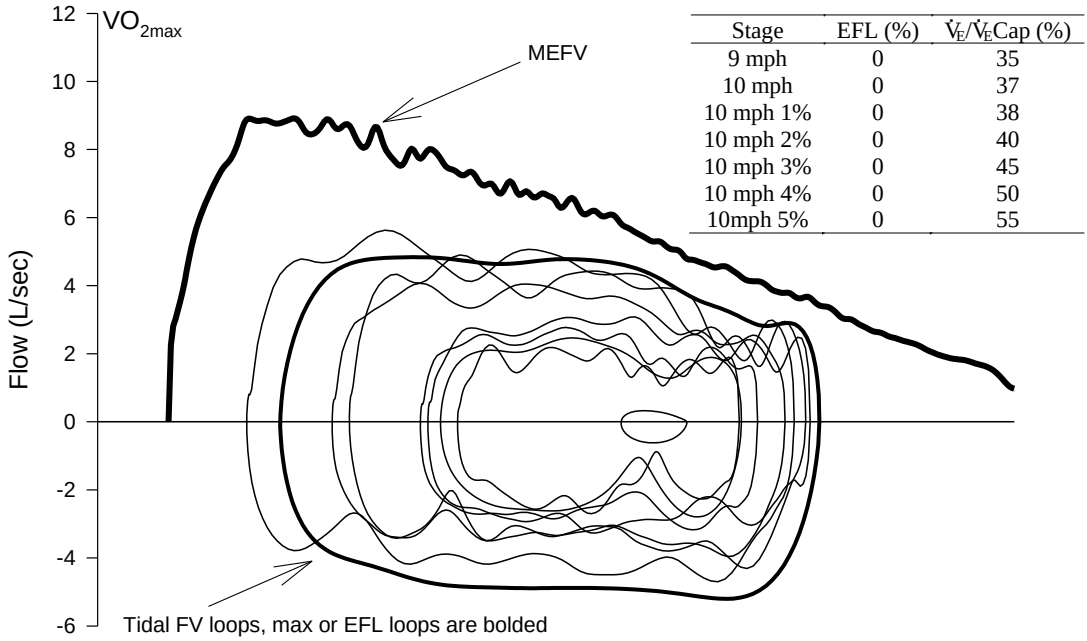
Figure 32- Example, MEFV curve and descriptors.

Subject SMcC- Big mountain skier, GNAR Supplement Daily *****EXAMPLE*****

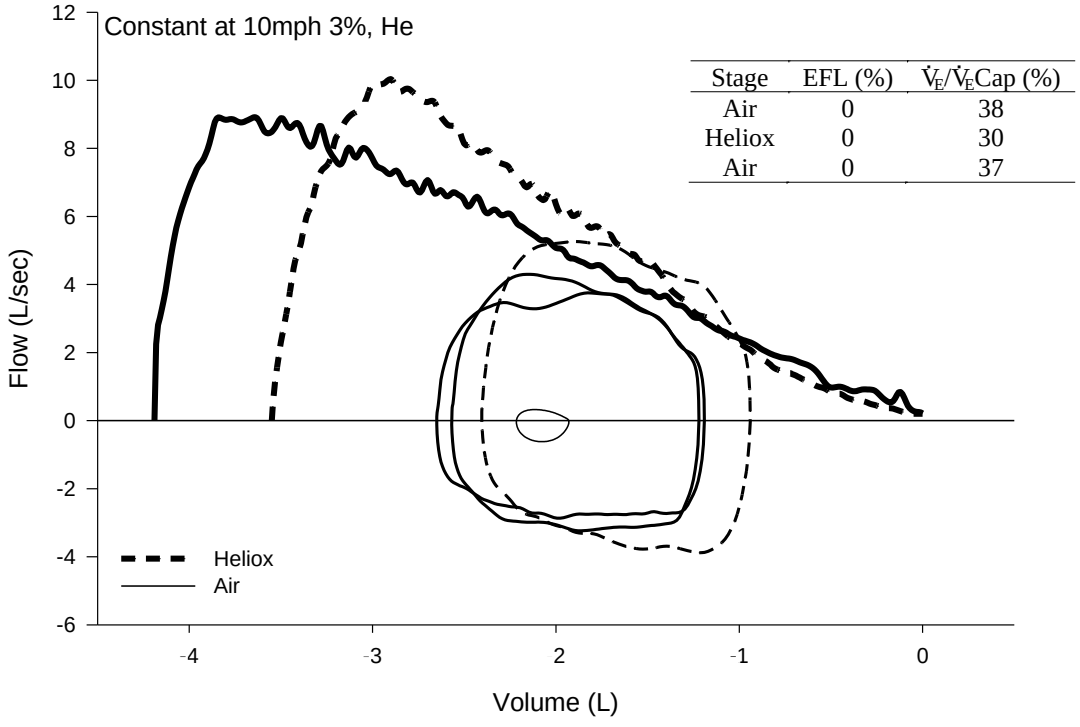
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
34	185	85	24.8	6.84	110	32.31	0.15	-150

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
5.55	65	5.98	165	1.08	3.2	52	0	32



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
9 mph	0	35
10 mph	0	37
10 mph 1%	0	38
10 mph 2%	0	40
10 mph 3%	0	45
10 mph 4%	0	50
10mph 5%	0	55



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	38
Heliox	0	30
Air	0	37

Figure 33- Example, arterial blood gases.

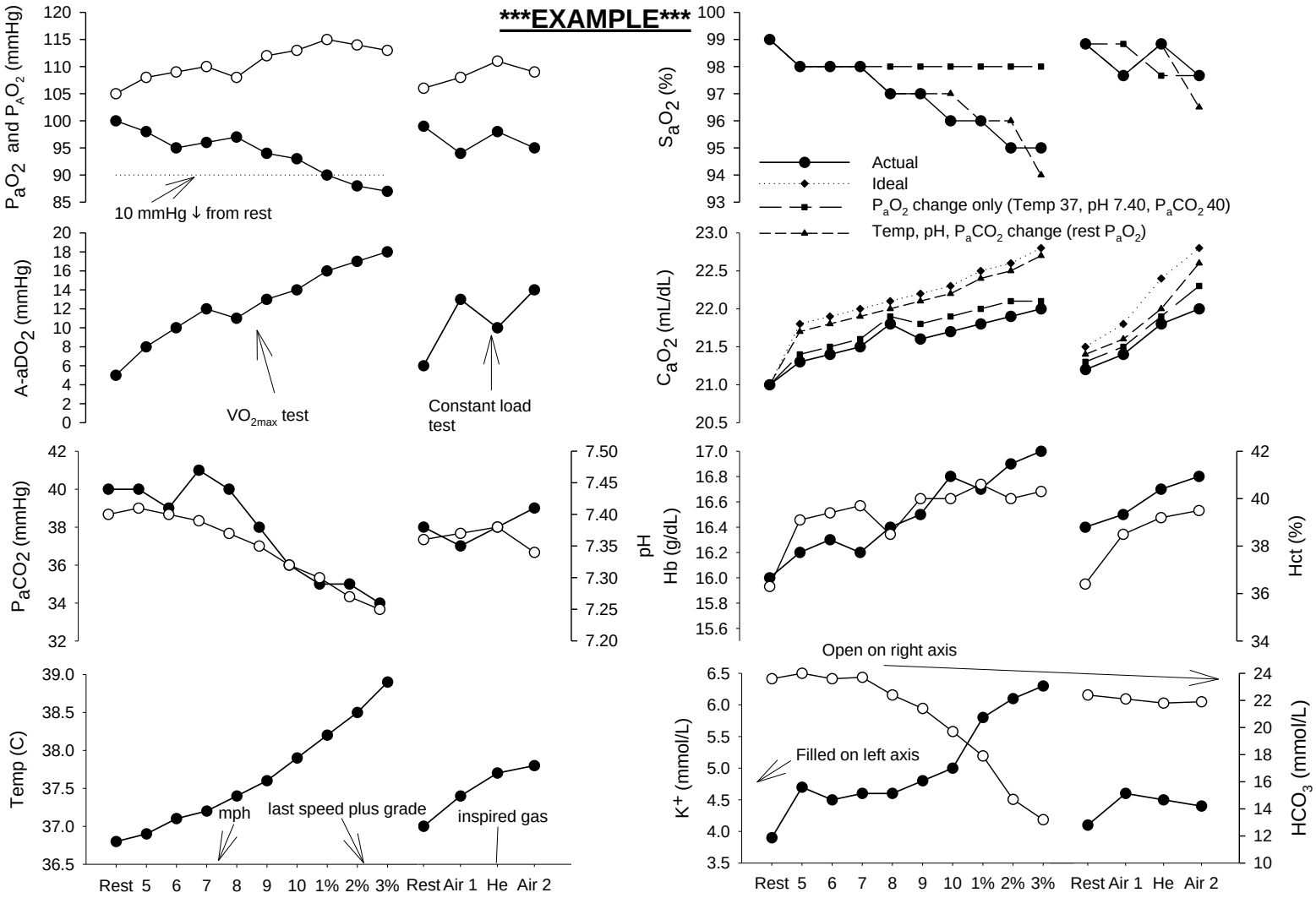


Figure 34- Example, respiratory mechanics.

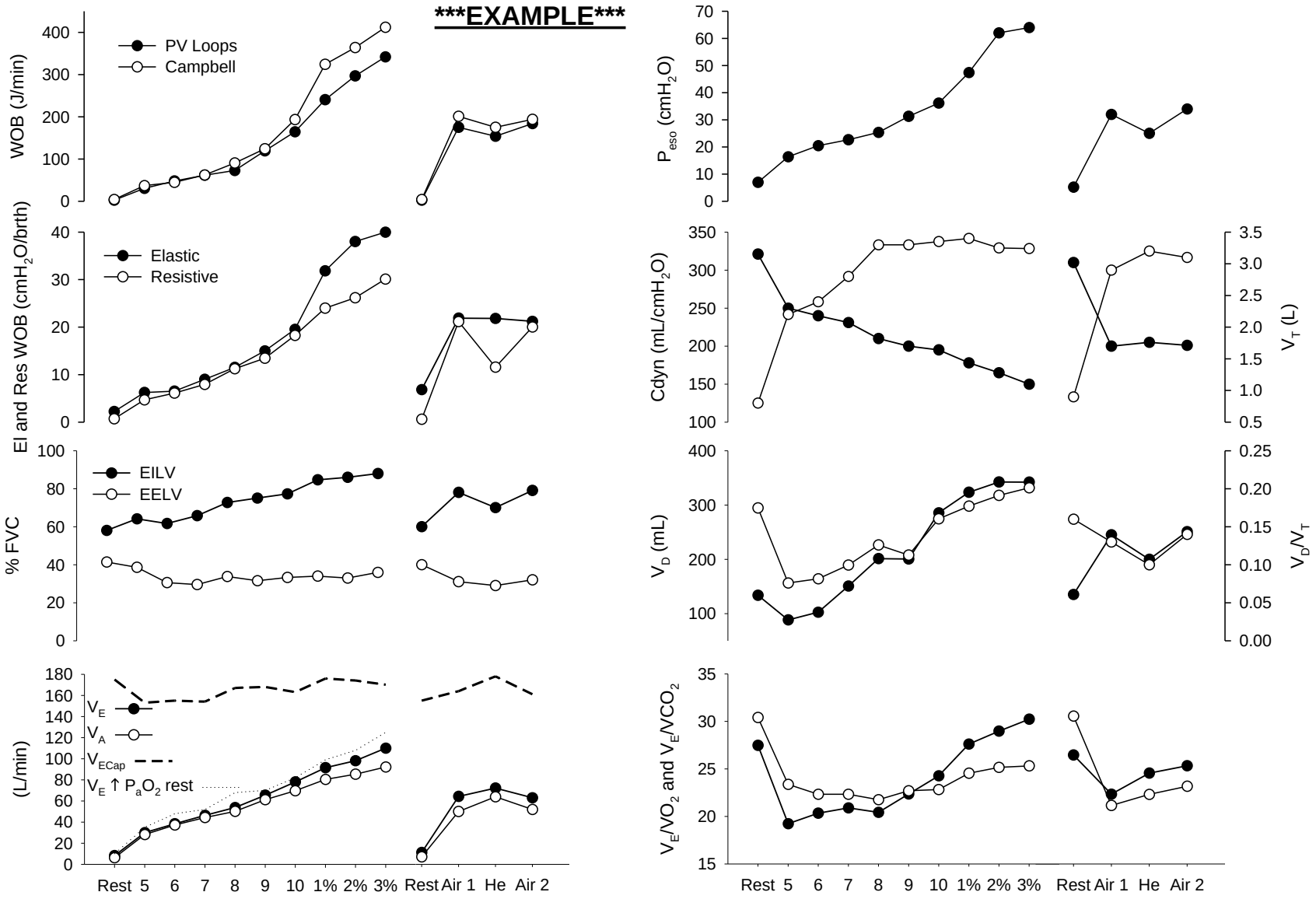


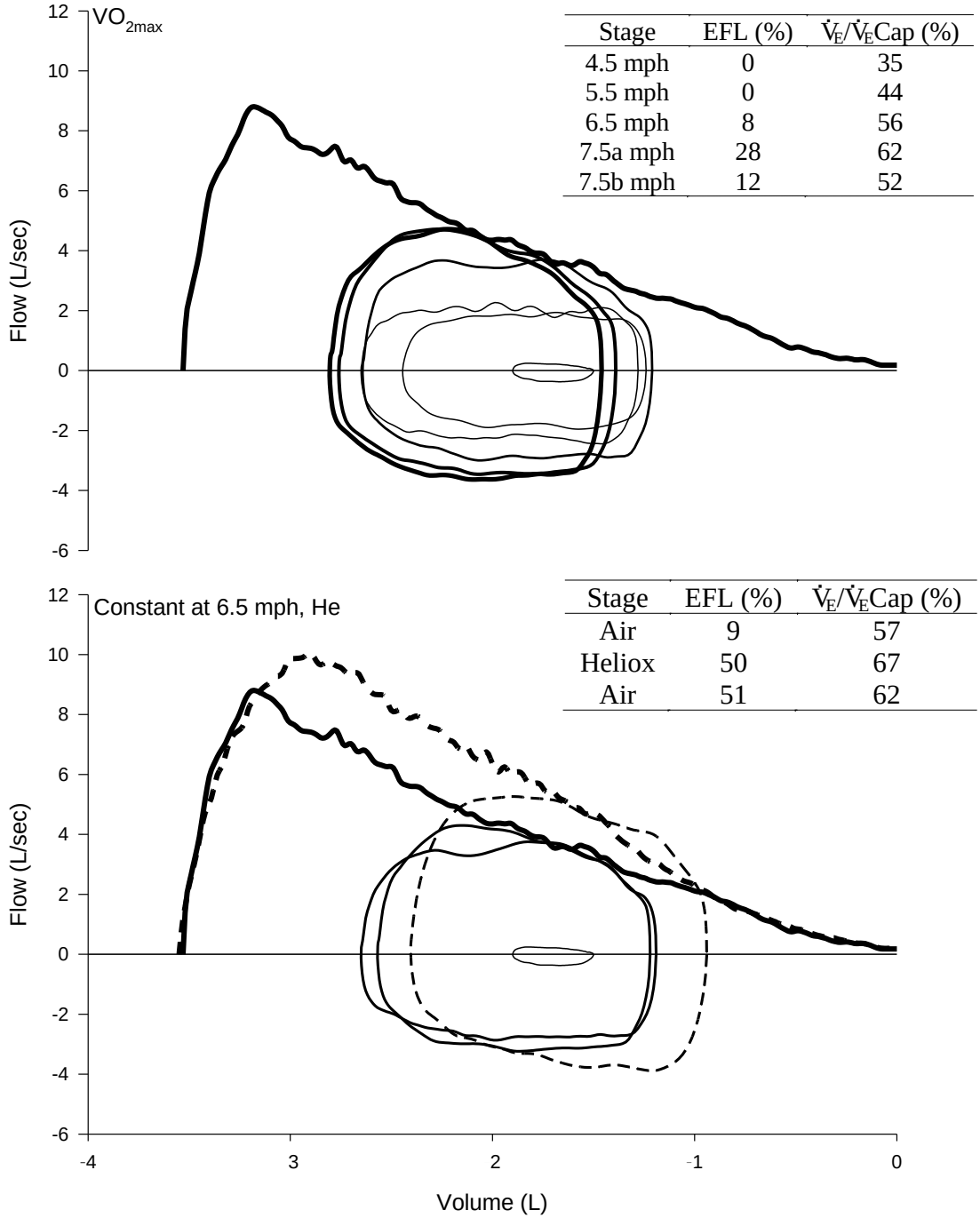
Figure 35- AC (Day 1), MEFV curve and descriptors**.**

Subject AC(Jun)- Cycle/Run (Rec). 30-60min/3-4x/wk. DAY 1

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
36	162	67.8	25.8	3.68	91	27.38	0.11	-115

Peak exercise, 7.5 mph

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.60	38	2.98	73	1.16	1.5	63	28	39



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4.5 mph	0	35
5.5 mph	0	44
6.5 mph	8	56
7.5a mph	28	62
7.5b mph	12	52

Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	9	57
Heliox	50	67
Air	51	62

Figure 36- AC (Day 1), arterial blood gases.

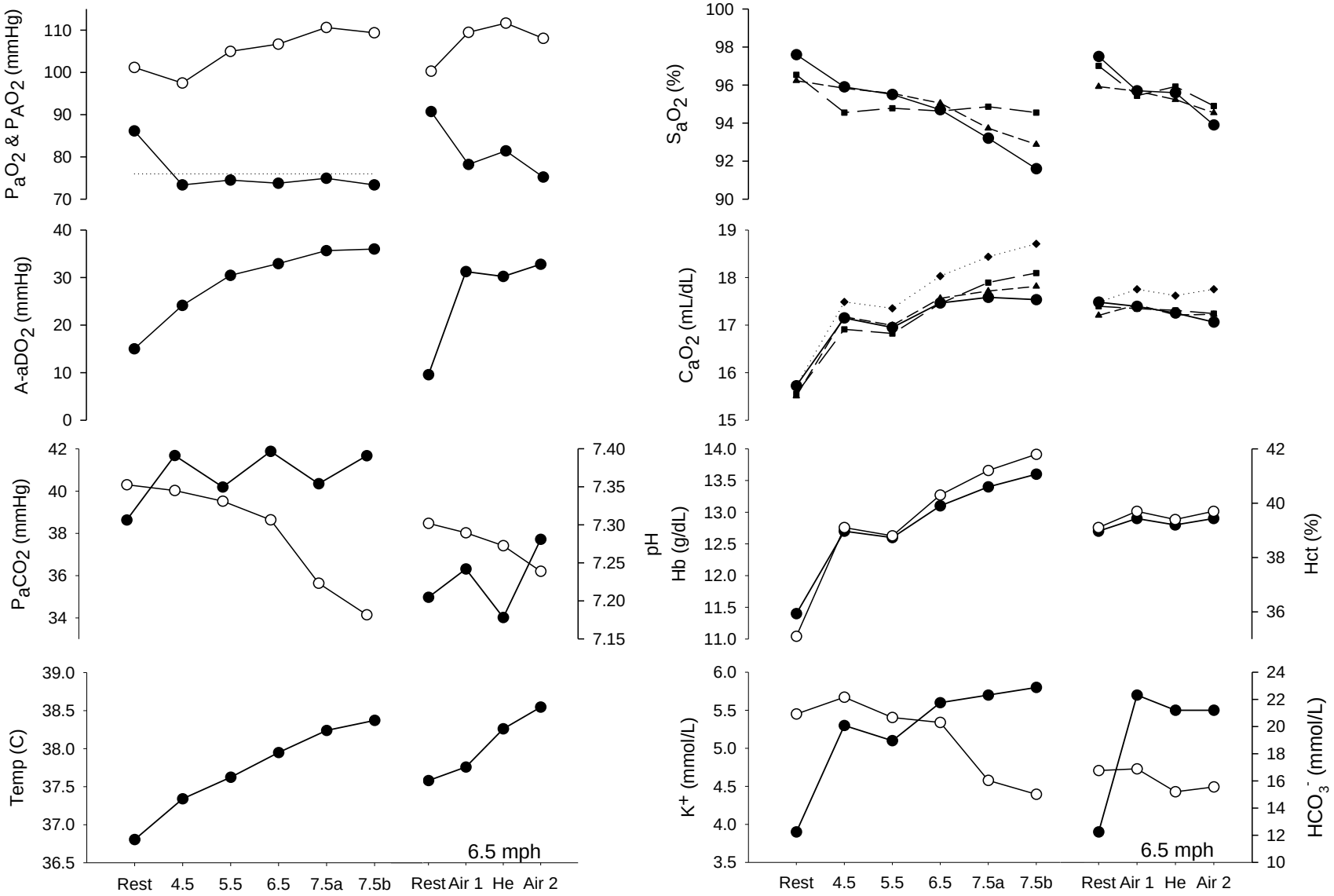


Figure 37- AC (Day 1), respiratory mechanics.

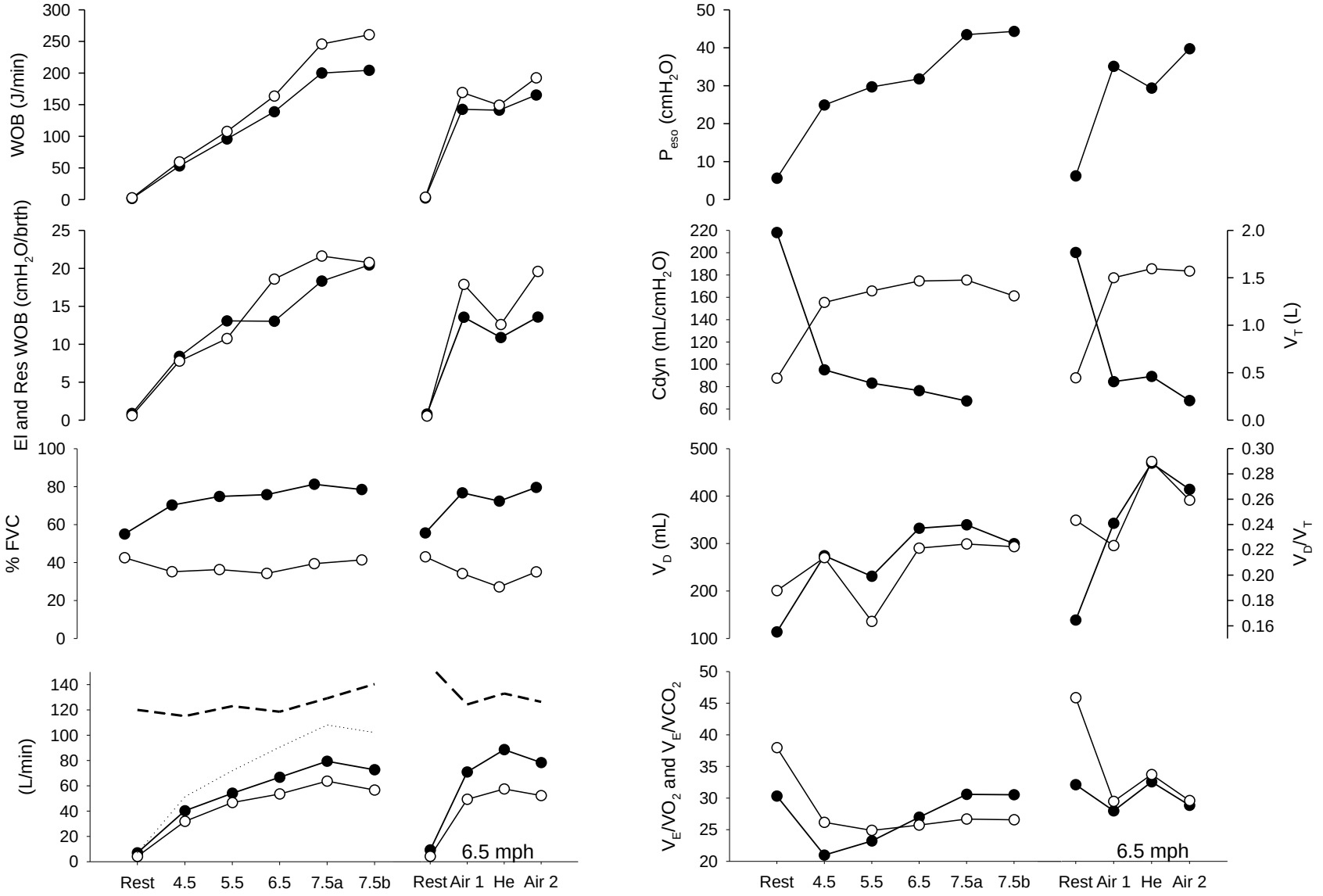


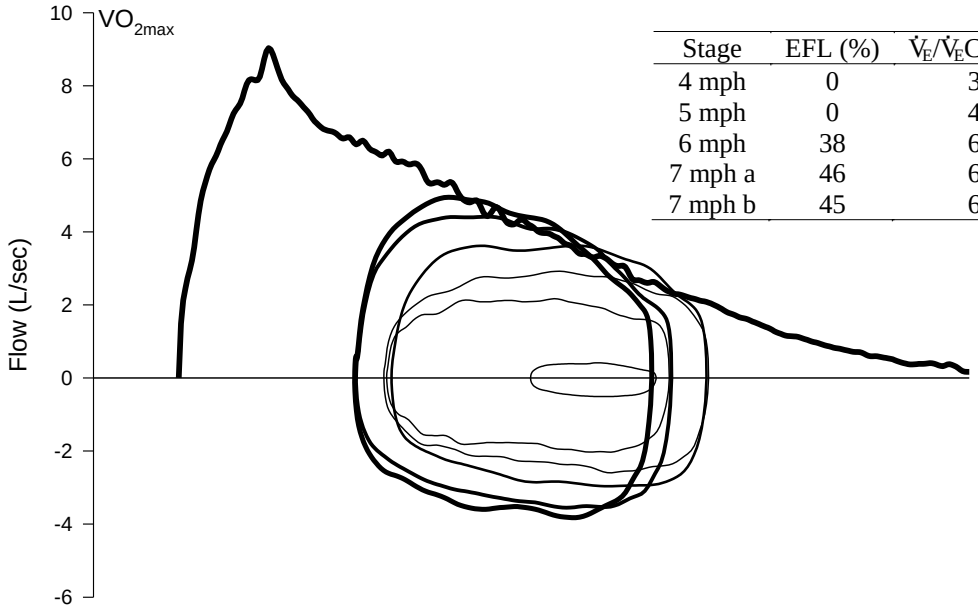
Figure 38- AC (Day 2), MEFV curve and descriptor.

Subject AC (NOV)-. Run (Rec). 30-45min/2-3x/wk. DAY 2

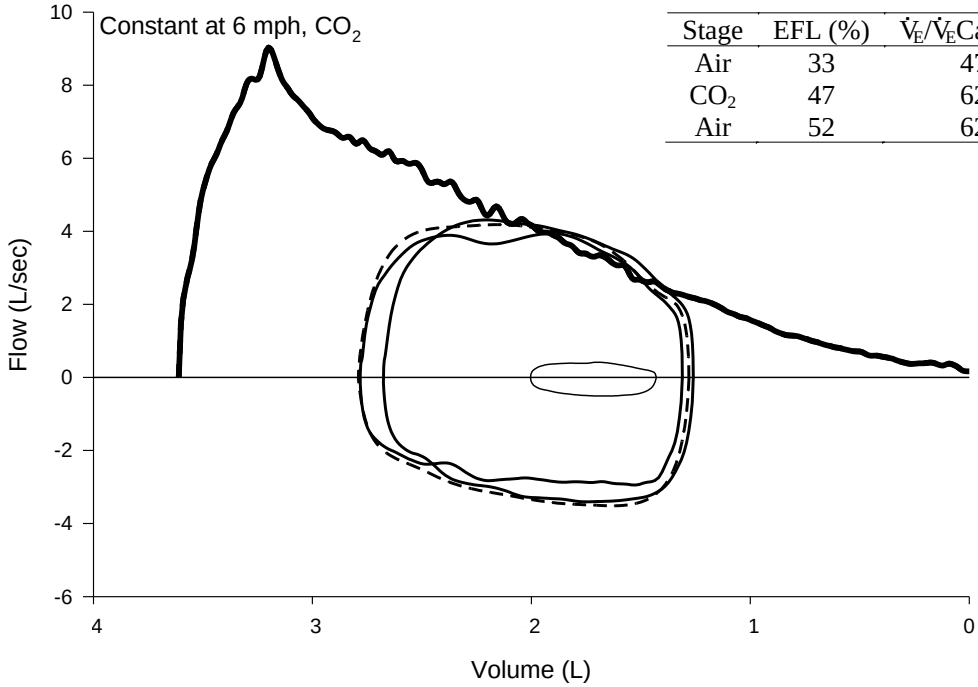
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
36	163	69	26.0	3.61	90	24.71	0.11	-106

Peak exercise, 7 mph

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.85	41	3.19	83	1.11	1.5	65	38	40



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4 mph	0	35
5 mph	0	49
6 mph	38	62
7 mph a	46	64
7 mph b	45	64



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	33	47
CO_2	47	62
Air	52	62

Figure 39- AC (Day 2), arterial blood gases.

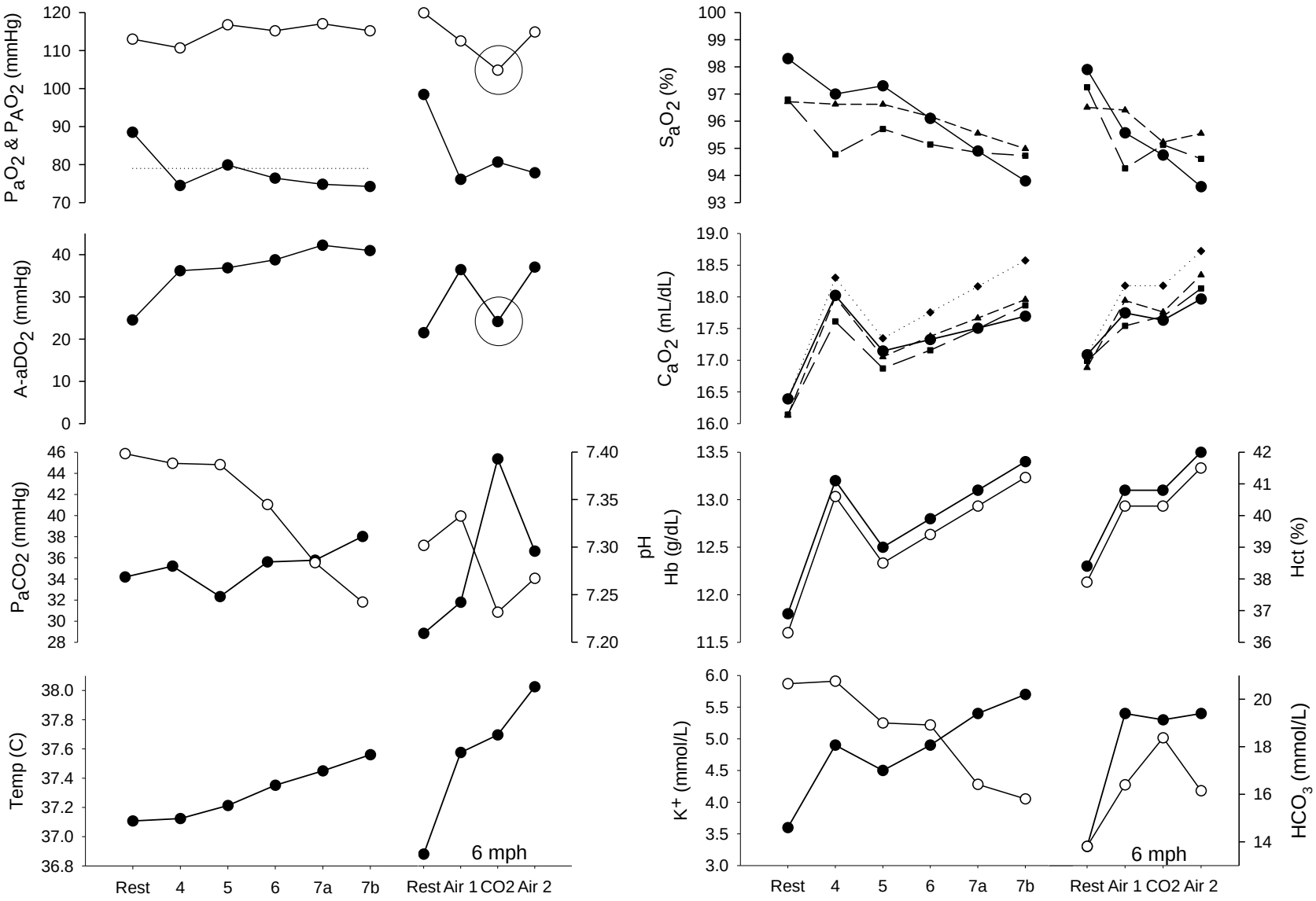


Figure 40- AC (Day 2), respiratory mechanics.

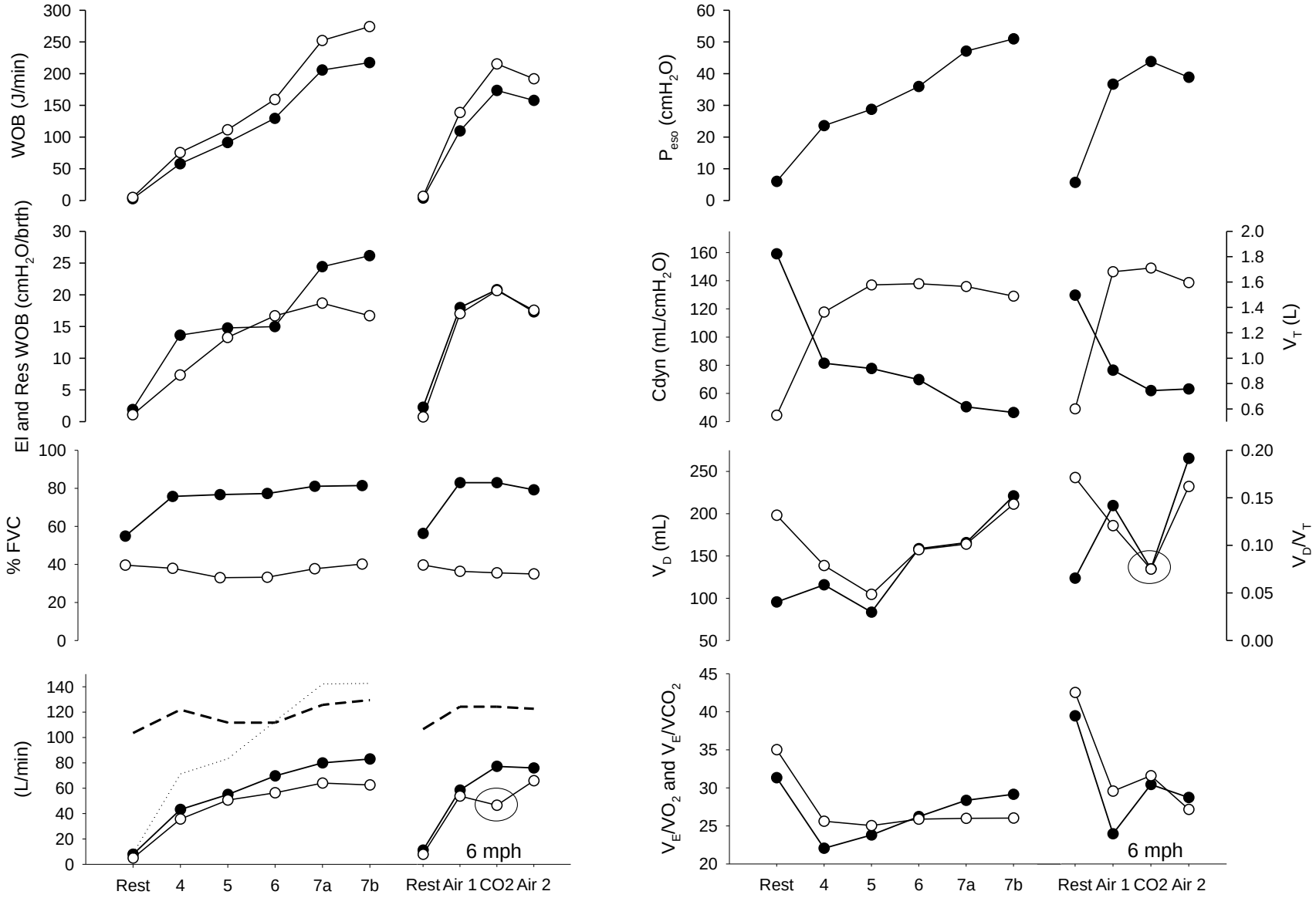


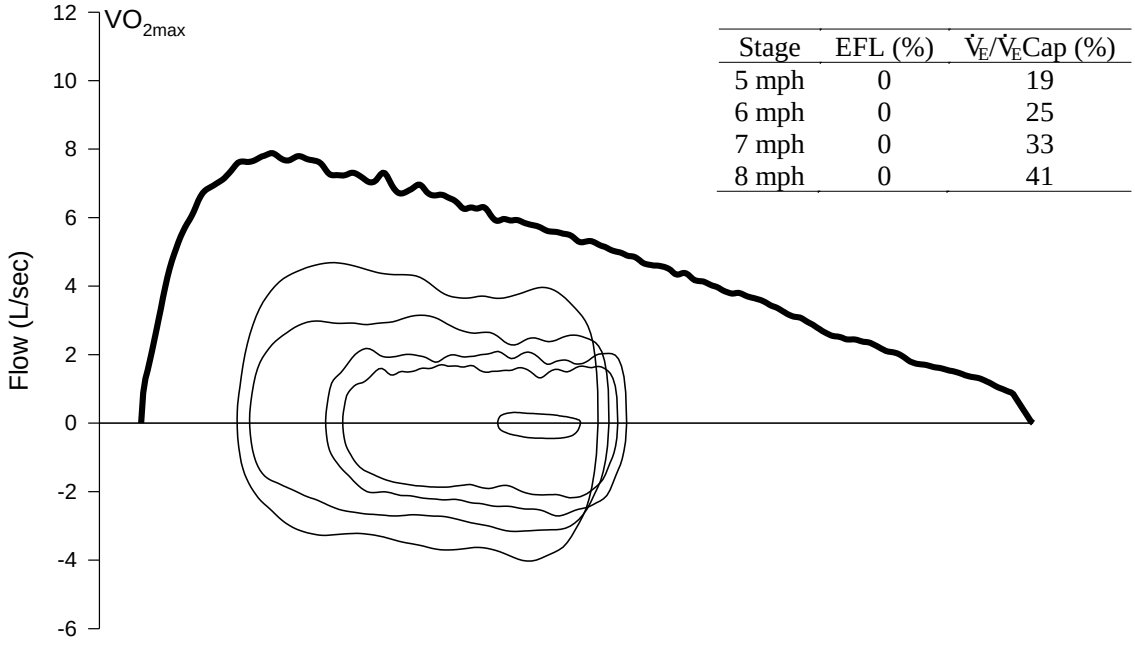
Figure 41- AH, MEFV curve and descriptors.

Subject AH- Run/Hike/Swim/Bike. 30-40min. 3-4x/wk.

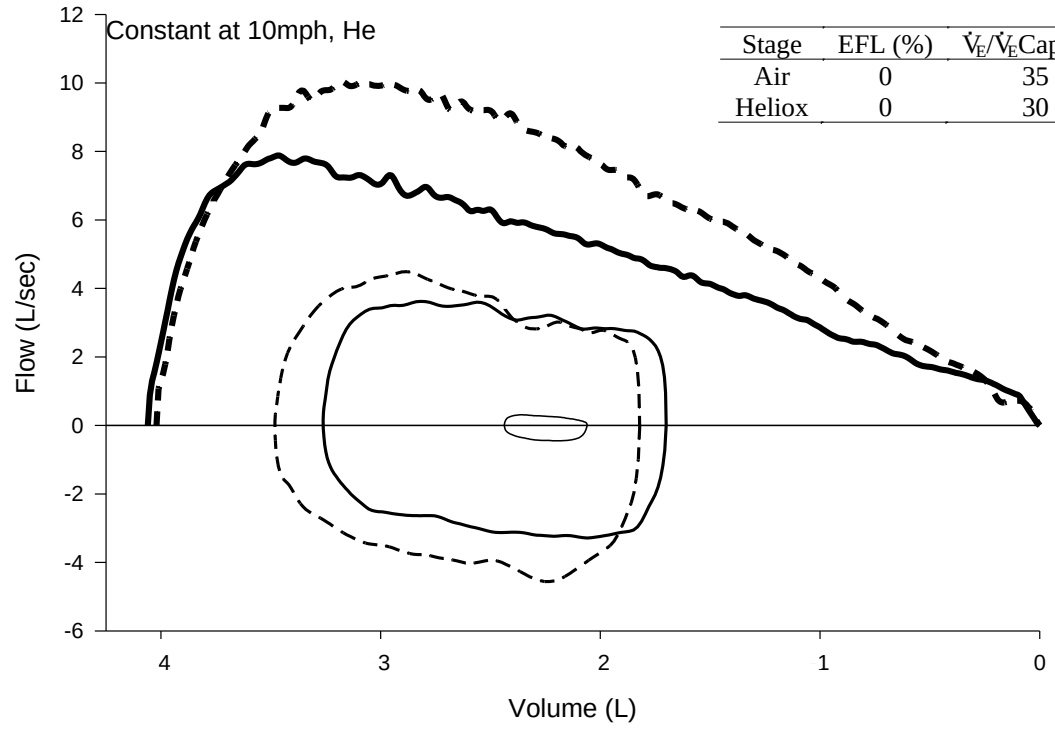
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
Yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
22	166	58.2	21.1	3.96	100	25.32	0.18	-120

Peak exercise, 8.5 mph, 2% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.00	51.5	3.27	87	1.06	1.8	57	0	49



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
5 mph	0	19
6 mph	0	25
7 mph	0	33
8 mph	0	41



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	35
Heliox	0	30

Figure 42- AH, arterial blood gases.

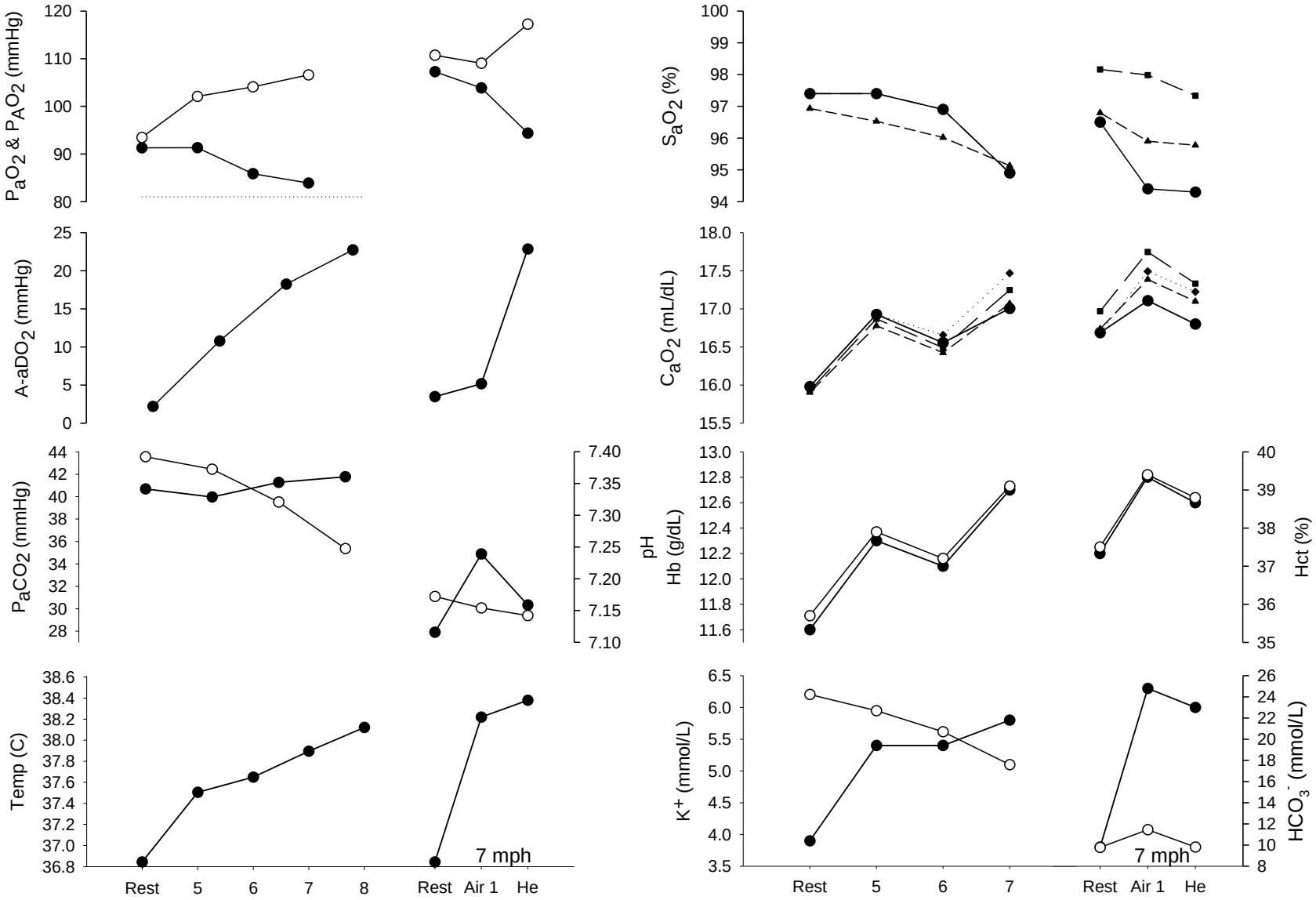


Figure 43- AH, respiratory mechanics.

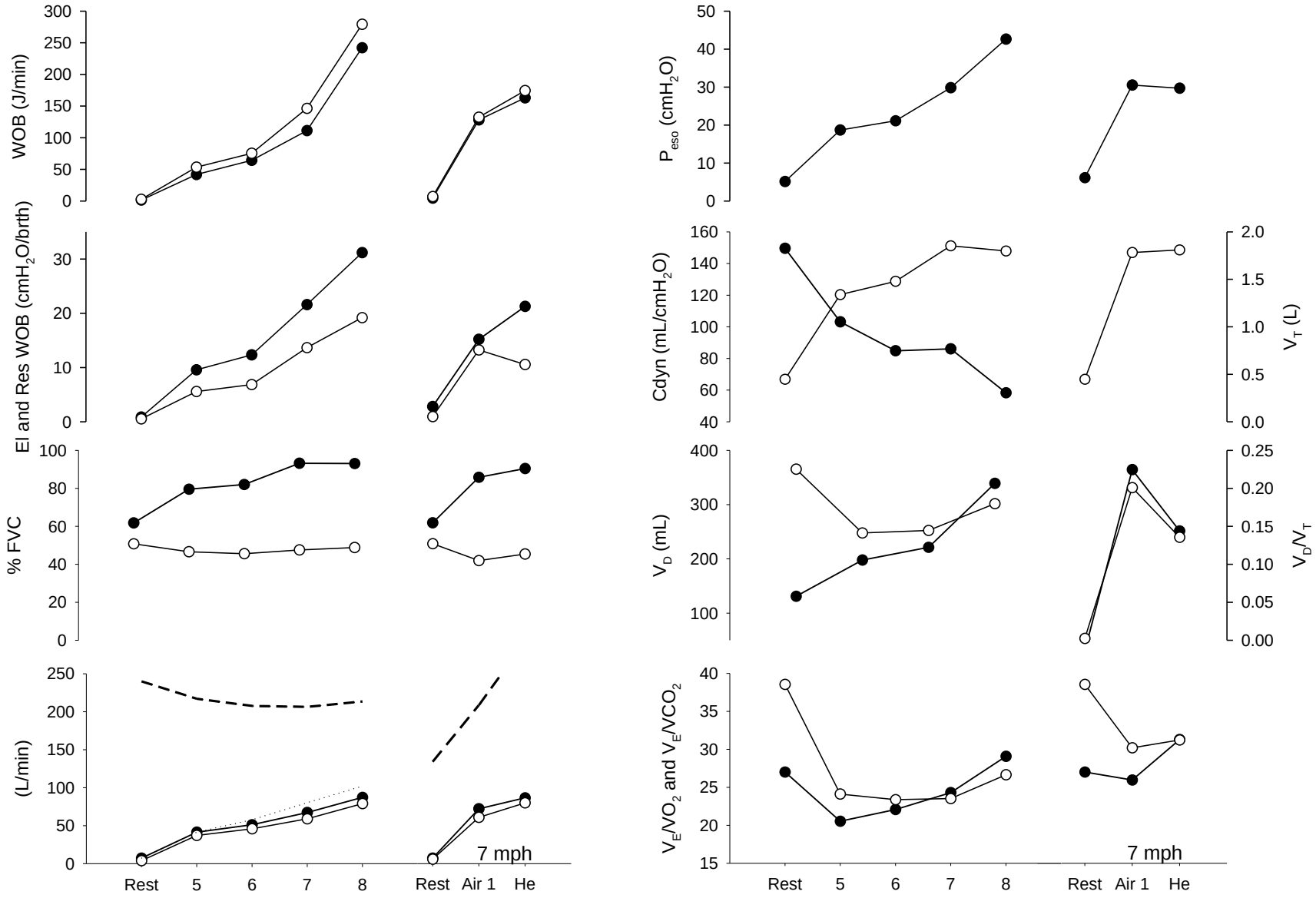


Figure 44- AM, MEFV curve and descriptors.

Subject AM- Run/Bike/Swim/Ski (Touring). 1.5hrs/4x/wk

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
19	162	60.2	22.9	3.95	104		0.3	-94

Peak exercise, 8.5 mph, 2% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.88	48	3.14	96	1.09	1.7	68	37	36

Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4.5 mph	0	22
5.5 mph	0	27
6.5 mph	0	33
7.5 mph	0	41
8.5 mph	0	62
8.5 mph 2%	37	67

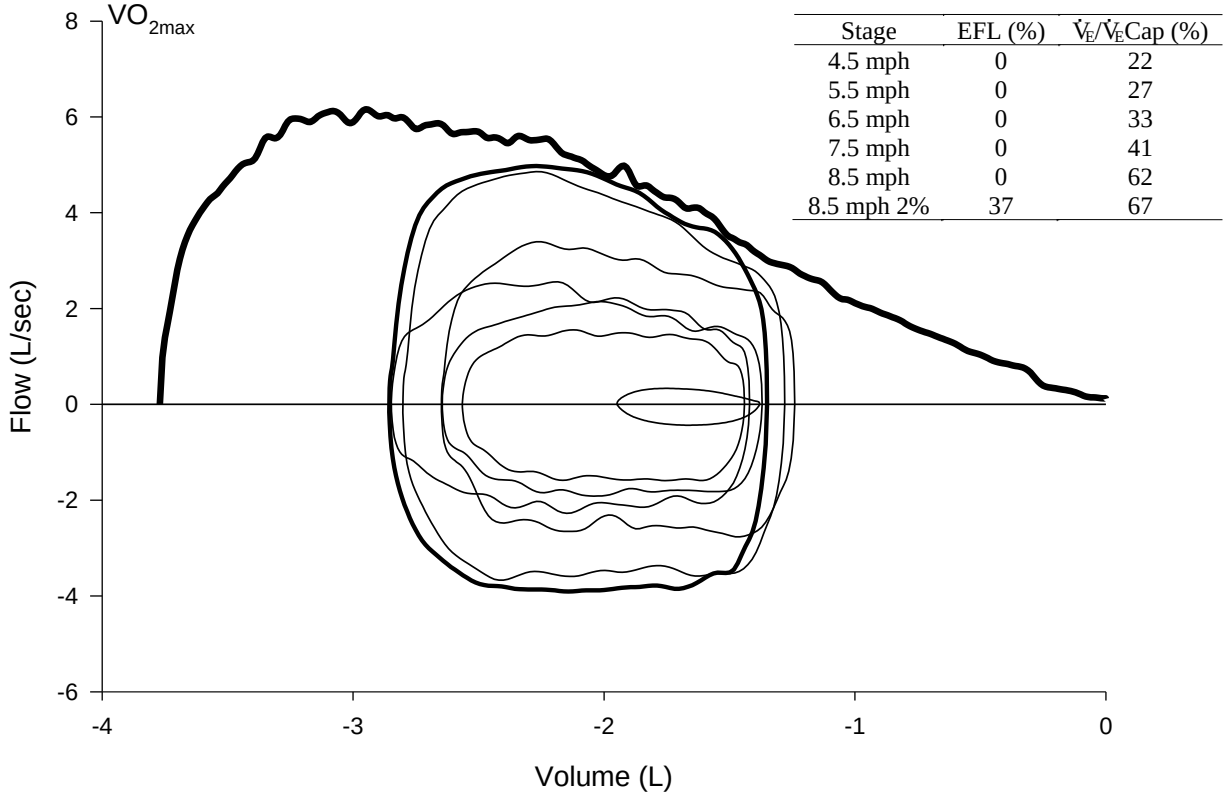


Figure 45- AM, arterial blood gases.

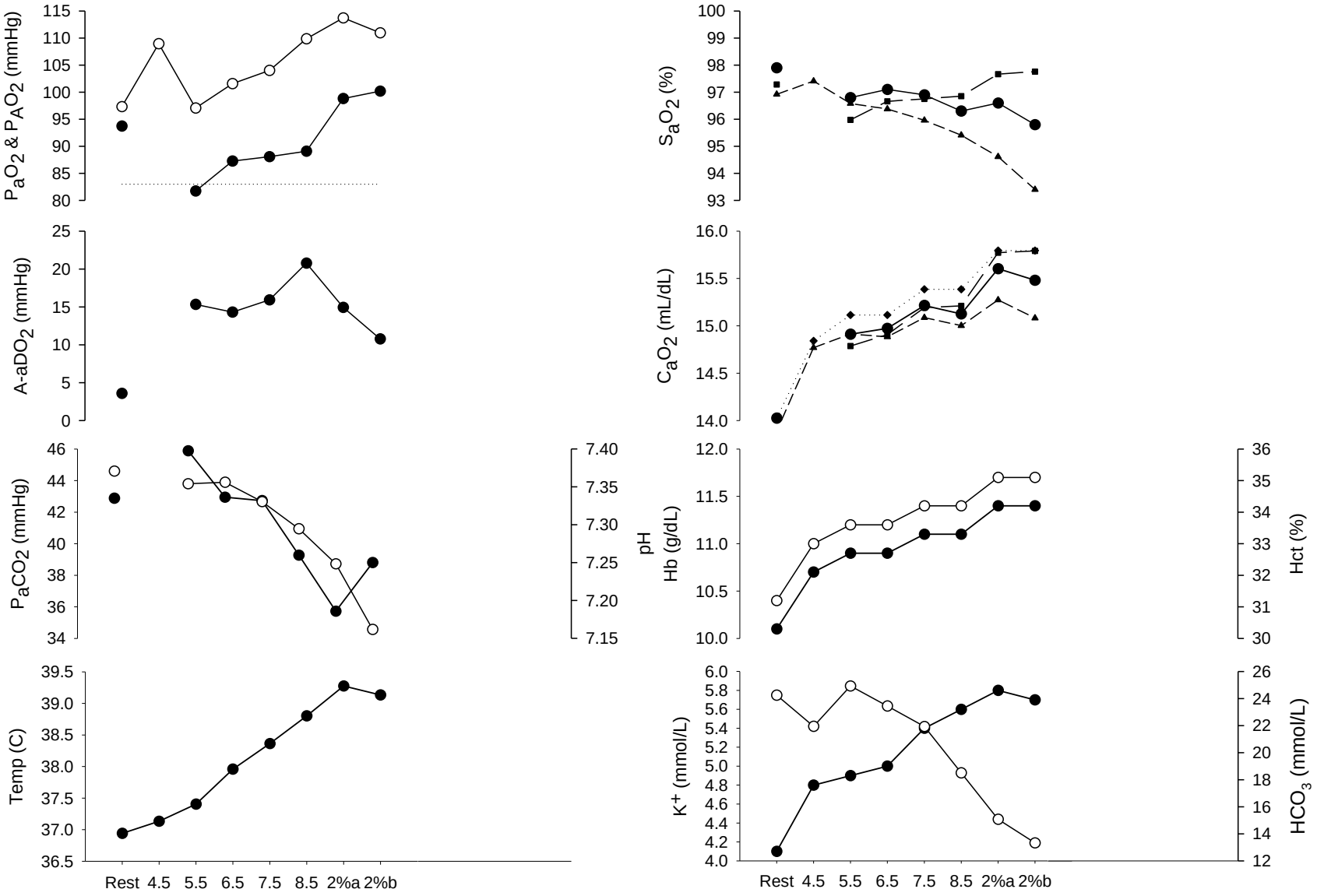


Figure 46- AM, respiratory mechanics.

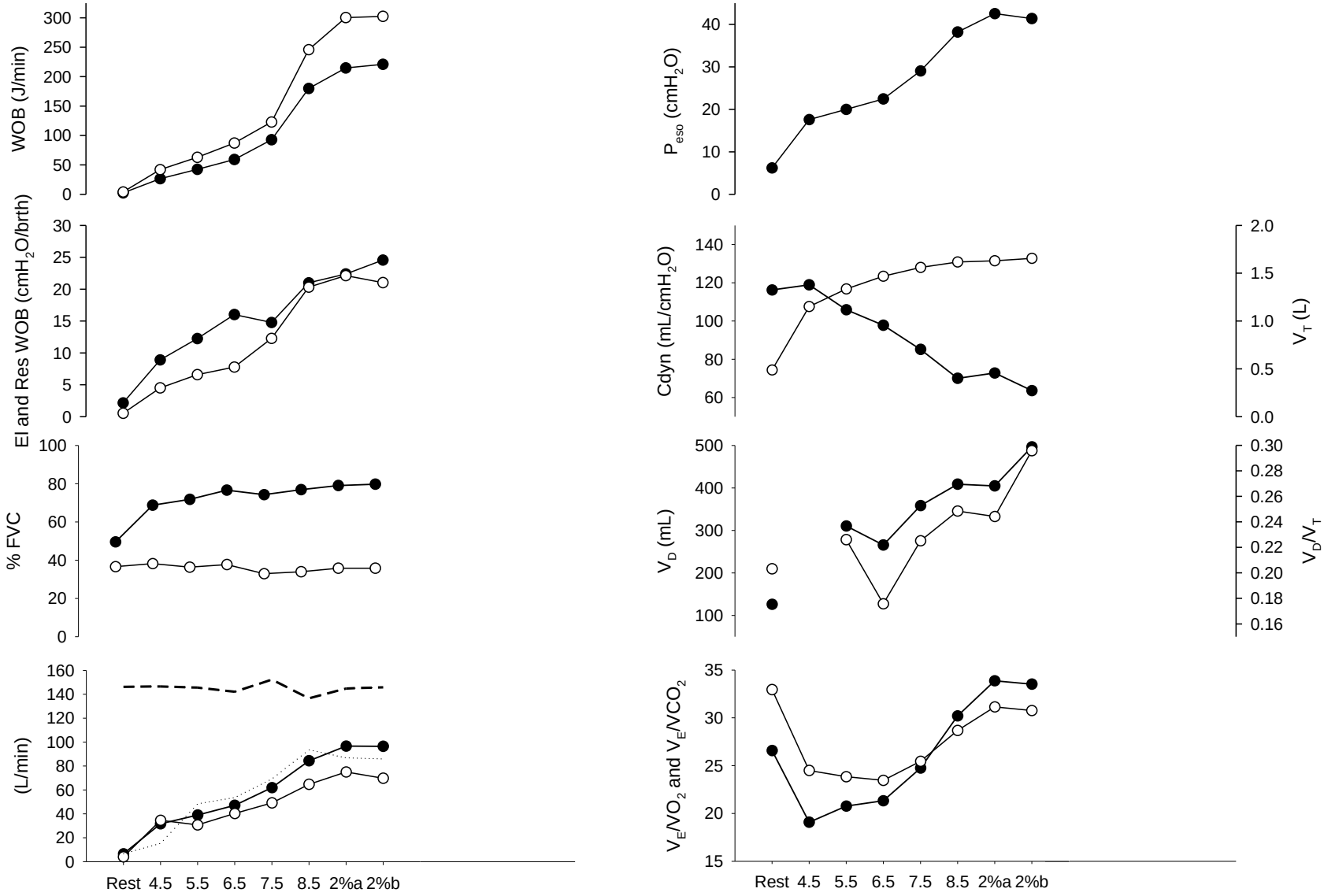


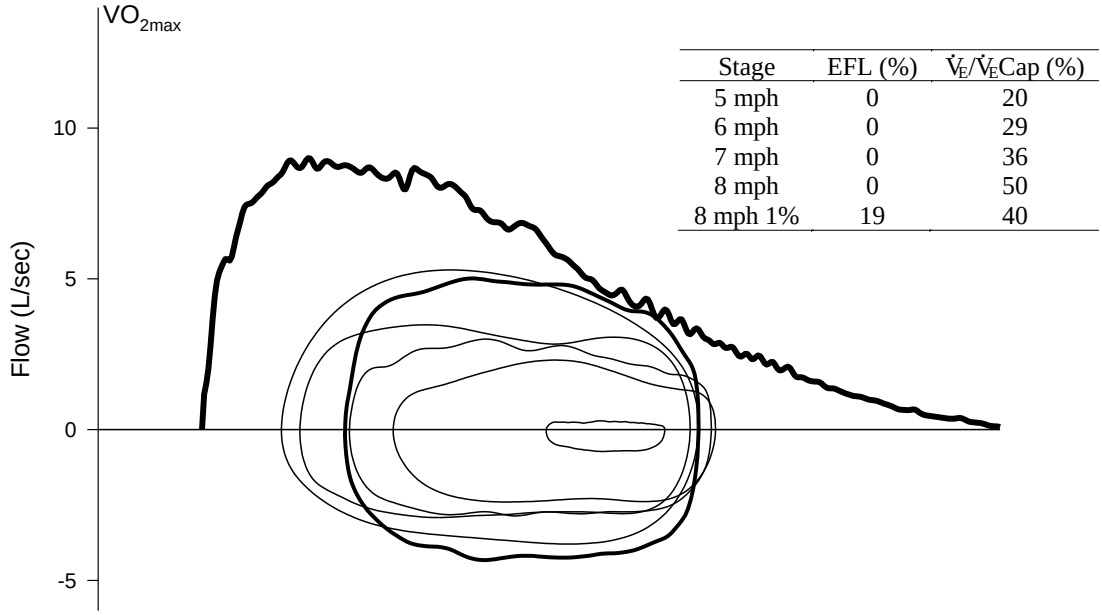
Figure 47- AS, MEFV curve and descriptors.

Subject AS- Running/Cycling/Hockey/Swim (Rec). ~1hr/5-6x week

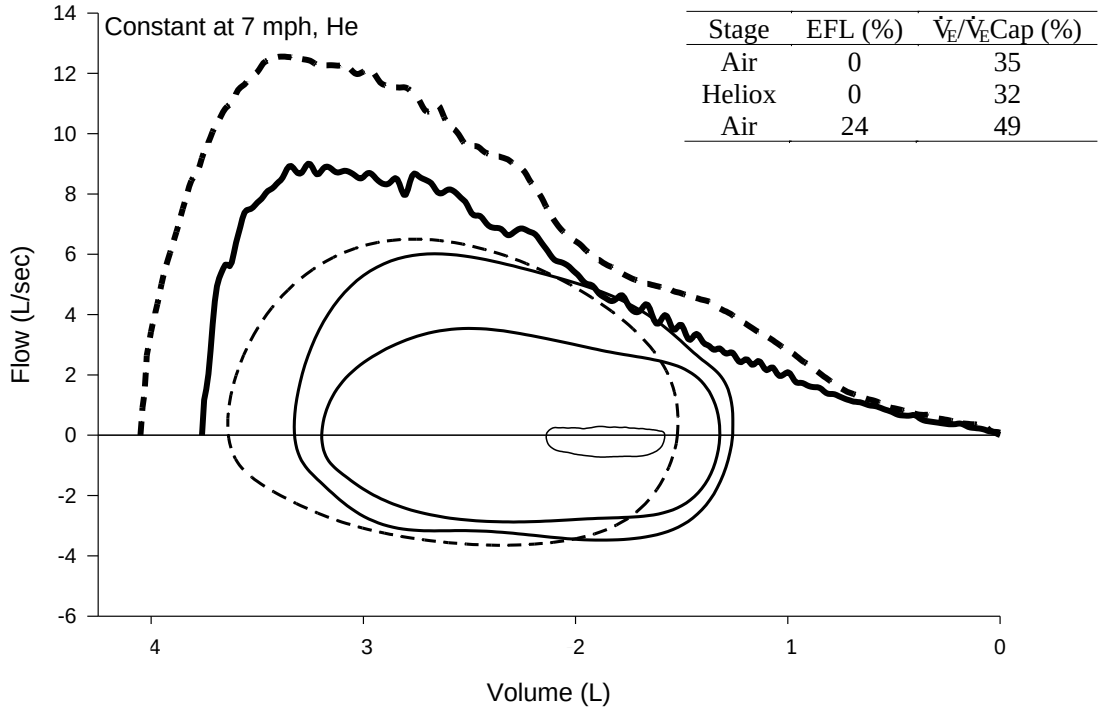
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
29	170	67.7	23.4	4.03	104			-110

Peak exercise, 8 mph. 1%

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.24	48	3.72	95	1.16	1.69	65	19	38



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
5 mph	0	20
6 mph	0	29
7 mph	0	36
8 mph	0	50
8 mph 1%	19	40



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	35
Heliox	0	32
Air	24	49

Figure 48- AS, arterial blood gases.

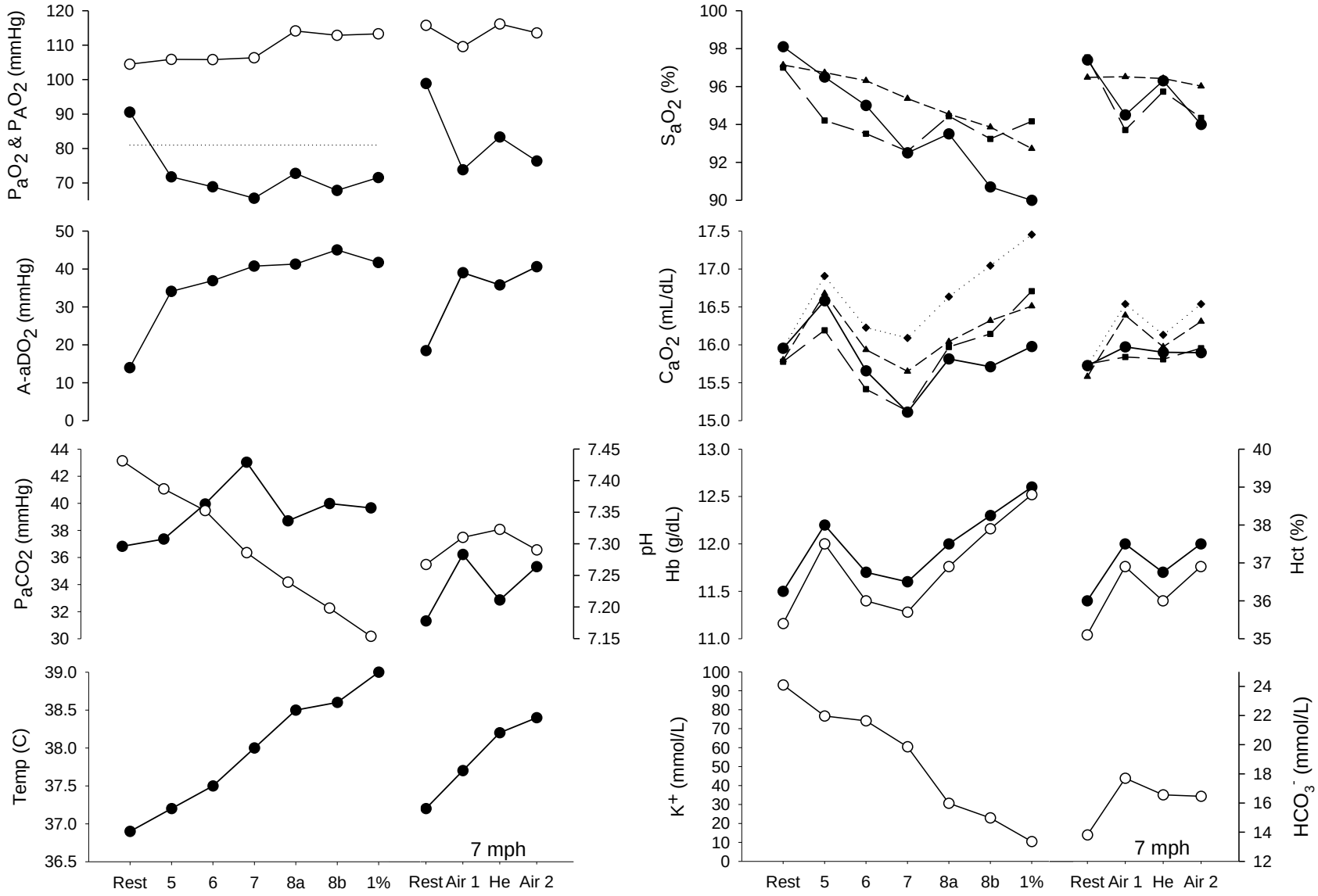


Figure 49- AS, respiratory mechanics.

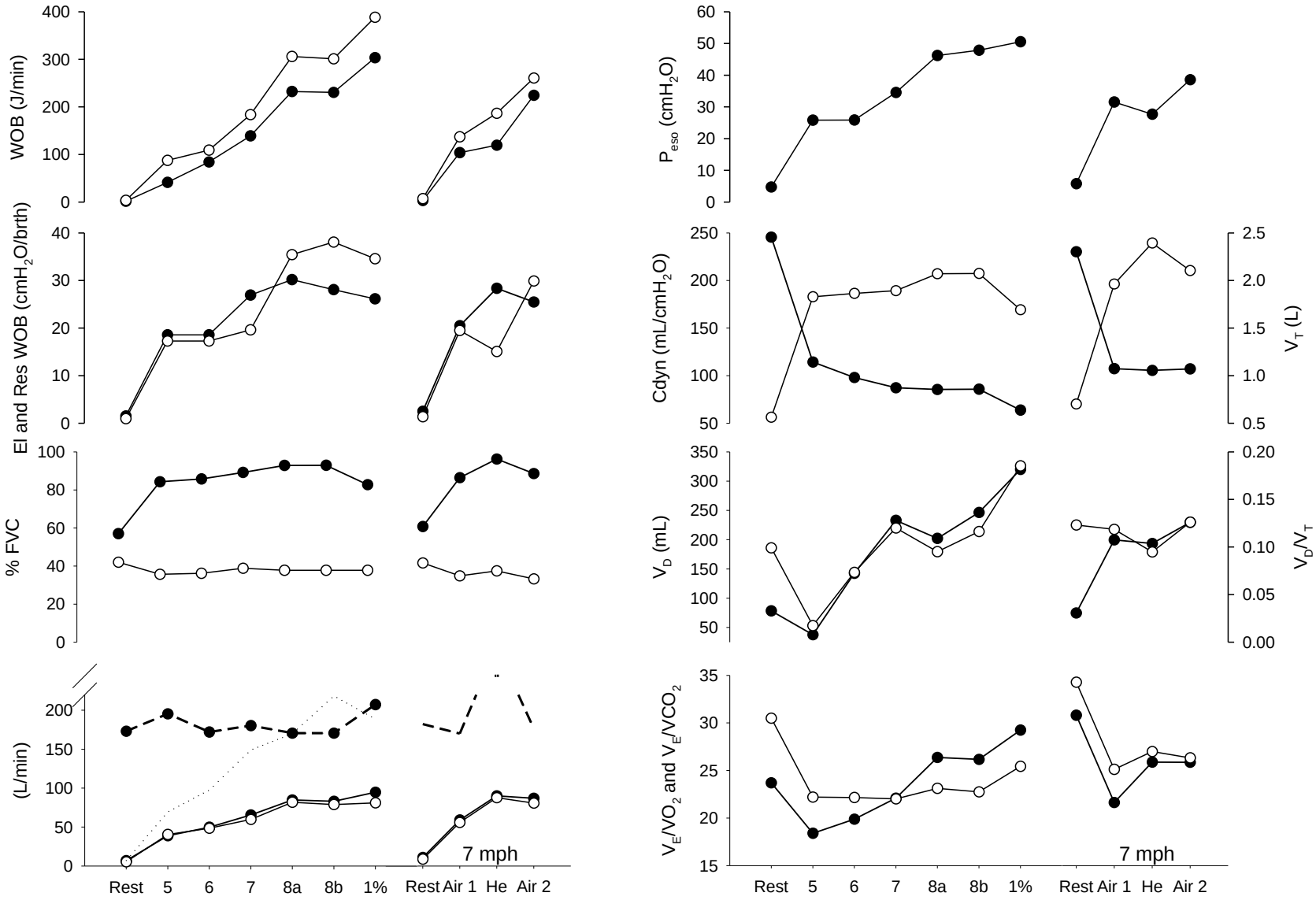


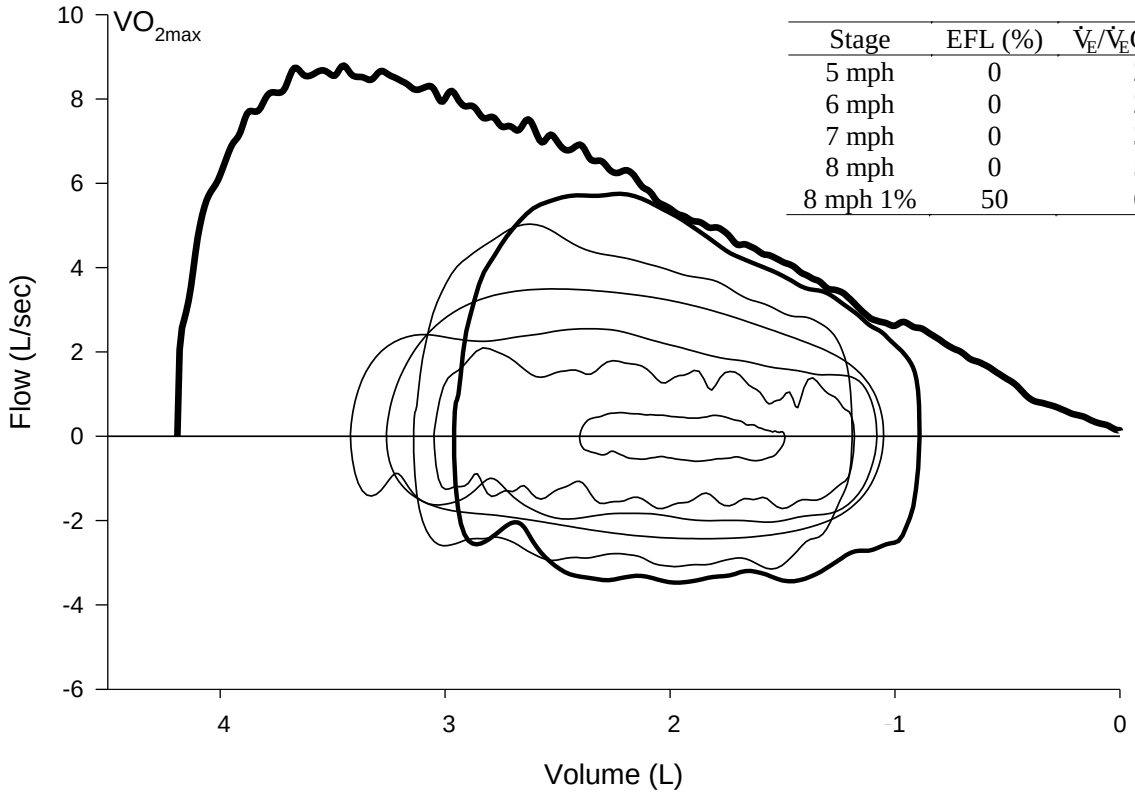
Figure 50- BS, MEFV curve and descriptors.

Subject BS- Run (Rec). 1-2hrs/3x/wk

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
22	173	60	20.0	4.53	108		0.18	-91

Peak exercise 8 mph, 1%

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.73	46	2.75	88	1.00	2.2	48	50	21



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
5 mph	0	20
6 mph	0	29
7 mph	0	38
8 mph	0	51
8 mph 1%	50	69

Figure 51- BS, arterial blood gases.

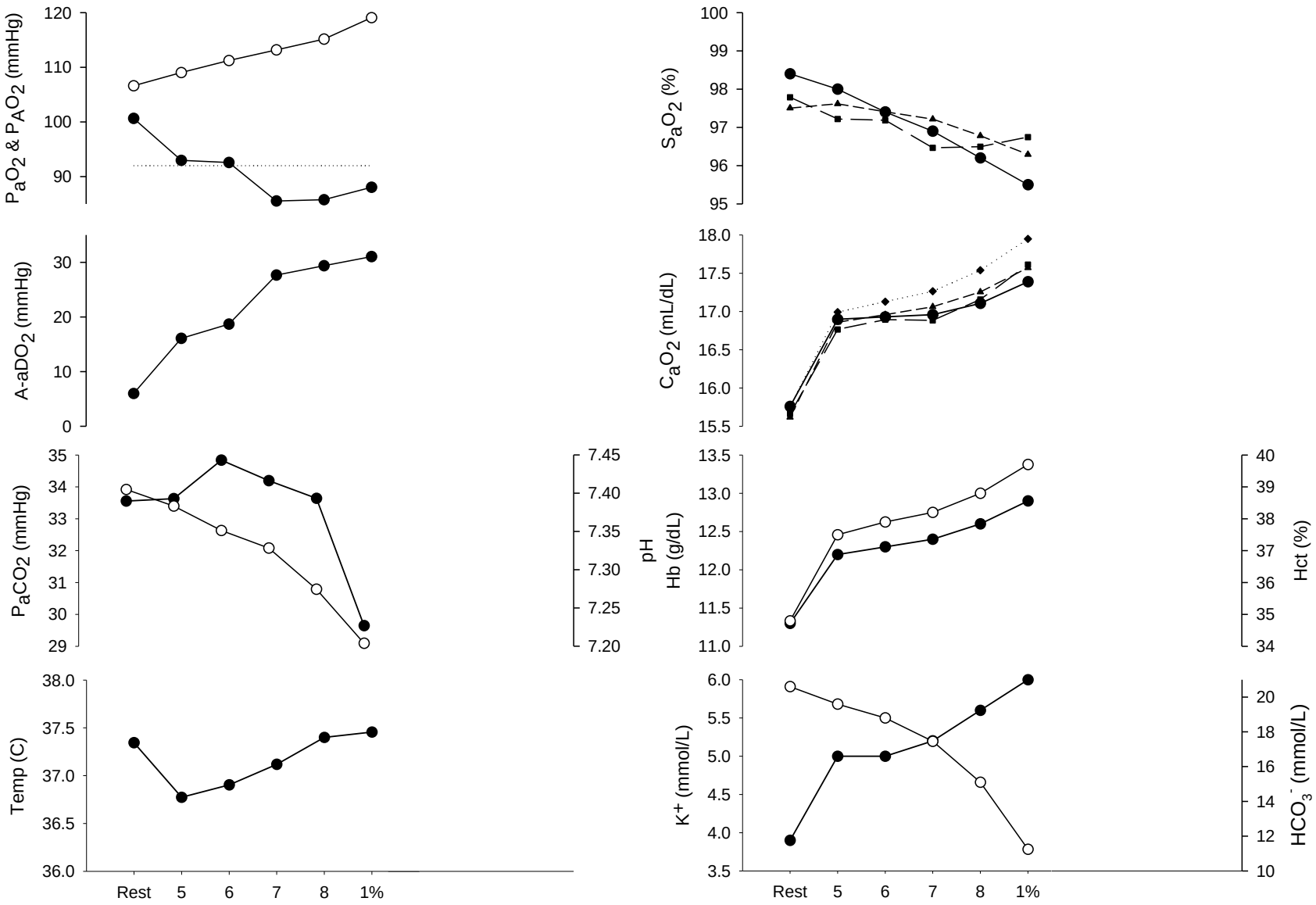


Figure 52- BS, respiratory mechanics.

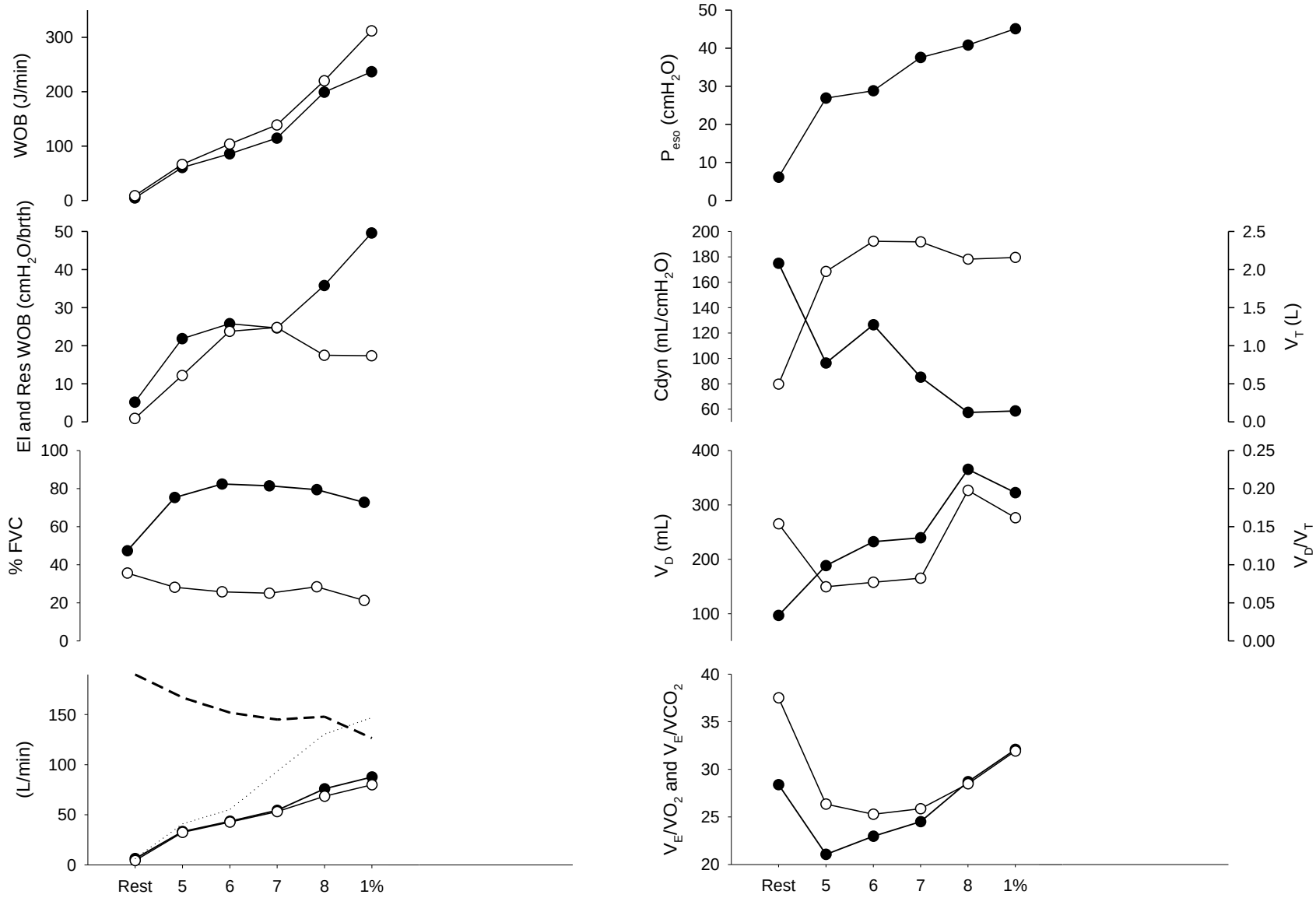


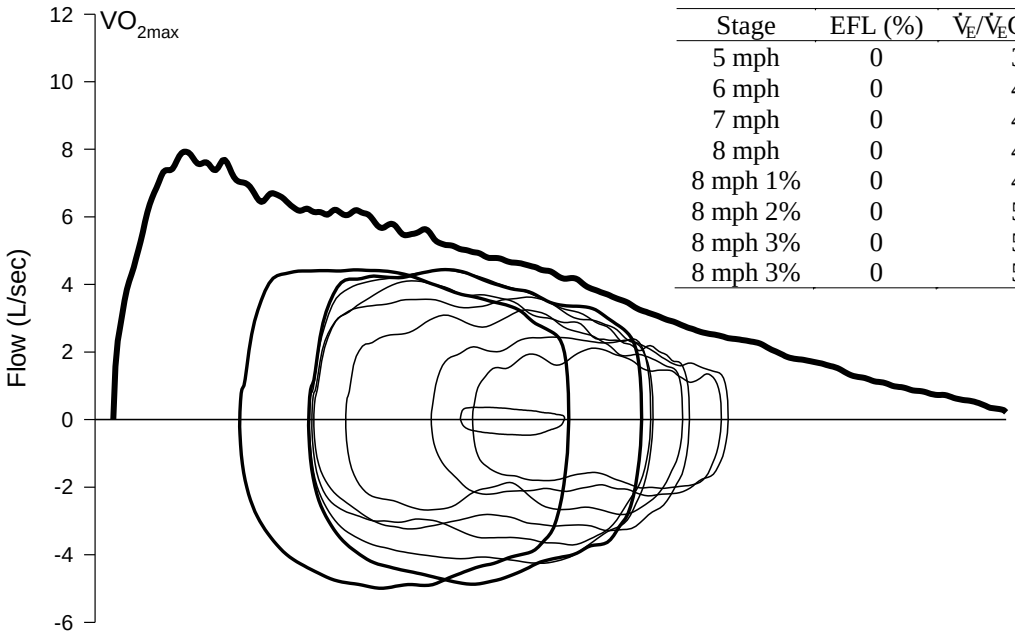
Figure 53- CM, MEFV curve and descriptors.

Subject CM- Varsity track (10km+), Nordic Skiing. Run/Bike/Swim 1+hr/daily

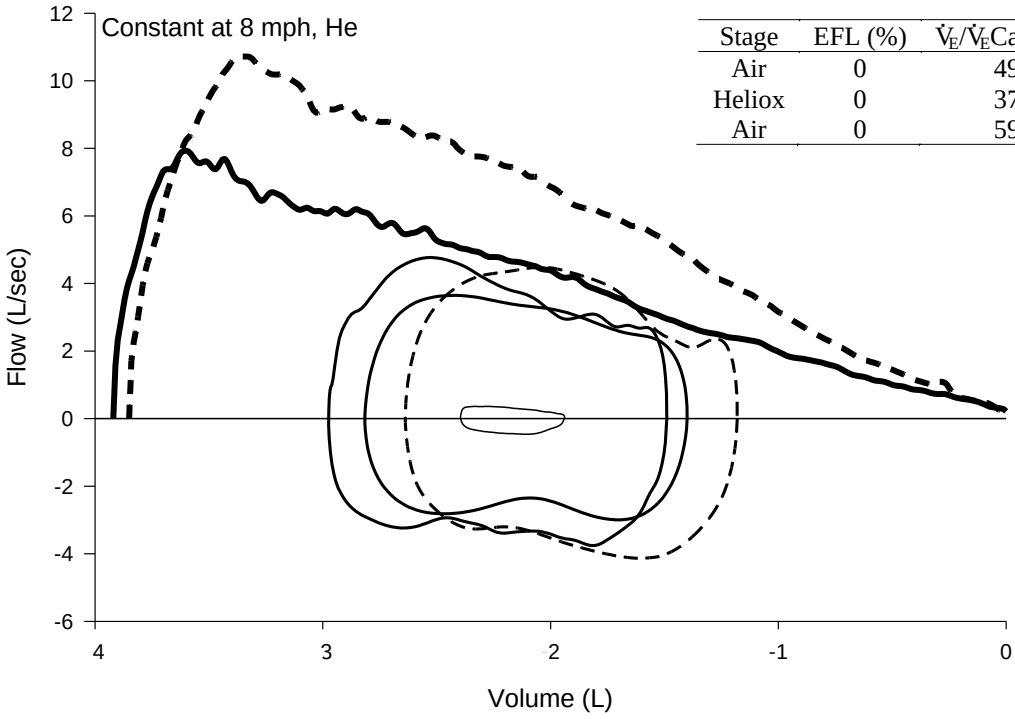
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
20	169	60.4	21.1	3.9	96	28.04		-86

Peak exercise, 8 mph, 3% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.41	56.5	3.67	97	1.07	1.58	71.2	0	49



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
5 mph	0	34
6 mph	0	40
7 mph	0	43
8 mph	0	49
8 mph 1%	0	48
8 mph 2%	0	58
8 mph 3%	0	58
8 mph 3%	0	51



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	49
Heliox	0	37
Air	0	59

Figure 54- CM, arterial blood gases.

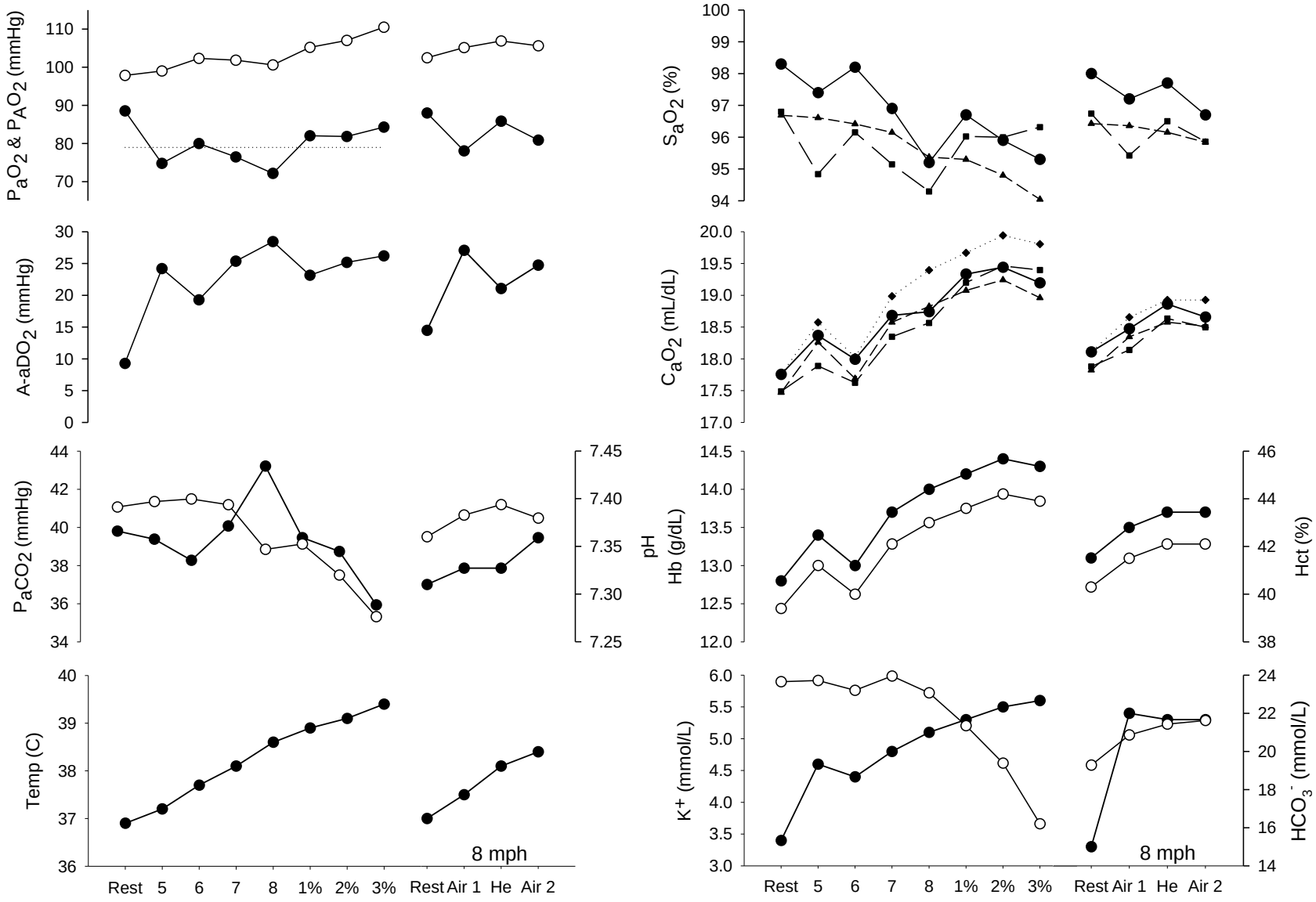


Figure 55- CM, respiratory mechanics.

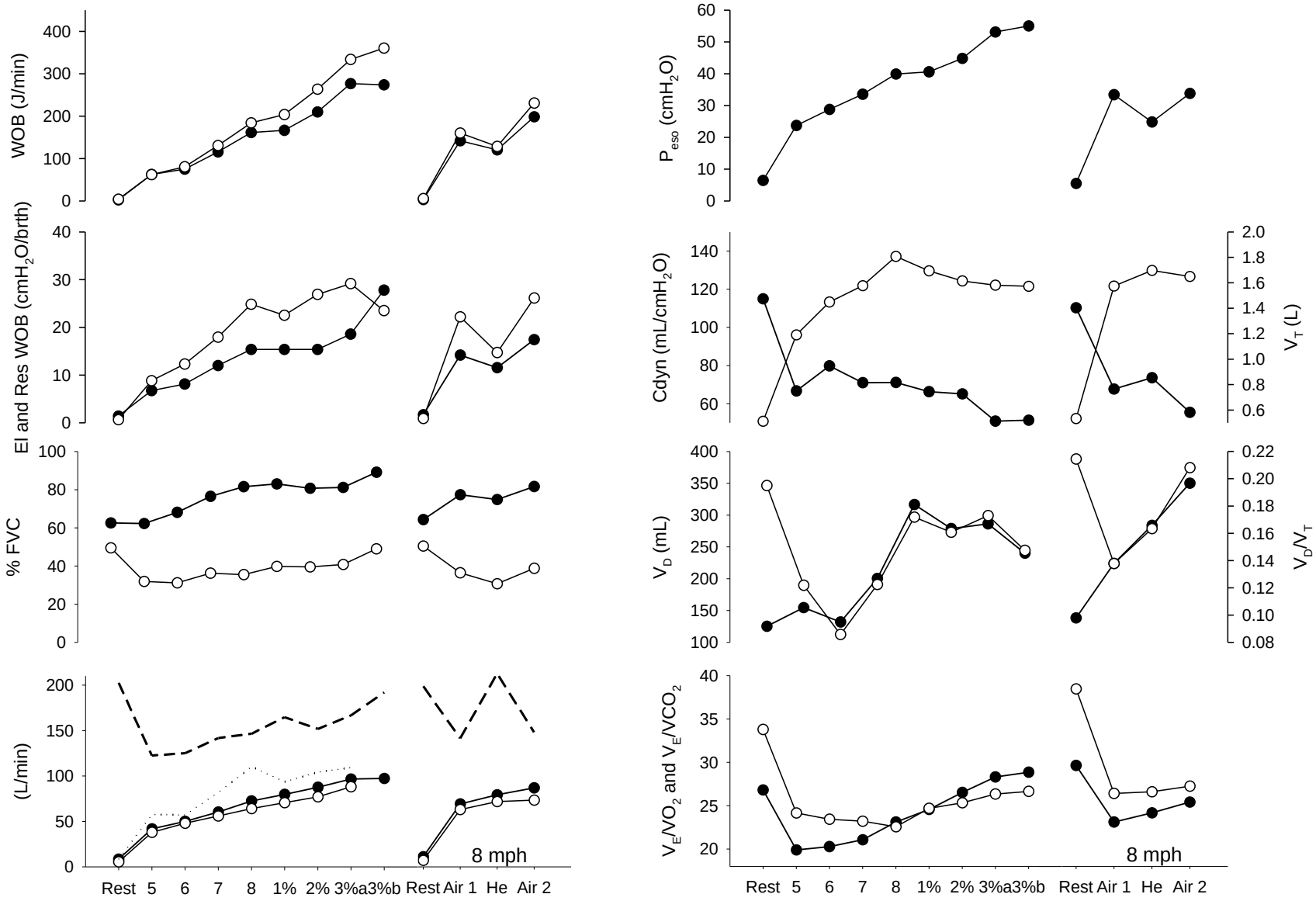


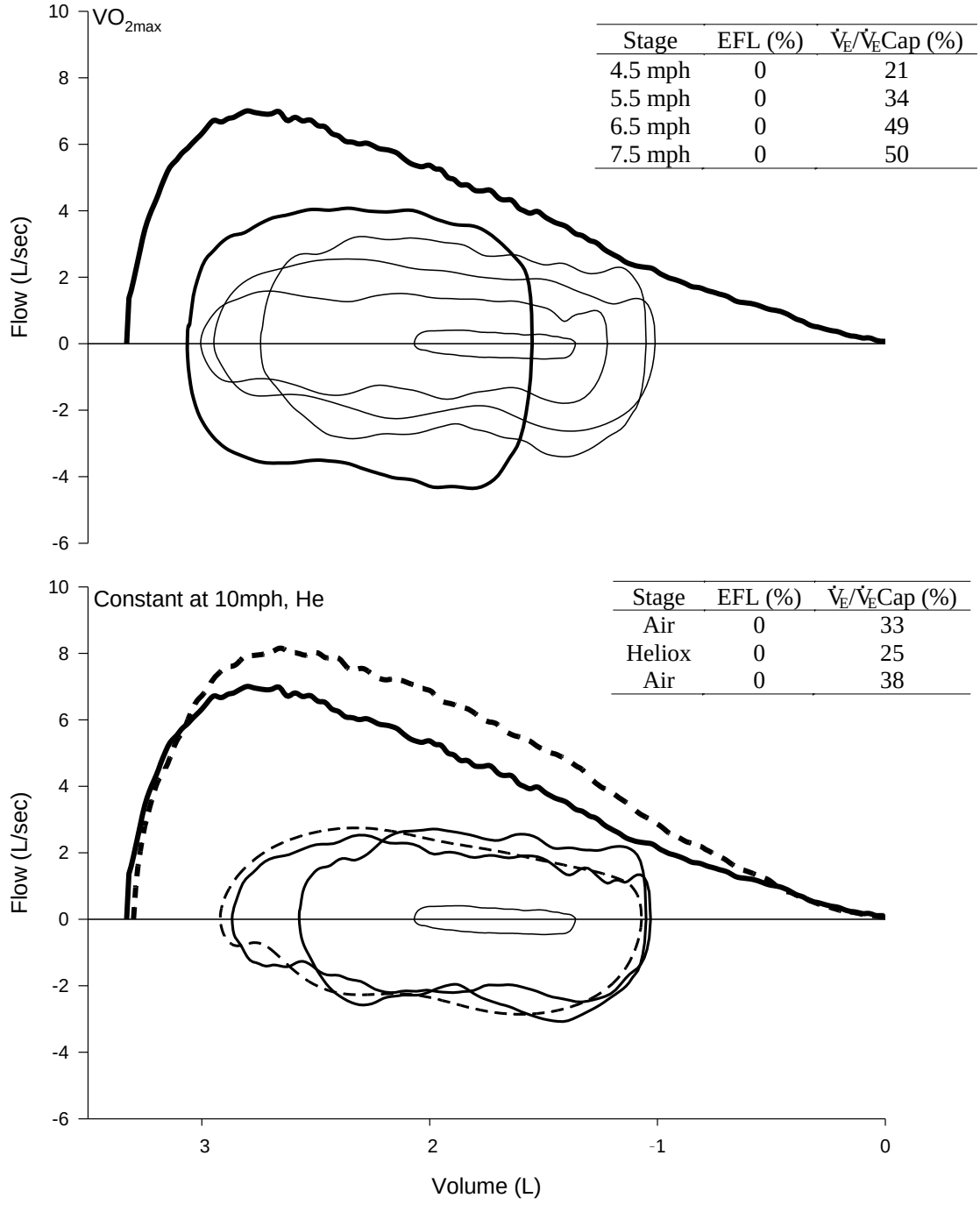
Figure 56- CR, MEFV curve and descriptors.

Subject CR- Run/Yoga (Rec). 60 min/4-6x/wk

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
22	158	58	23.2	3.66	104	21.47	0.24	-123

Peak exercise, 7.5 mph

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.69	46	2.99	90	1.11	1.6	66	0	47



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4.5 mph	0	21
5.5 mph	0	34
6.5 mph	0	49
7.5 mph	0	50

Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	33
Heliox	0	25
Air	0	38

Figure 57- CR, arterial blood gases.

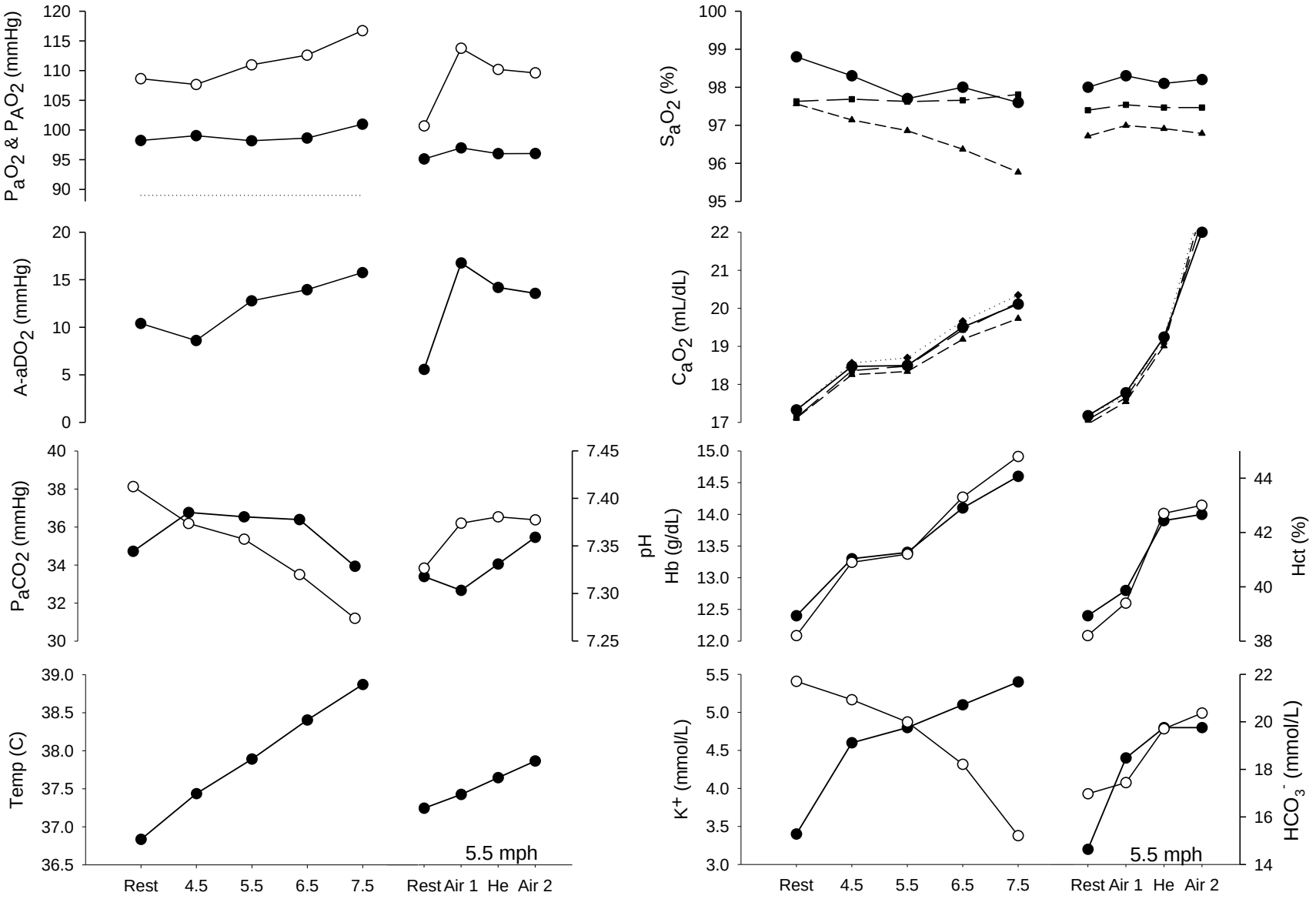


Figure 58- CR, respiratory mechanics.

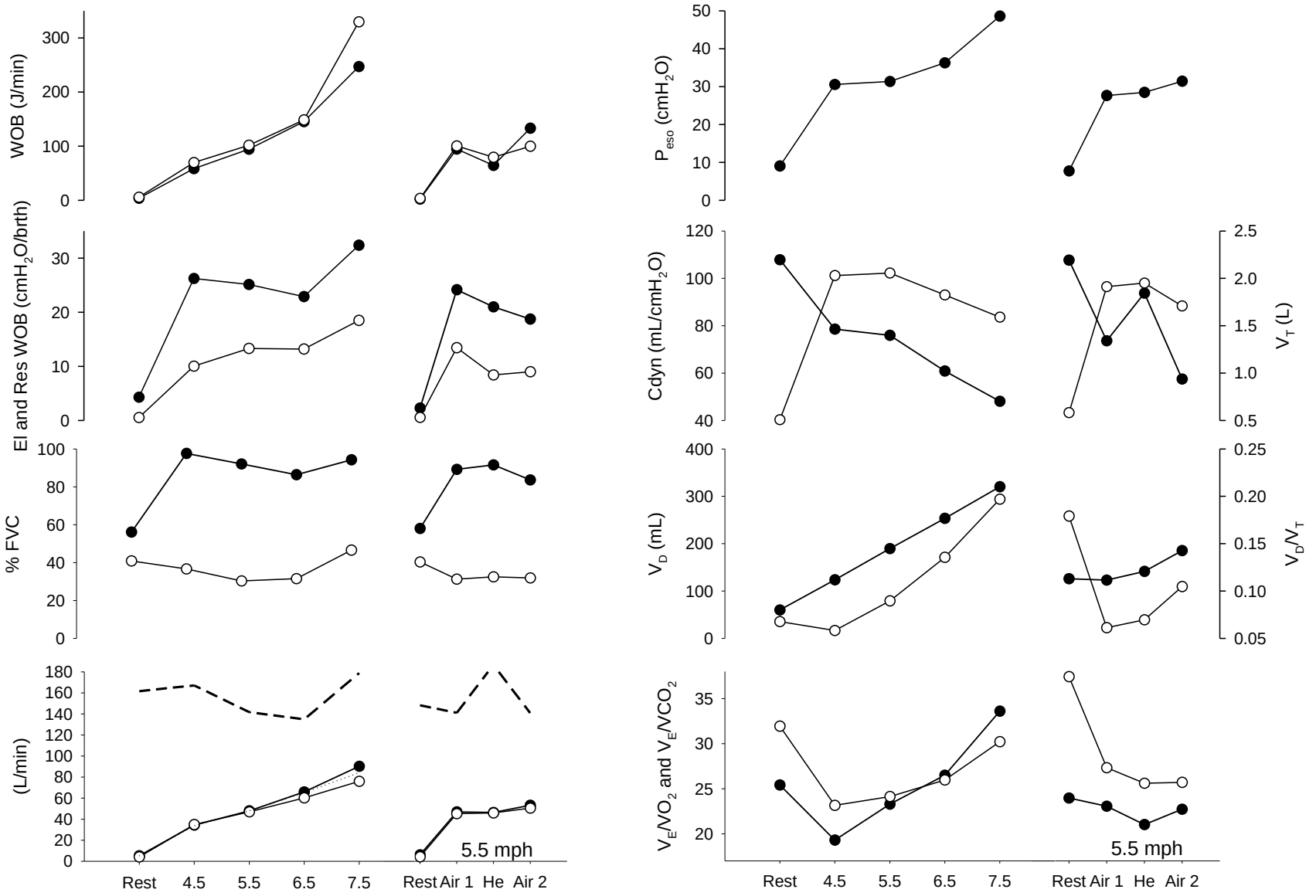


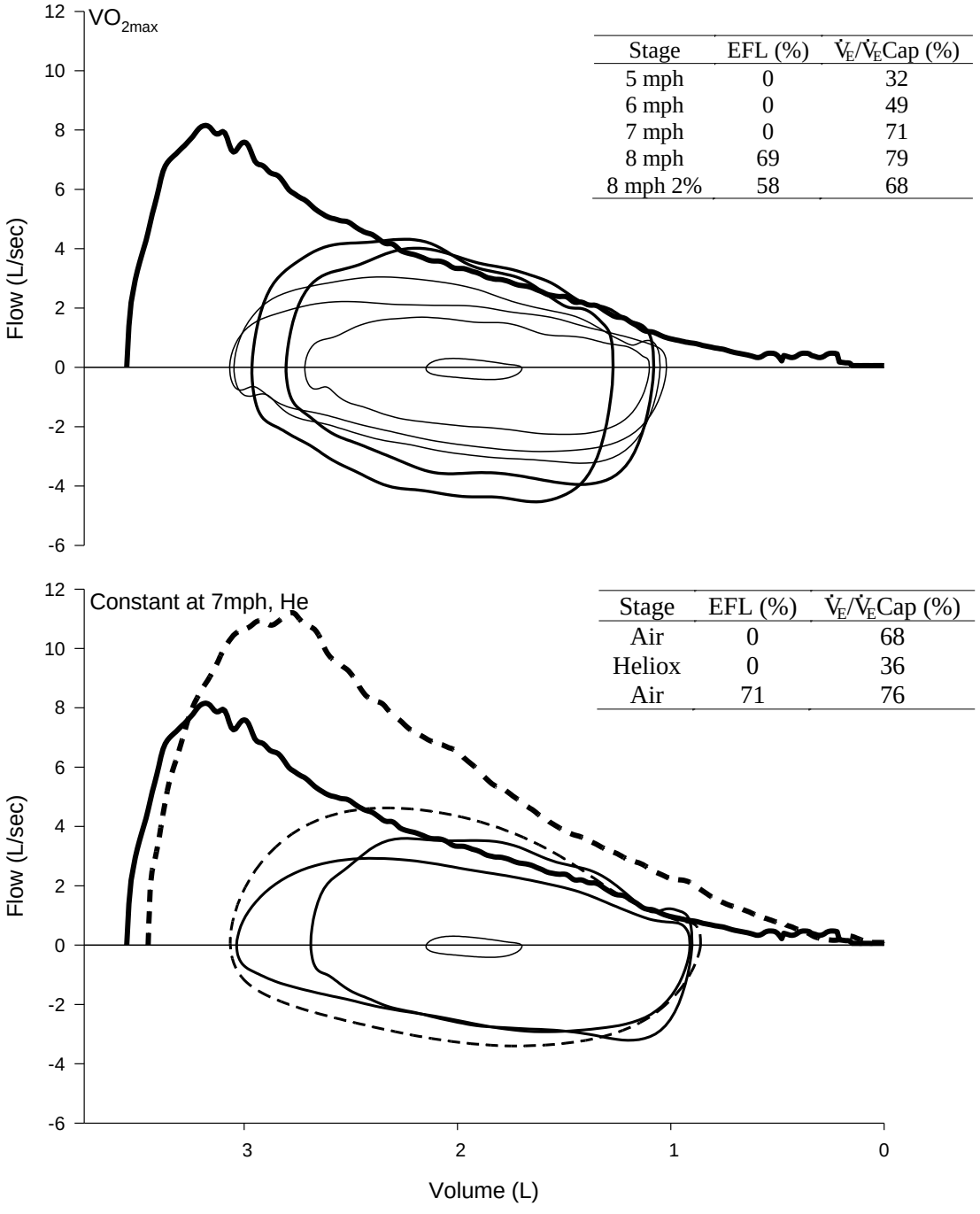
Figure 59-EM, MEFV curve and descriptors.

Subject EM- Wrestling/Canoeing/Rollerderby. 1-2hrs/daily

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
28	163	60	22.6	3.76	104	35.58		-124

Peak exercise, 8 mph, 2% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.99	50	3.15	81	1.1	1.66	57	57	36



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
5 mph	0	32
6 mph	0	49
7 mph	0	71
8 mph	69	79
8 mph 2%	58	68

Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	68
Heliox	0	36
Air	71	76

Figure 60- EM, arterial blood gases.

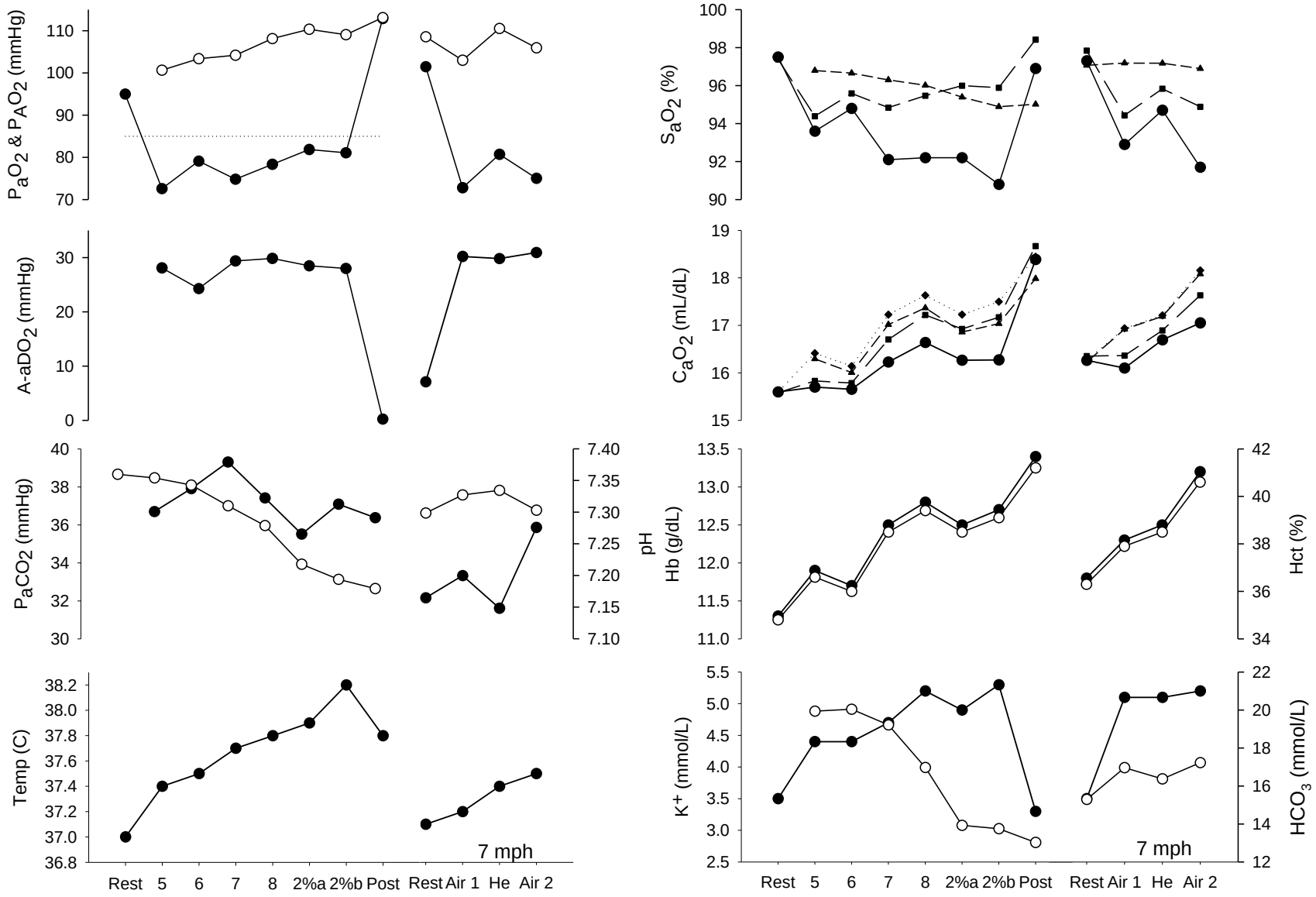


Figure 61- EM, respiratory mechanics.

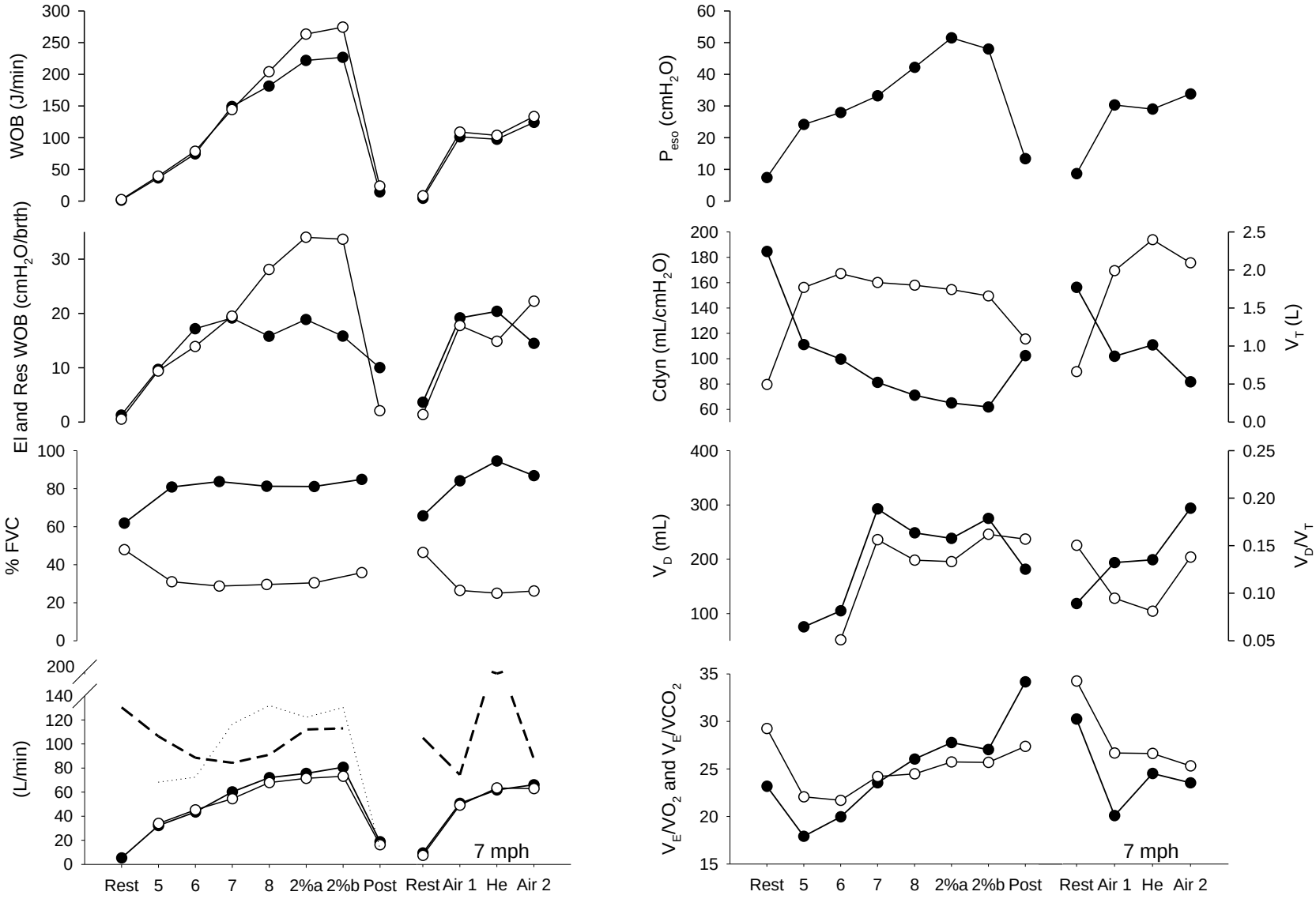


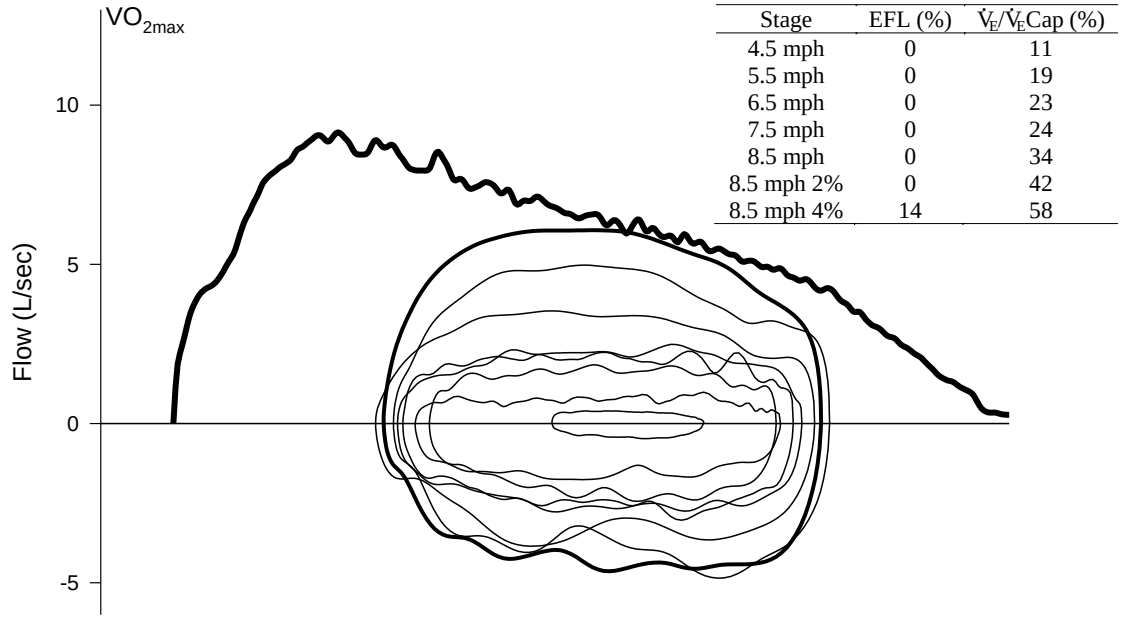
Figure 62- GLY, MEFV curve and descriptors.

Subject GLY- Soccer/Run/Cycle. 1hr/3-5x/wk

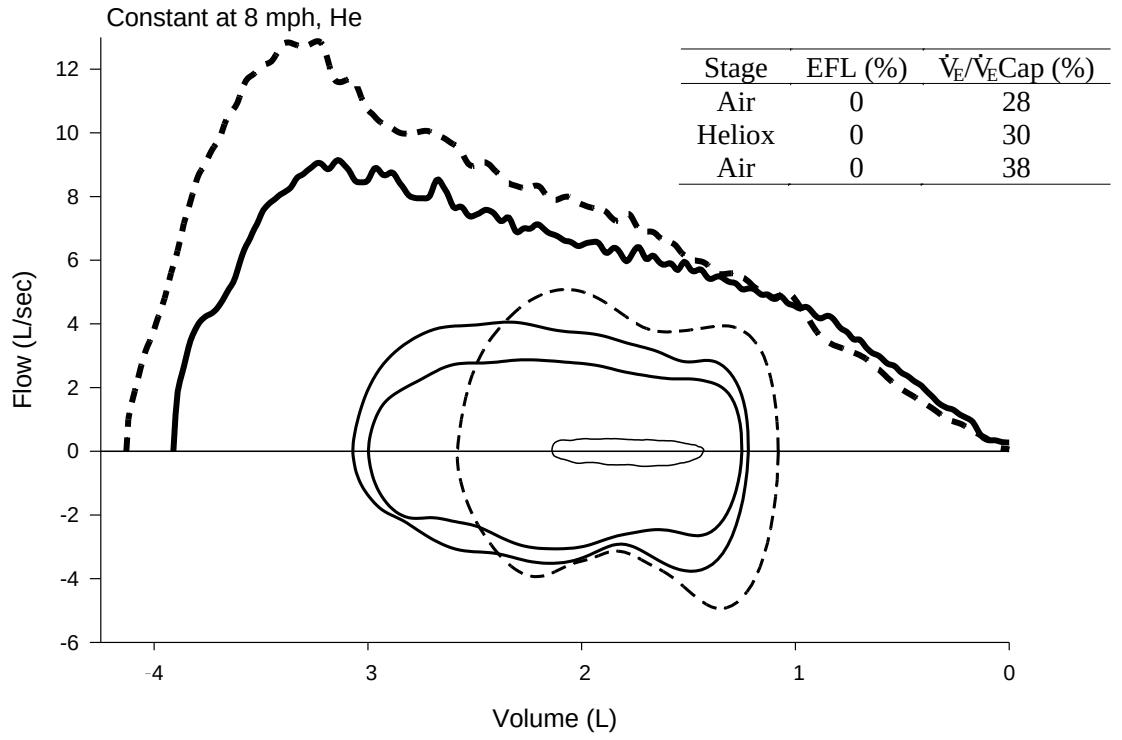
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
23	174	68	22.5	3.97	94		0.24	-103

Peak exercise, 8.5 mph, 4% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.75	53	4.01	106	1.4	2.1	59	14	23



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4.5 mph	0	11
5.5 mph	0	19
6.5 mph	0	23
7.5 mph	0	24
8.5 mph	0	34
8.5 mph 2%	0	42
8.5 mph 4%	14	58



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	28
Heliox	0	30
Air	0	38

Figure 63- GLY, arterial blood gases.

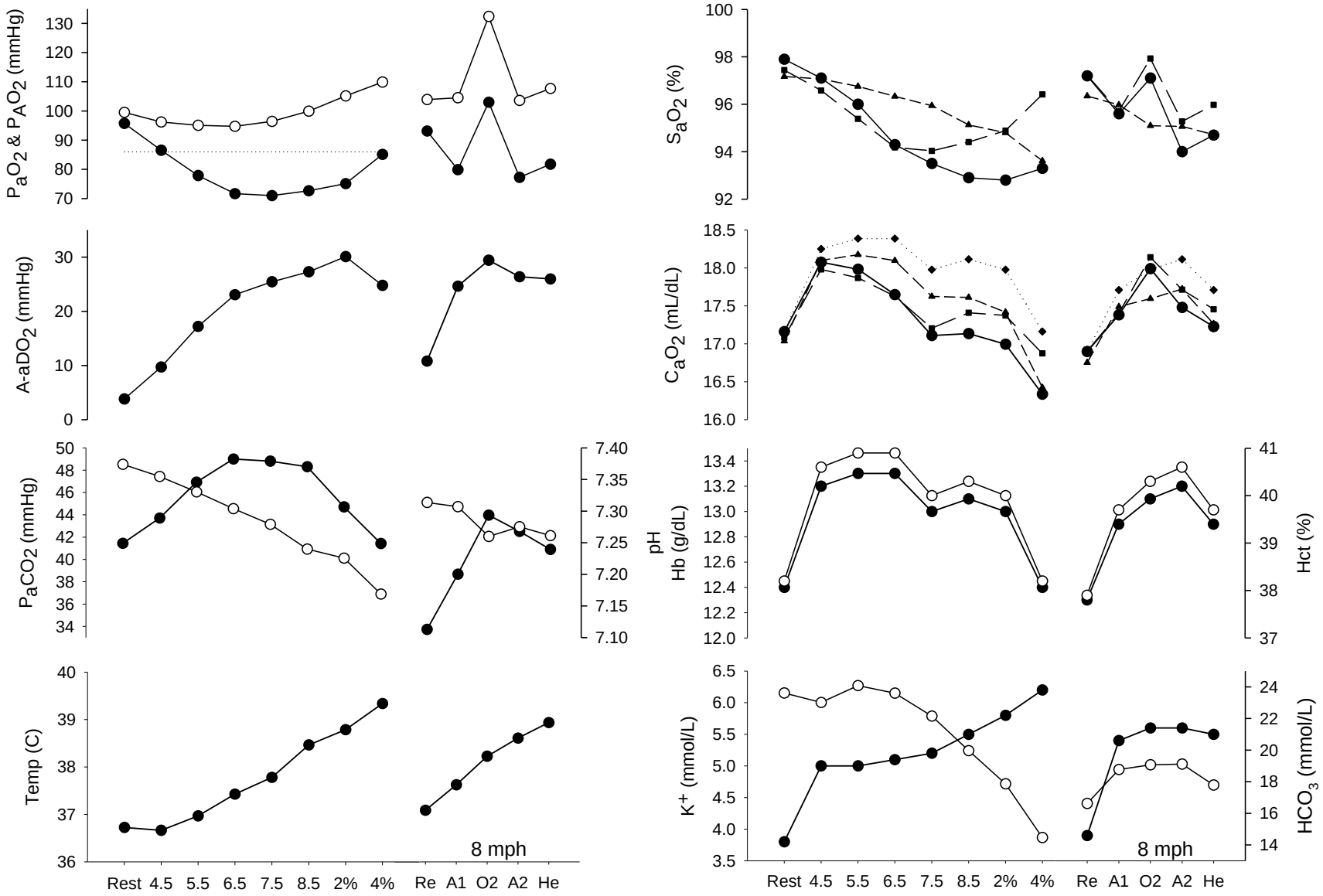


Figure 64-GLY, respiratory mechanics.

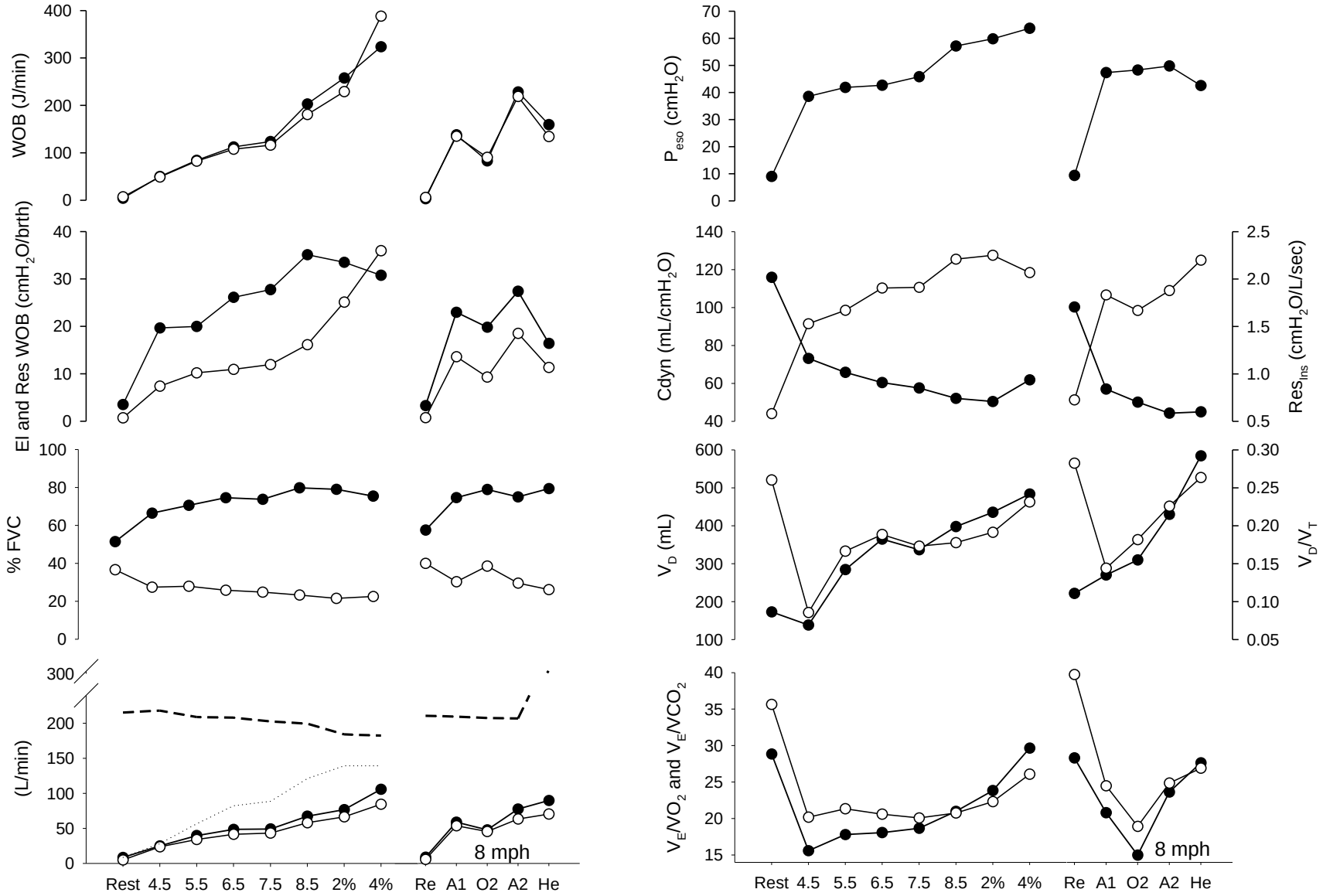


Figure 65- JB (Dec), MEFV curve and descriptors.

Subject JB (Dec)- Rugby. 1.5-2.5hrs/4x/wk.

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
21	157	72.4	29.4	4	114	26.02		-103

Peak exercise, 7 mph

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.25	46	3.32	77	1.03	1.7	38	0	50

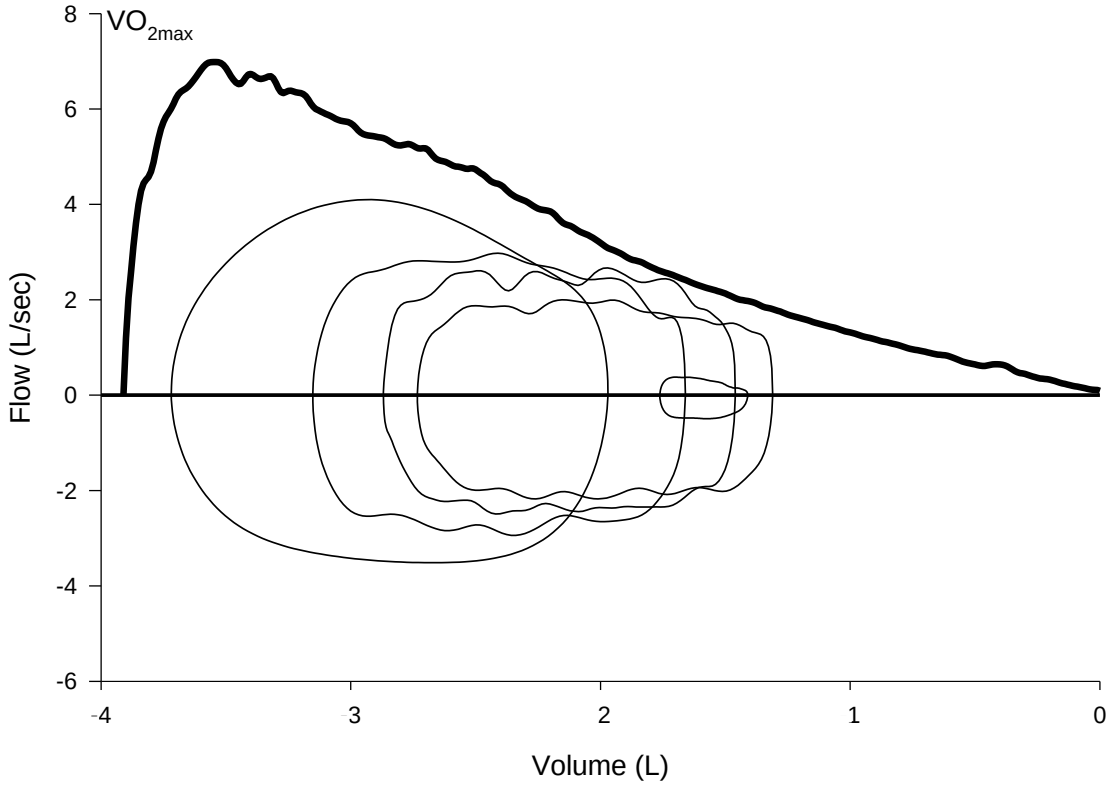


Figure 66- JB (Dec), arterial blood gases.

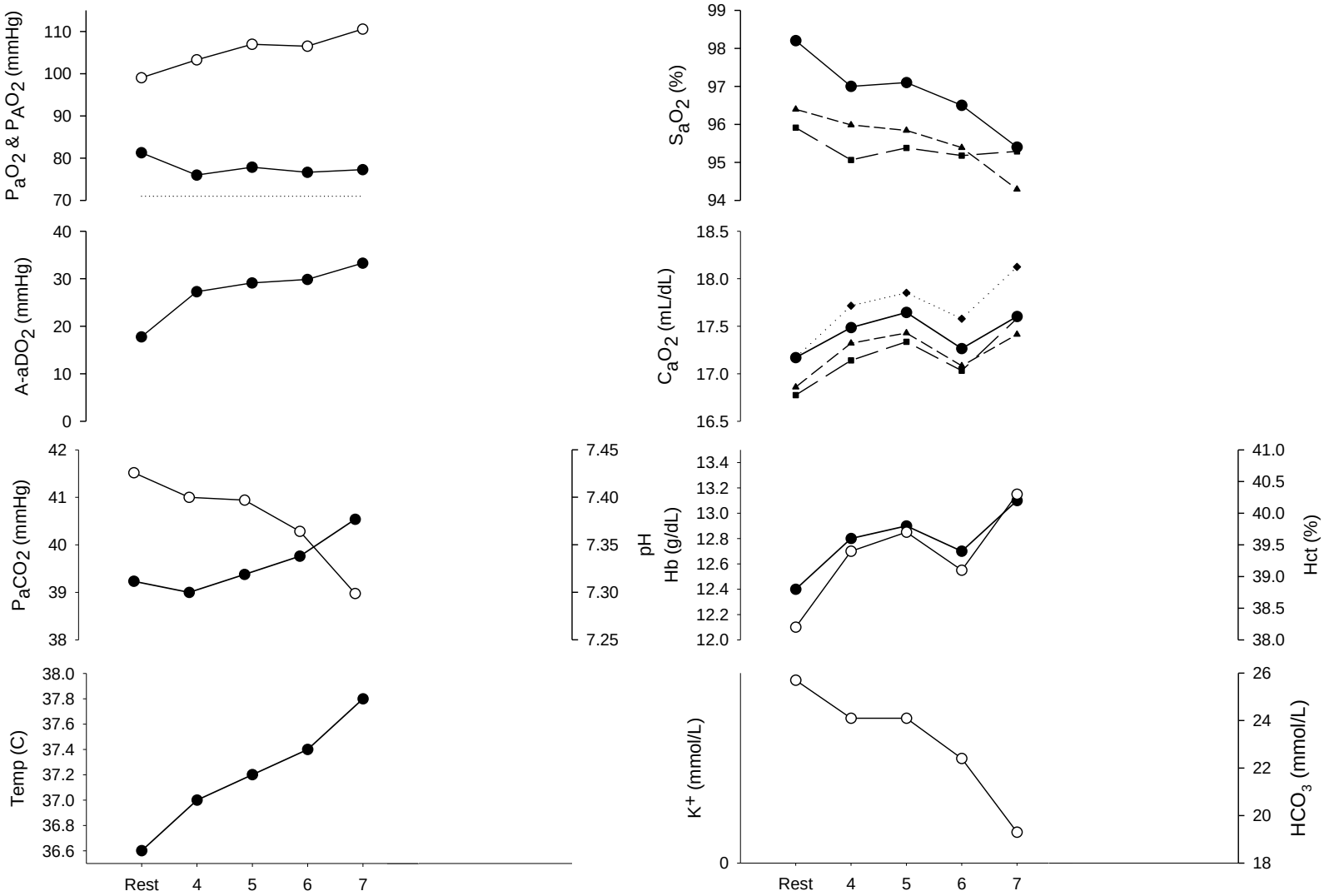


Figure 67- JB (Dec), respiratory mechanics.

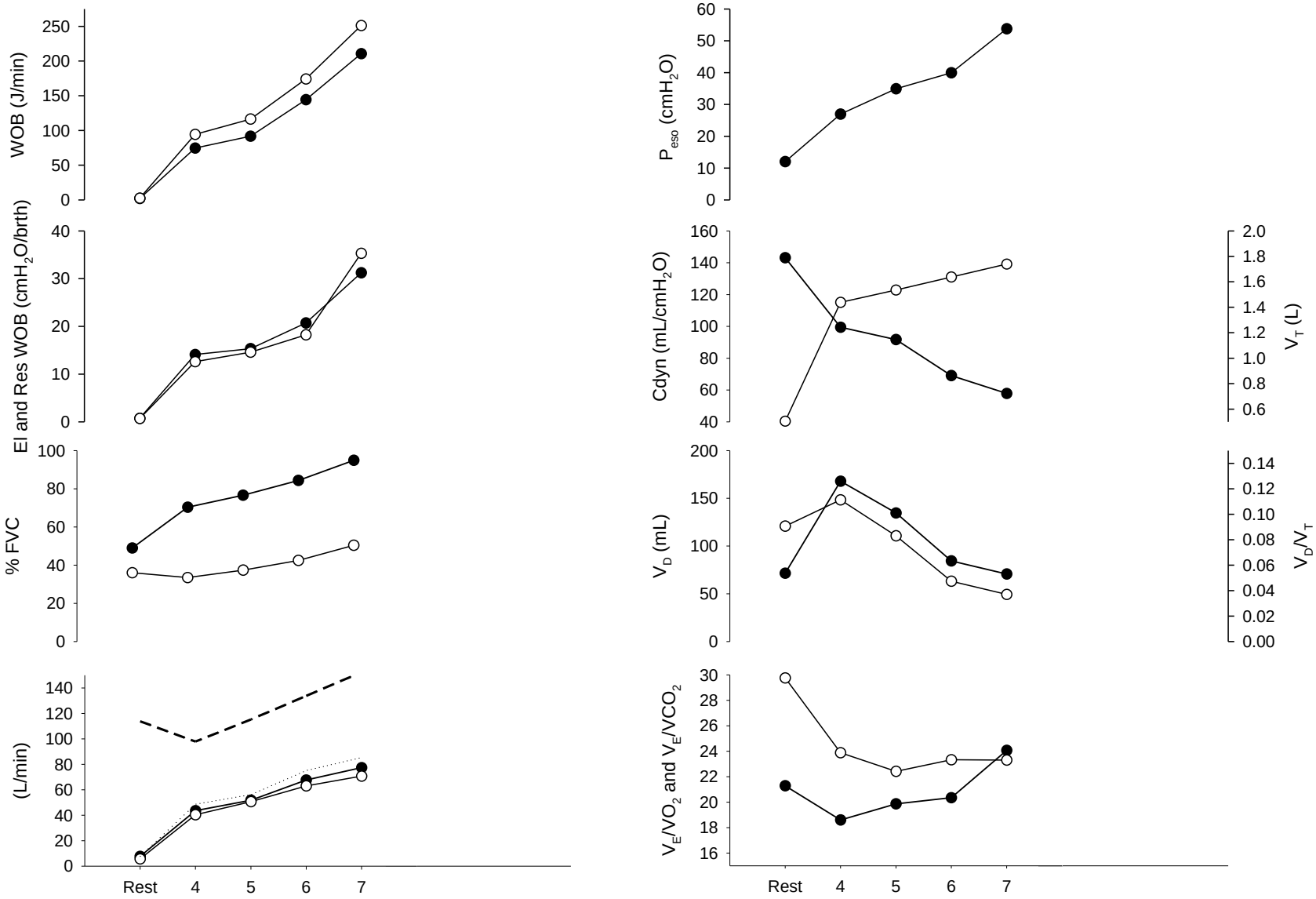


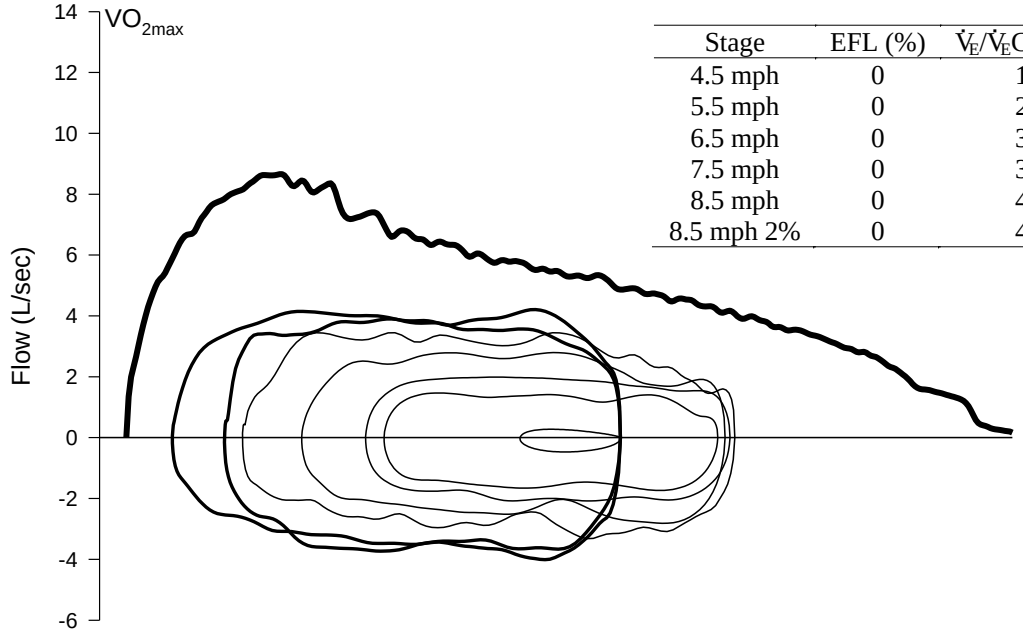
Figure 68- JB, MEFV curve and descriptors.

Subject JB- Varsity softball. Running/Gym, 1.5hrs/4x week

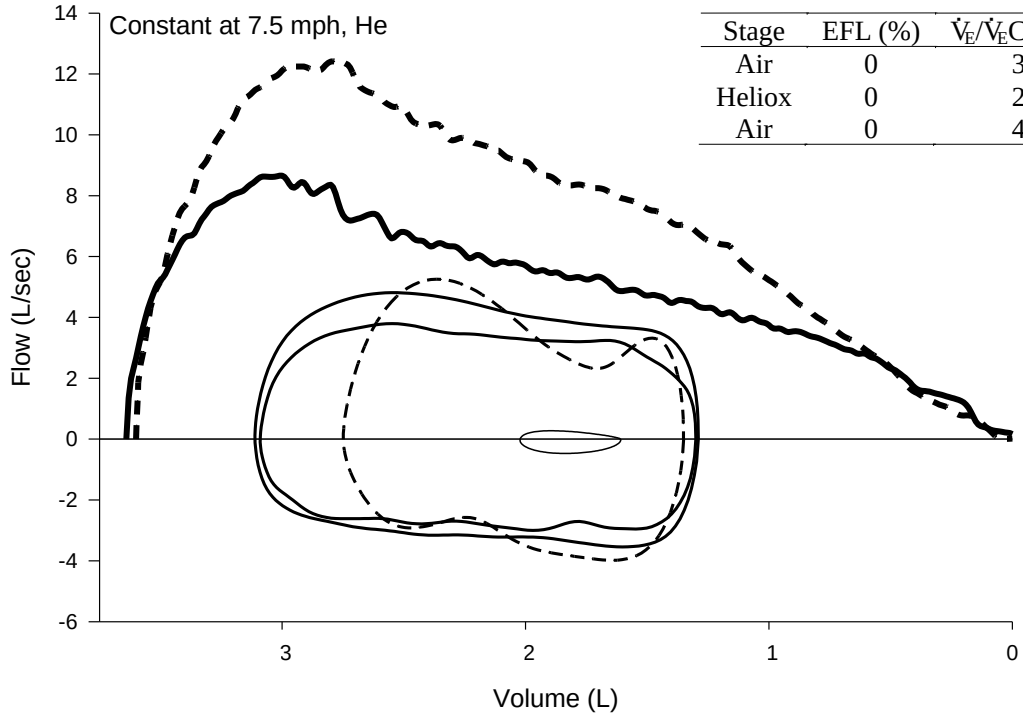
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
Yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
23	177	64	20.4	4.14	95		0.22	-107

Peak exercise, 8.5 mph, 2% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.98	46.6	2.96	84	1.01	1.76	56	0	44



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4.5 mph	0	19
5.5 mph	0	26
6.5 mph	0	31
7.5 mph	0	39
8.5 mph	0	42
8.5 mph 2%	0	45



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	37
Heliox	0	27
Air	0	42

Figure 69- JB, arterial blood gases.

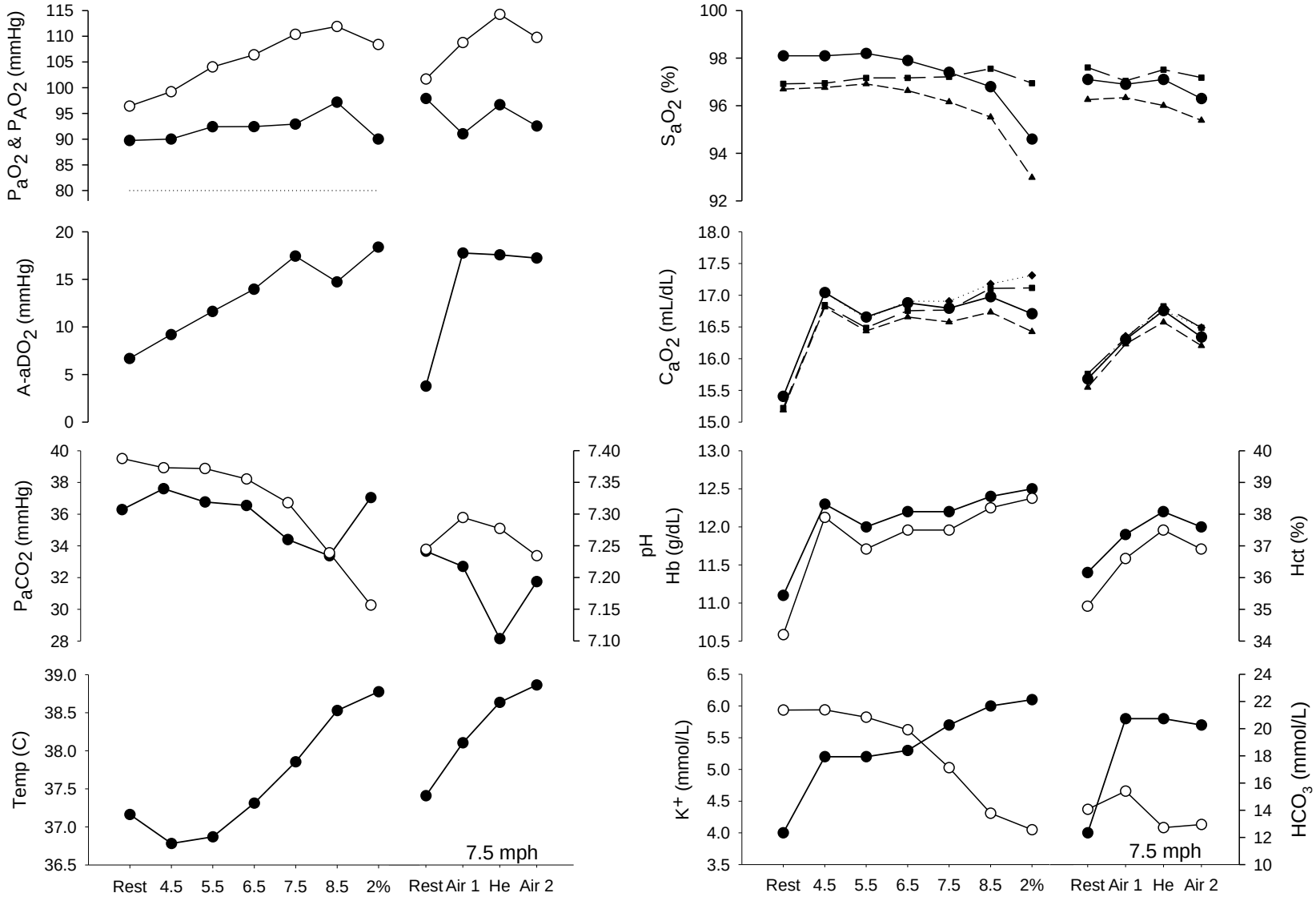


Figure 70- JB, respiratory mechanics.

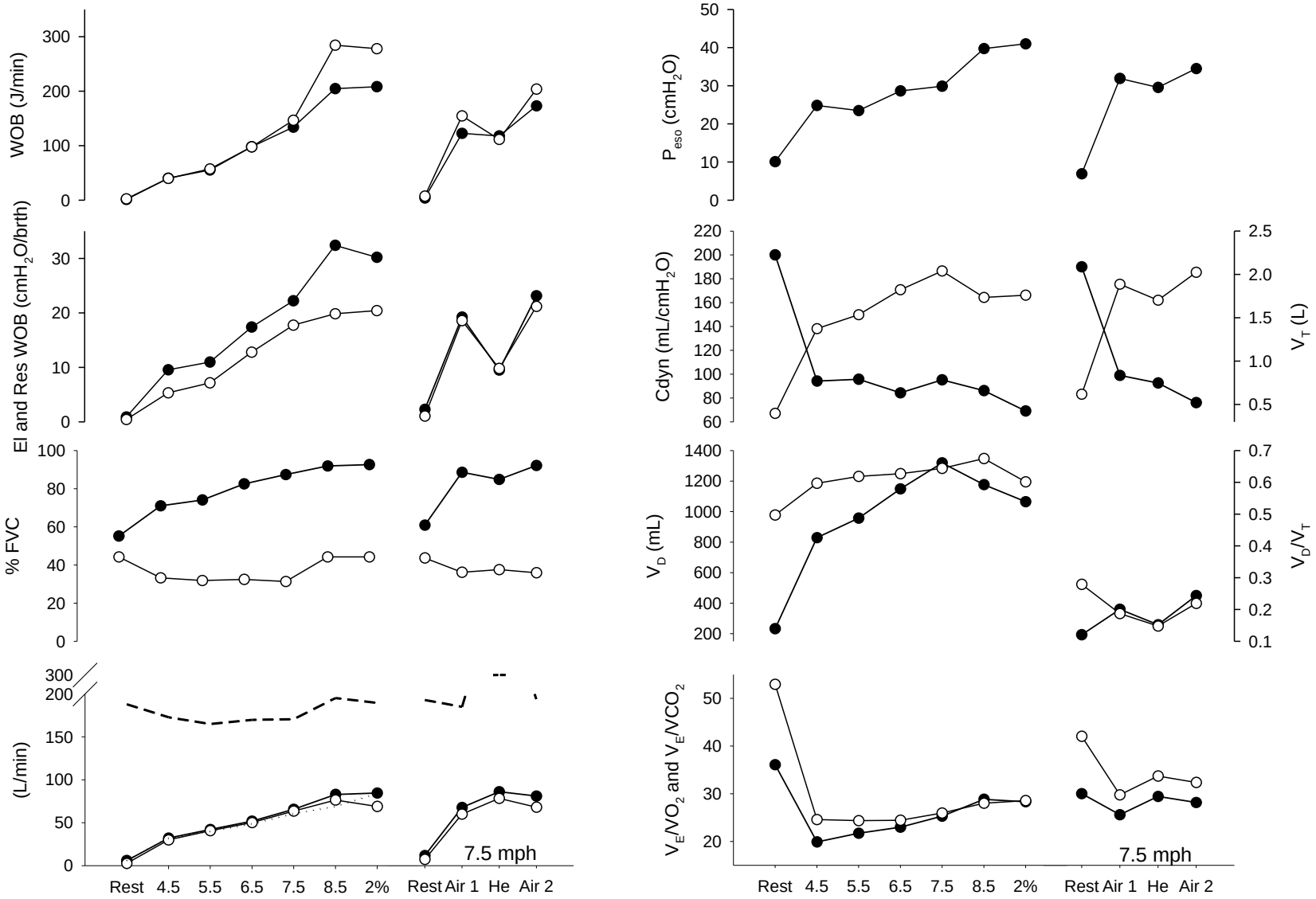


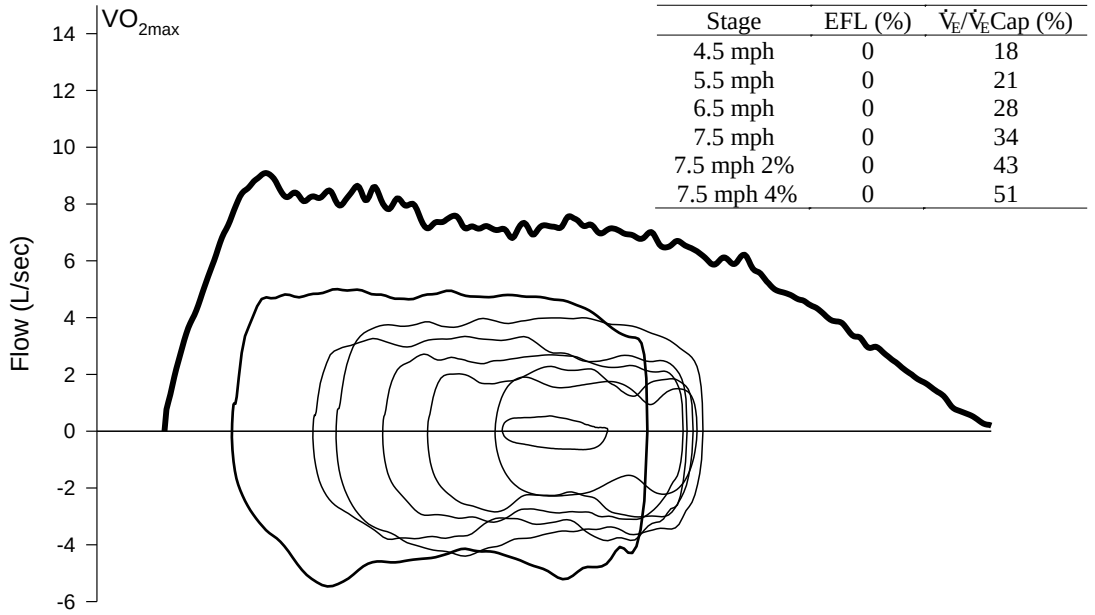
Figure 71- JC, MEFV curve and descriptors.

Subject JC- Run/Basketball. 90min/3-5x/wk

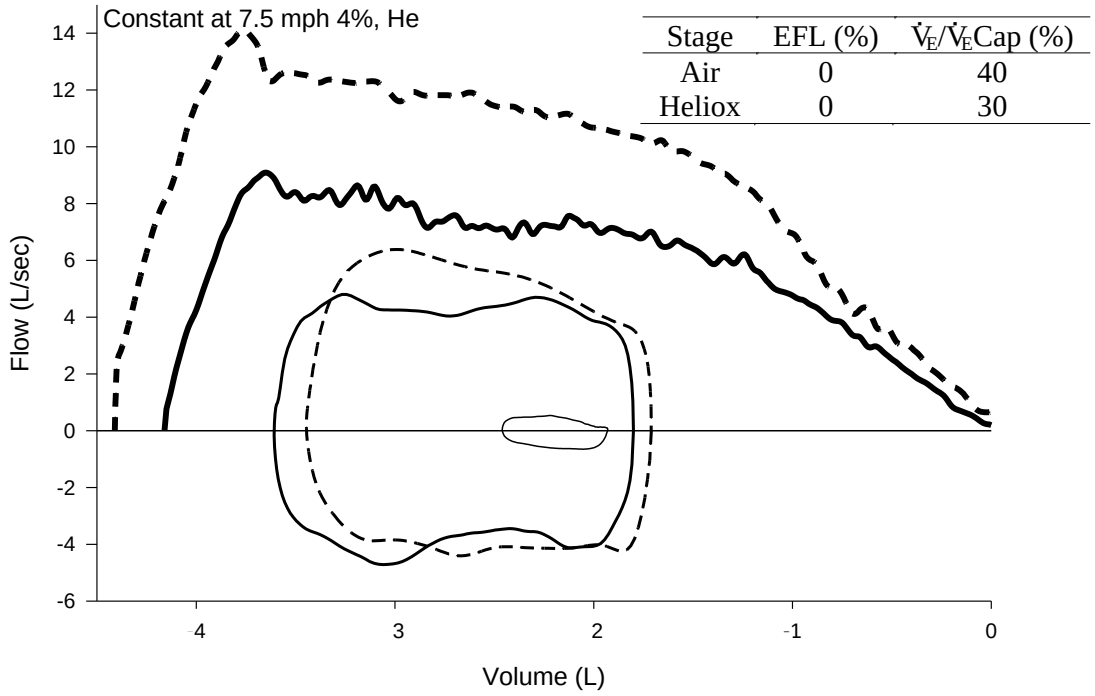
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
23	173	72	24.1	4.23	101			-103

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.69	51	3.83	109	1.04	2.2	60	42	47



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4.5 mph	0	18
5.5 mph	0	21
6.5 mph	0	28
7.5 mph	0	34
7.5 mph 2%	0	43
7.5 mph 4%	0	51



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	40
Heliox	0	30

Figure 72- JC, arterial blood gases.

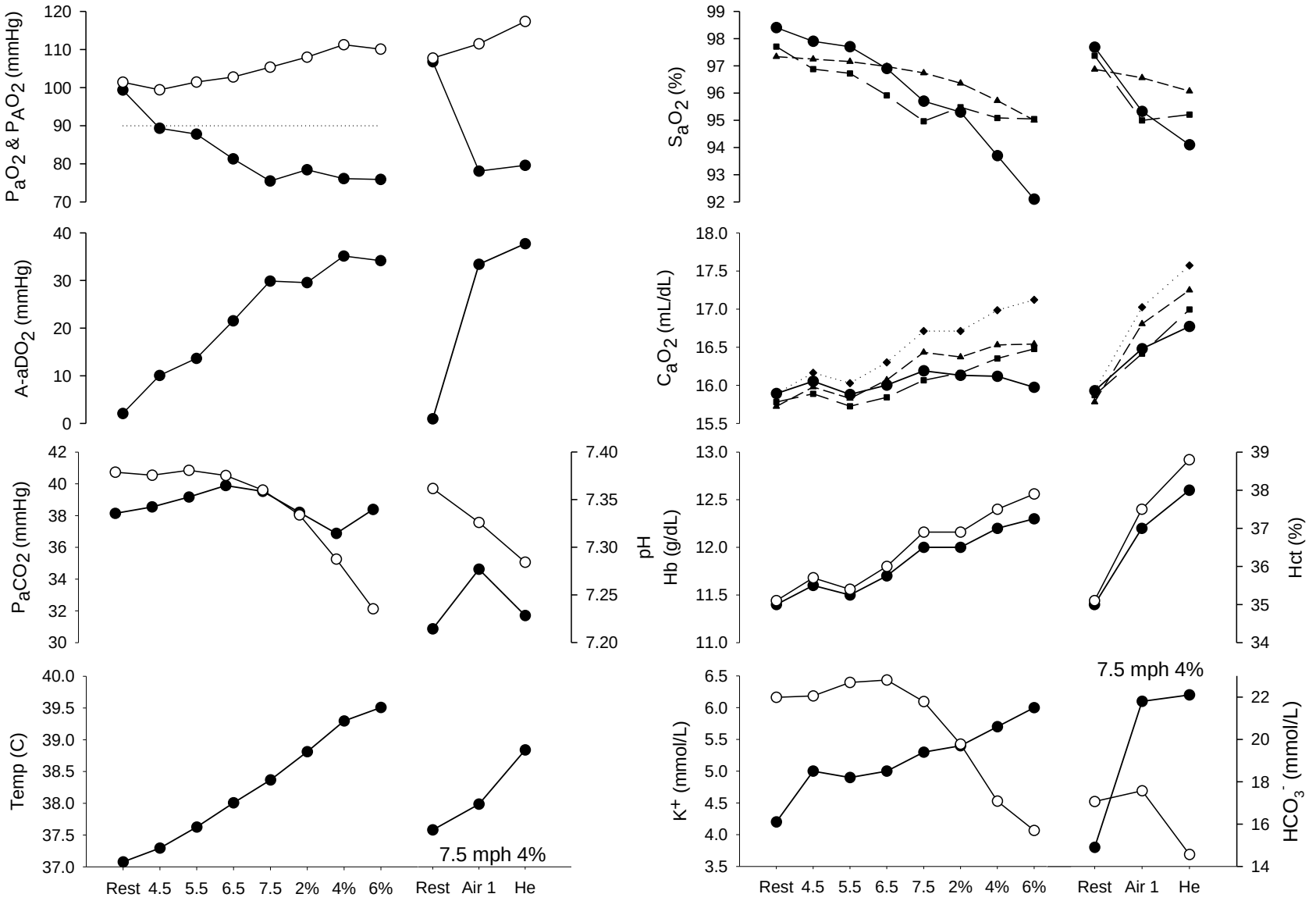


Figure 73- JC, respiratory mechanics.

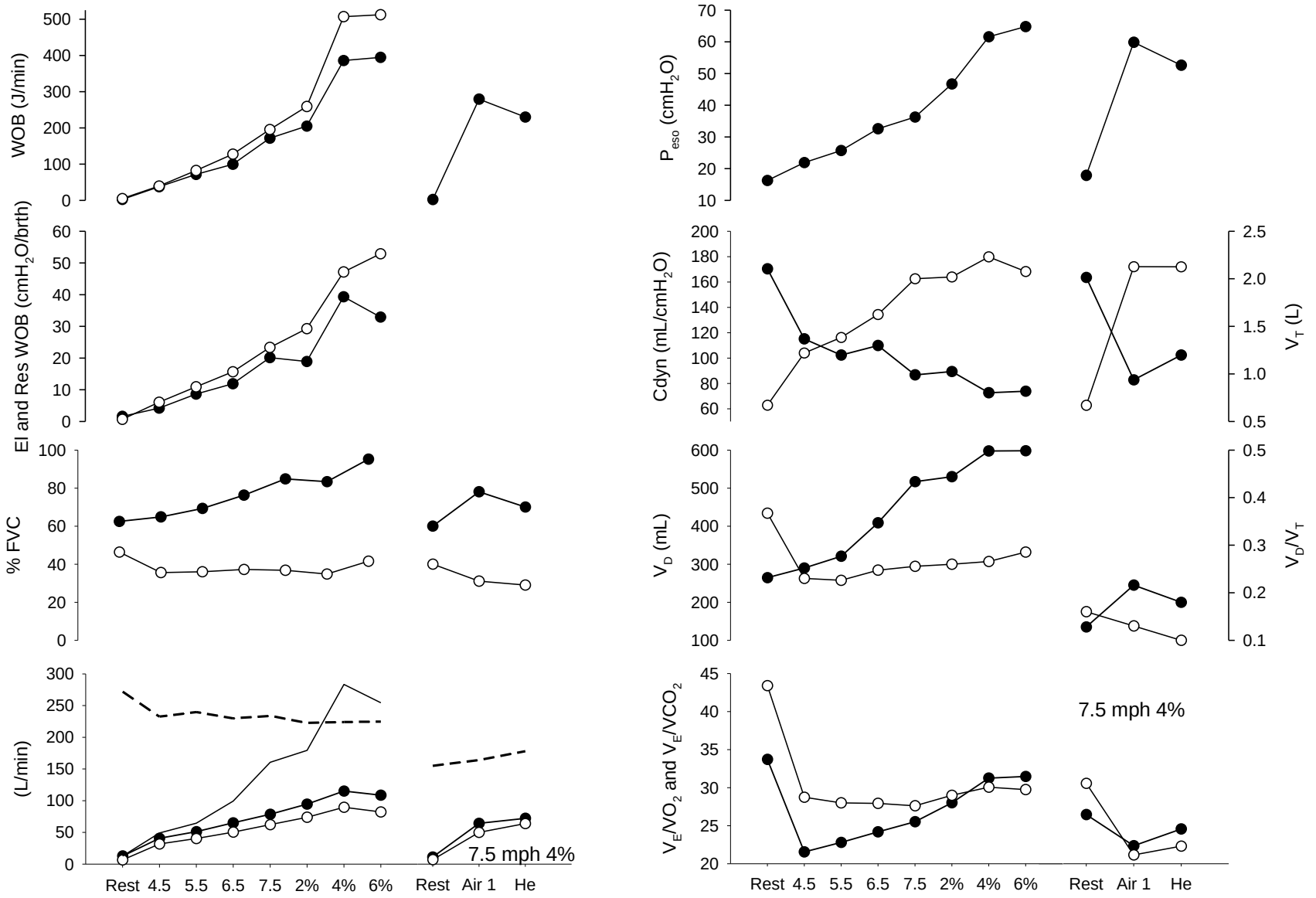


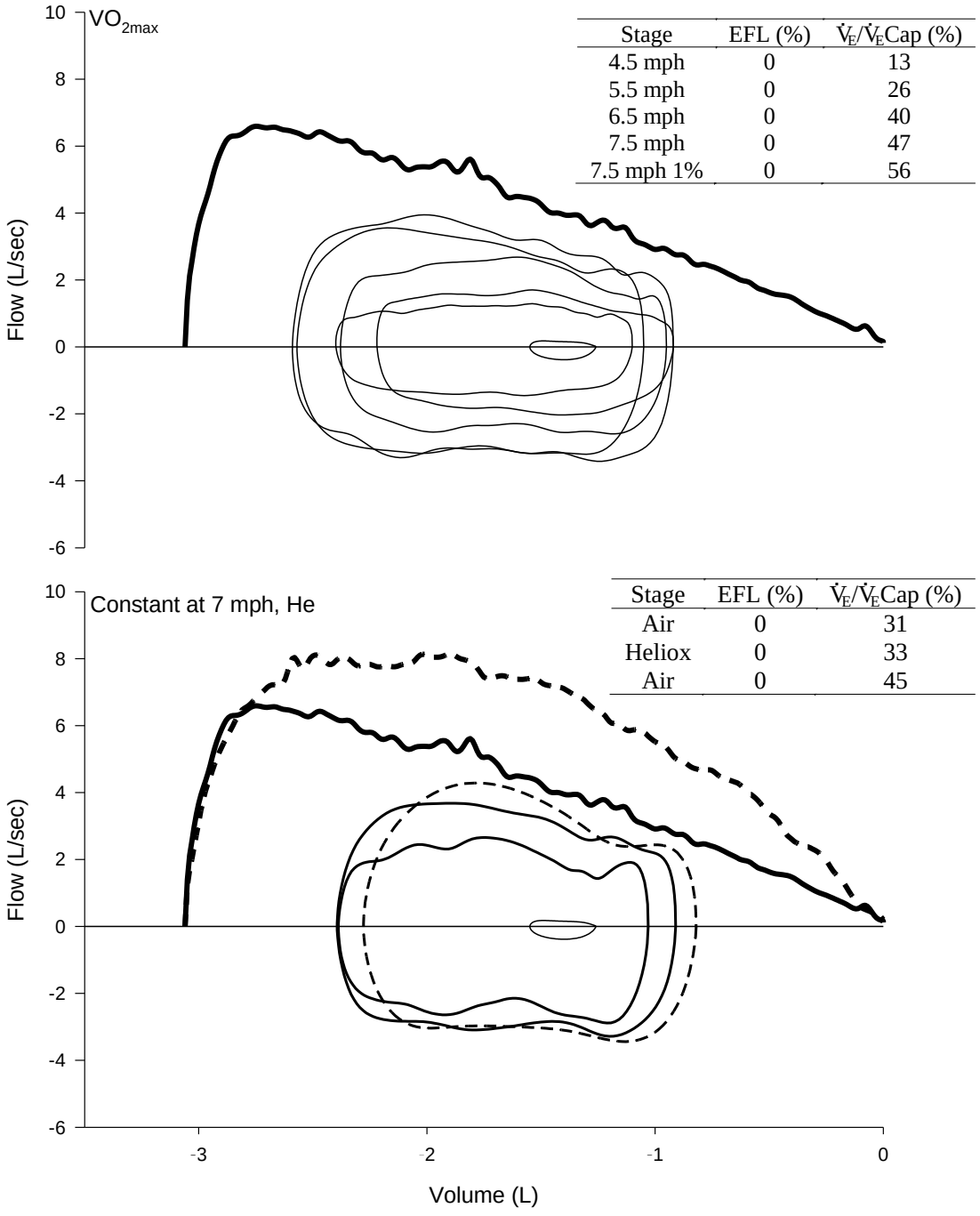
Figure 74- JL, MEFV curve and descriptors.

Subject JL- Weight training/light cardio. 1hr/1-3x/wk.

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
21	164	59	21.9	3.77	98	22.78	0.37	-41

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.37	40	2.72	80	1.16	1.8	53	0	30



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4.5 mph	0	13
5.5 mph	0	26
6.5 mph	0	40
7.5 mph	0	47
7.5 mph 1%	0	56

Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	31
Heliox	0	33
Air	0	45

Figure 75- JL, arterial blood gases.

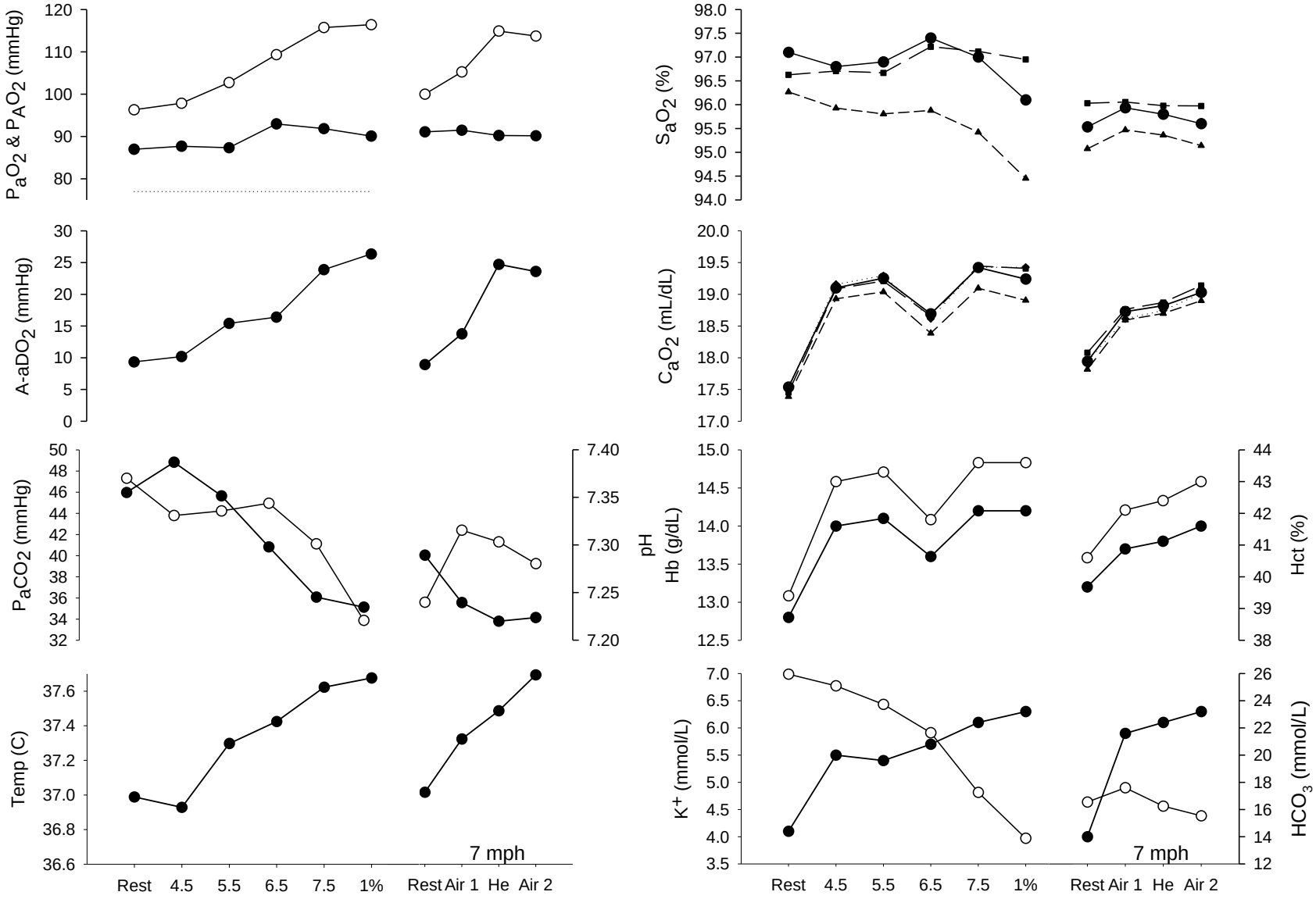


Figure 76- JL, respiratory mechanics.

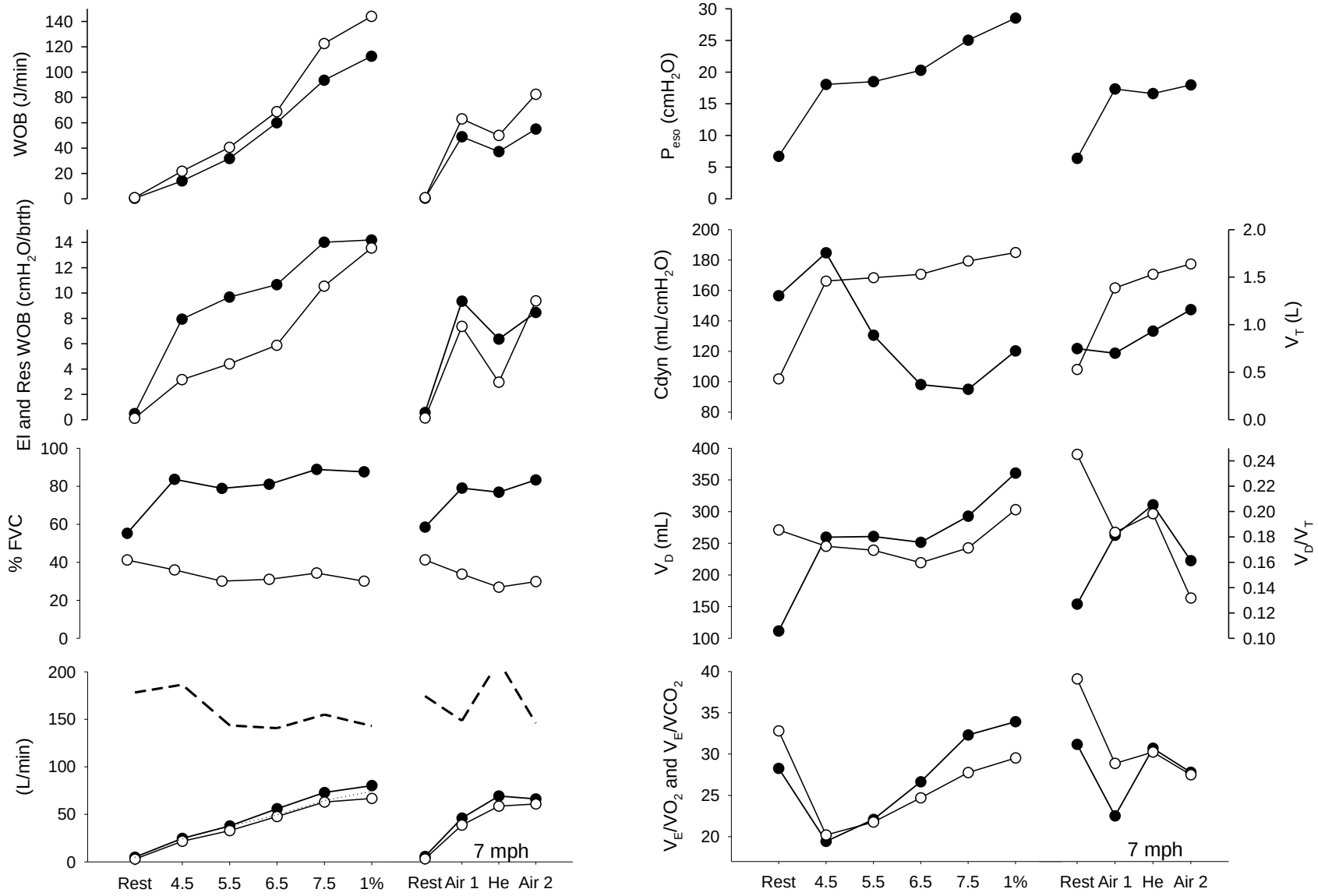


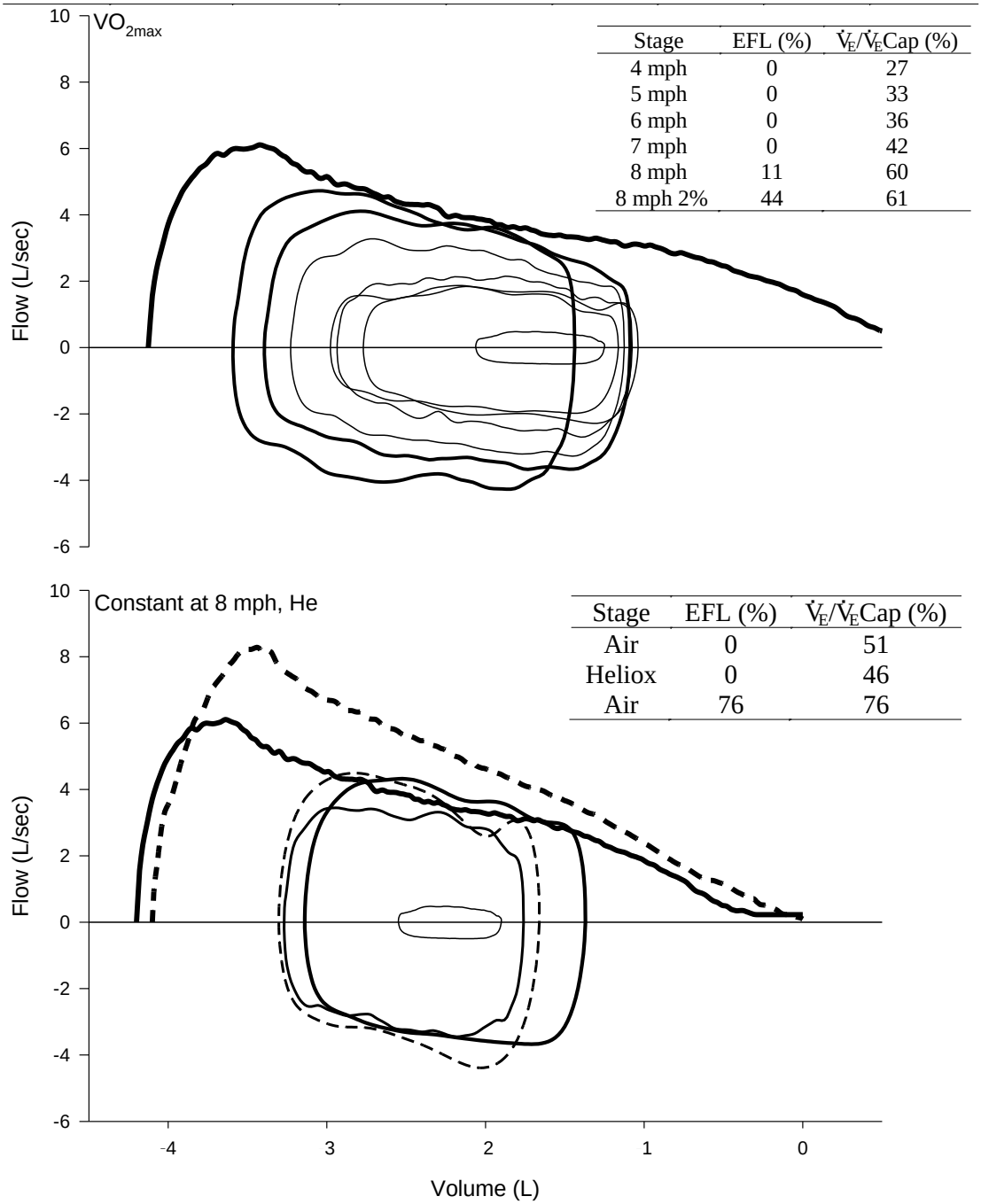
Figure 77- JS (Dec), MEFV curve and descriptors.

Subject JS(DEC)- Rowing (Varsity). 1-2hrs/2xdaily.

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
19	177	63.8	20.4	4.36	98	26.45	0.13	-62

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.50	55	3.85	101	1.10	1.8	65	44	49



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4 mph	0	27
5 mph	0	33
6 mph	0	36
7 mph	0	42
8 mph	11	60
8 mph 2%	44	61

Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	51
Heliox	0	46
Air	76	76

Figure 78- JS (Dec), arterial blood gases.

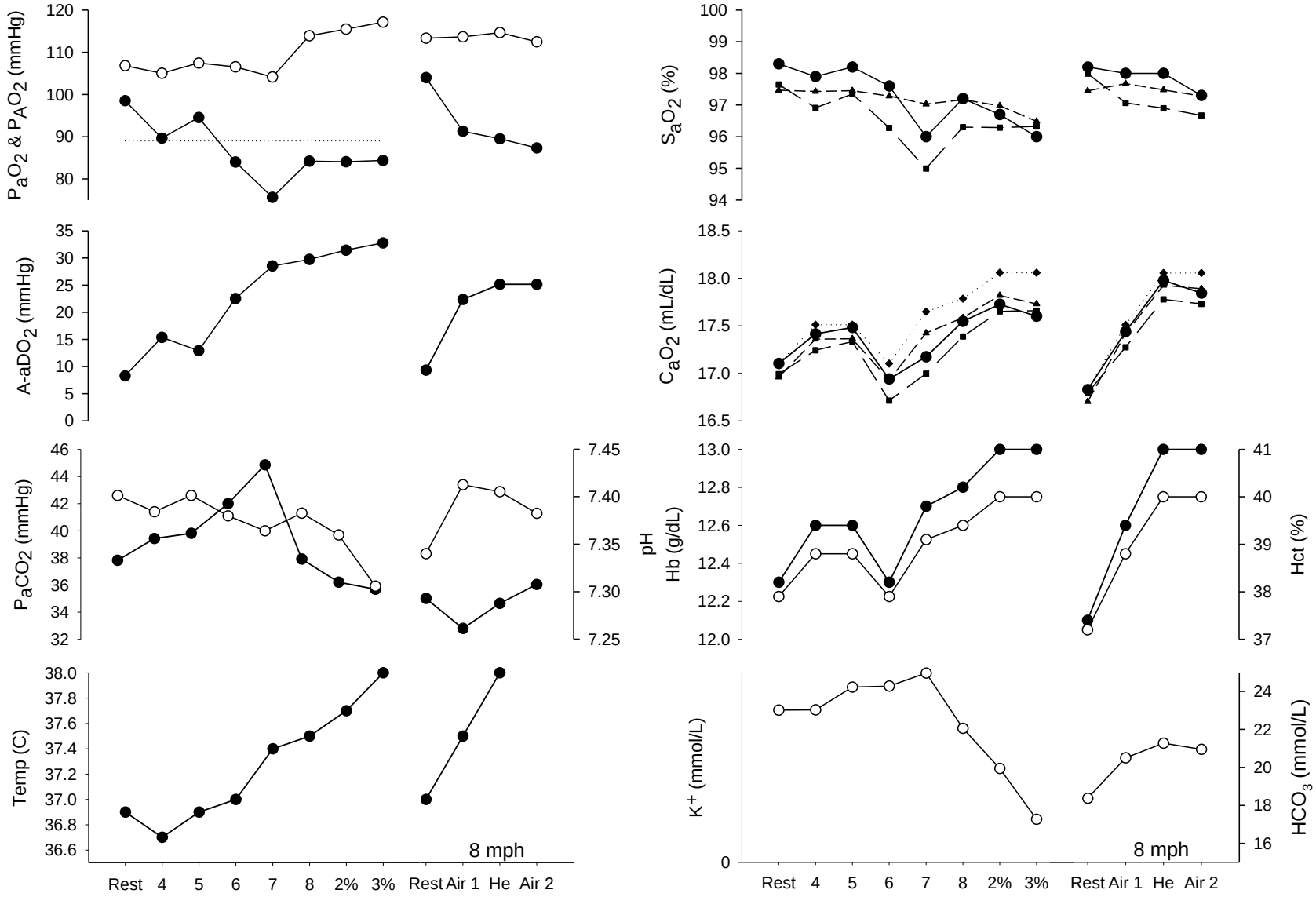


Figure 79- JS (Dec), respiratory mechanics.

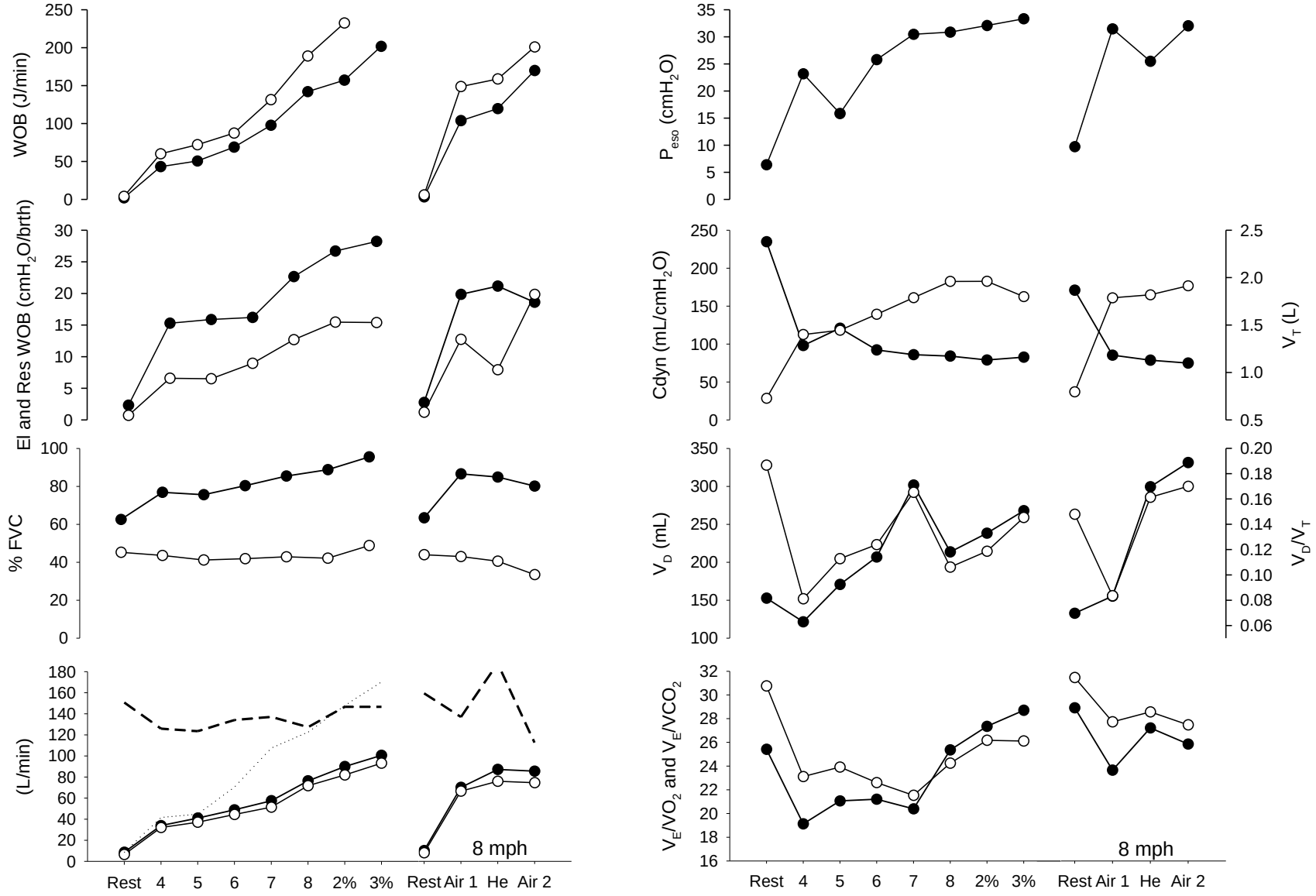


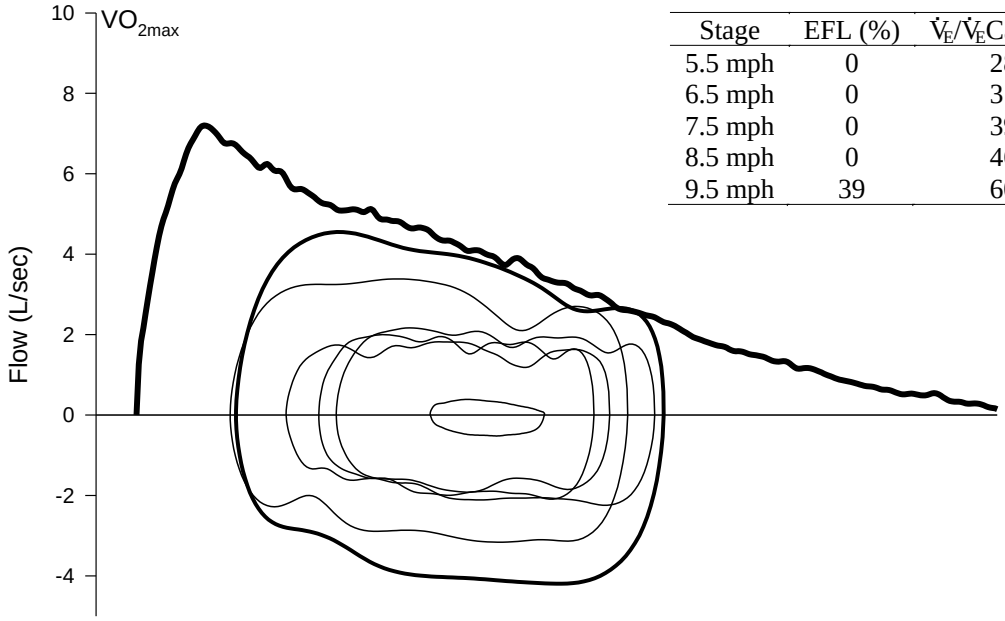
Figure 80- JS (Nov), MEFV curve and descriptors.

Subject JS (NOV)- Run(Marathon)/Bike/Soccer/Skiing. 1hr+/daily

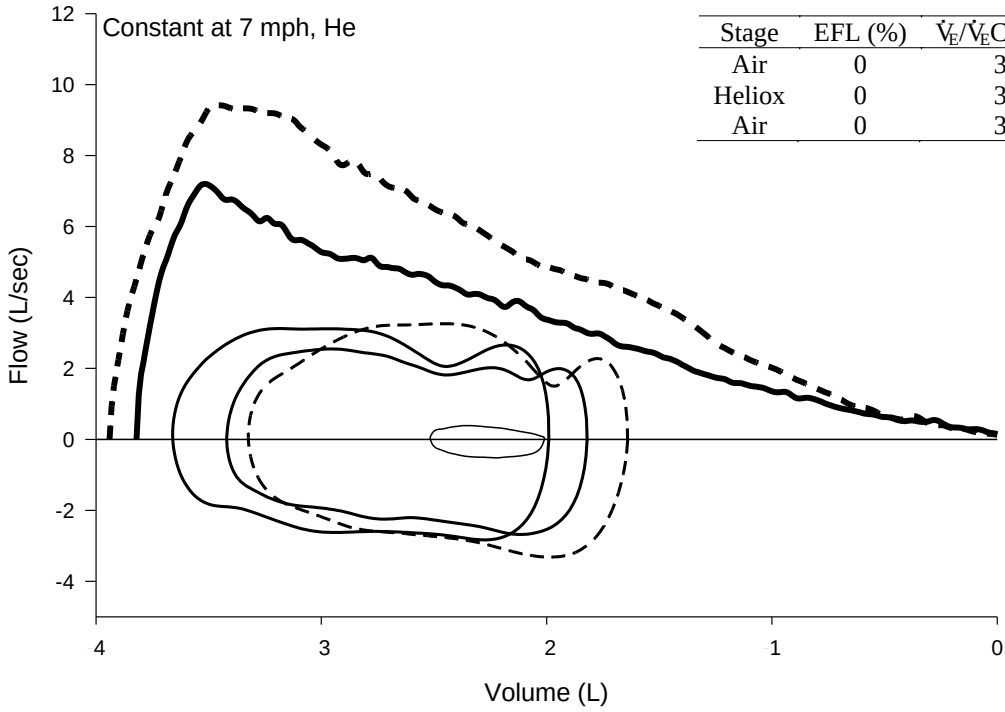
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
38	165	54.5	20.0	3.9	113	24.45	0.12	-75

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.14	58	3.32	87	1.06	2.0	51	39	41



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
5.5 mph	0	28
6.5 mph	0	31
7.5 mph	0	39
8.5 mph	0	46
9.5 mph	39	60



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	36
Heliox	0	32
Air	0	38

Figure 81- JS (Nov), arterial blood gases.

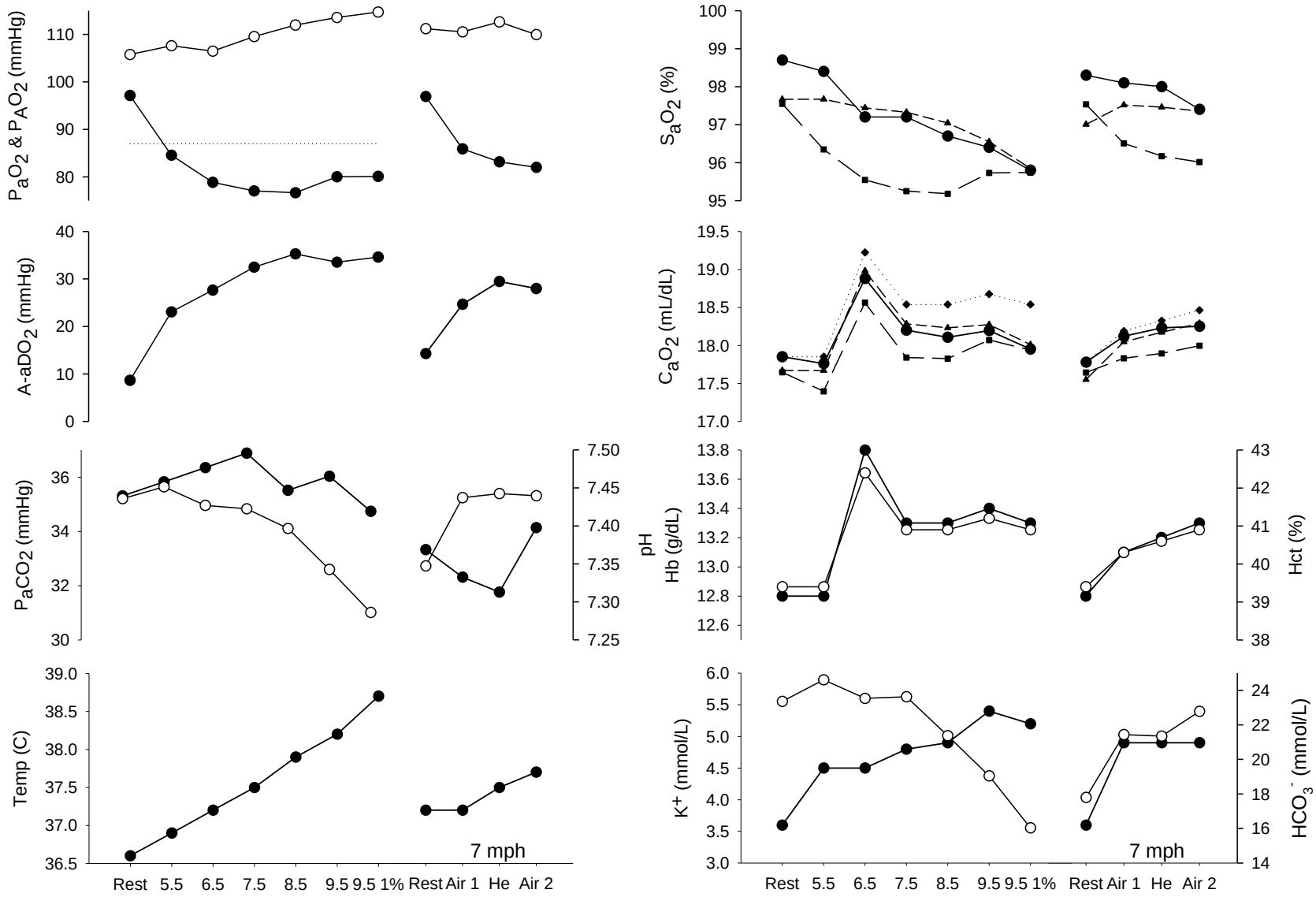


Figure 82- JS (Nov), respiratory mechanics.

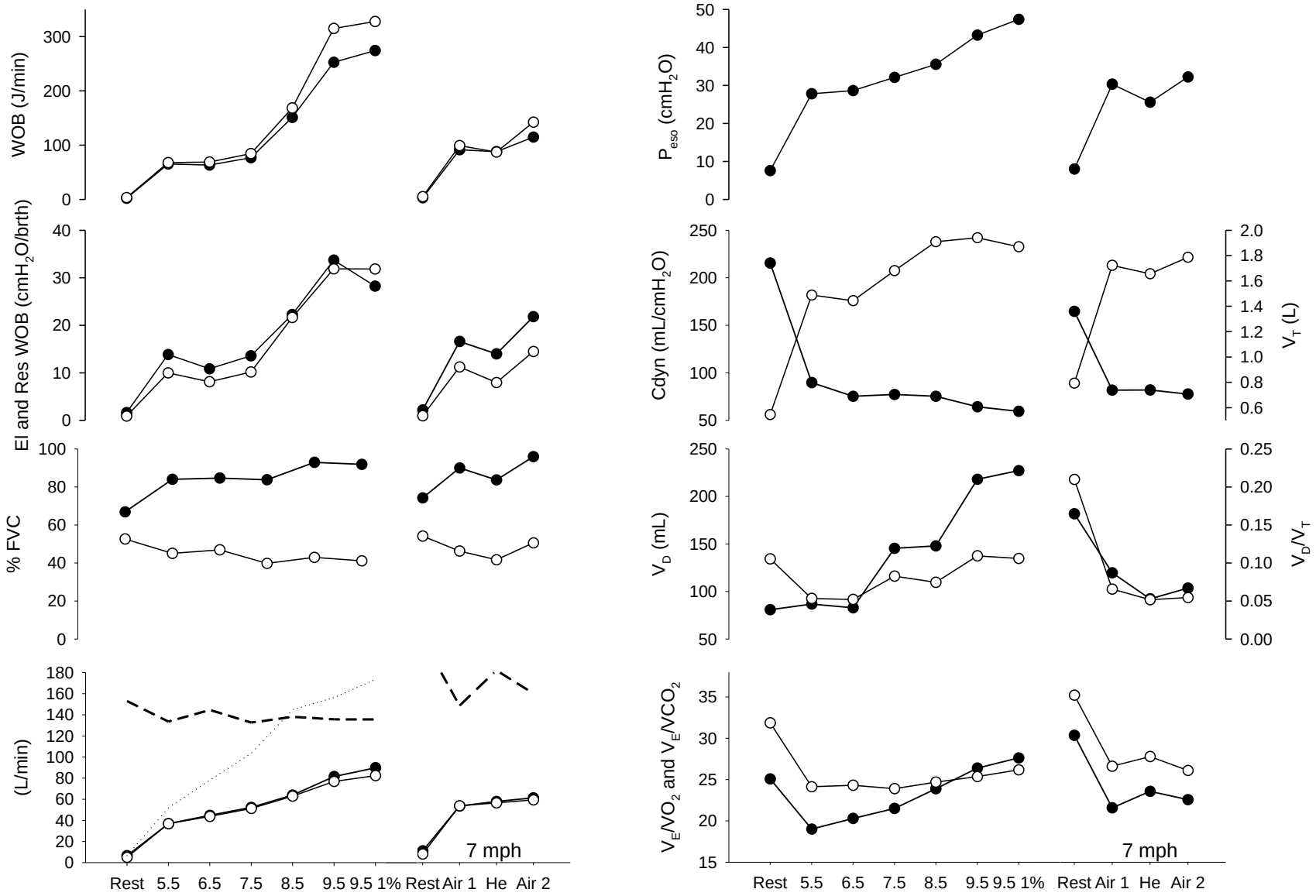


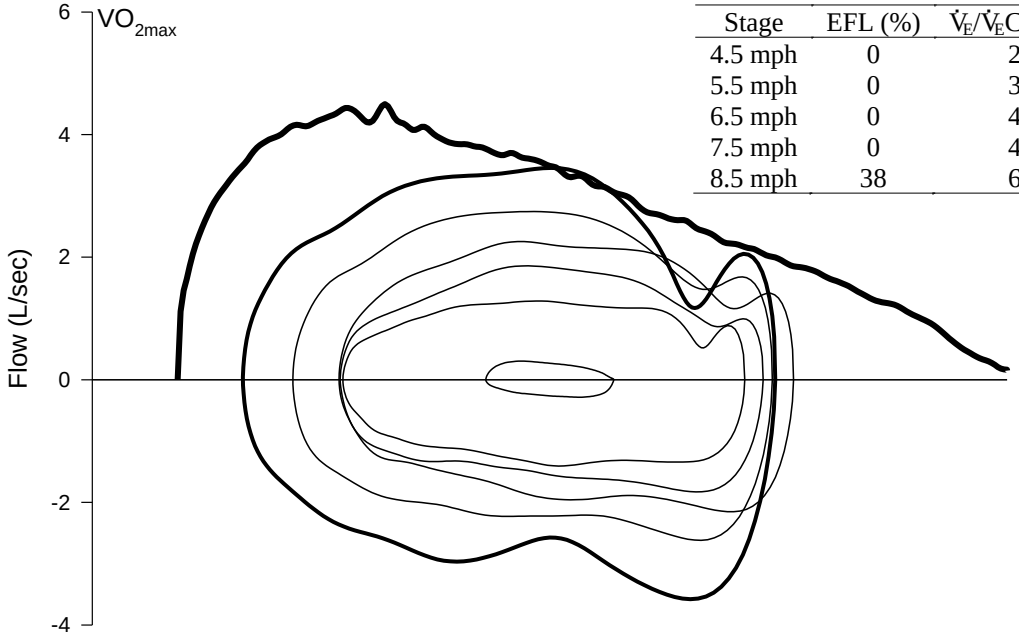
Figure 83- KM, MEFV curve and descriptors.

Subject KM- Run/Wight-train/Pilates. 1-1.5hrs/6x/wk.

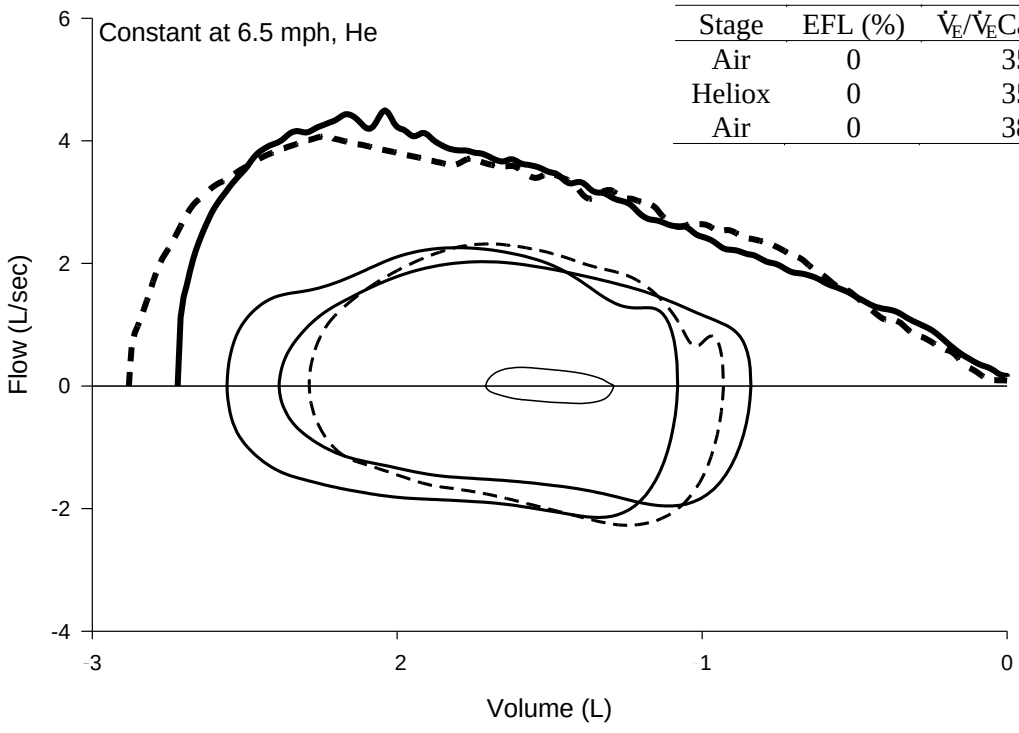
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
26	161	50.5	19.5	2.92	82	22.28	0.35	-66

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.41	48	2.86	63	1.19	1.8	40	38	28



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4.5 mph	0	26
5.5 mph	0	32
6.5 mph	0	43
7.5 mph	0	49
8.5 mph	38	62



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	35
Heliox	0	35
Air	0	38

Figure 84- KM, arterial blood gases.

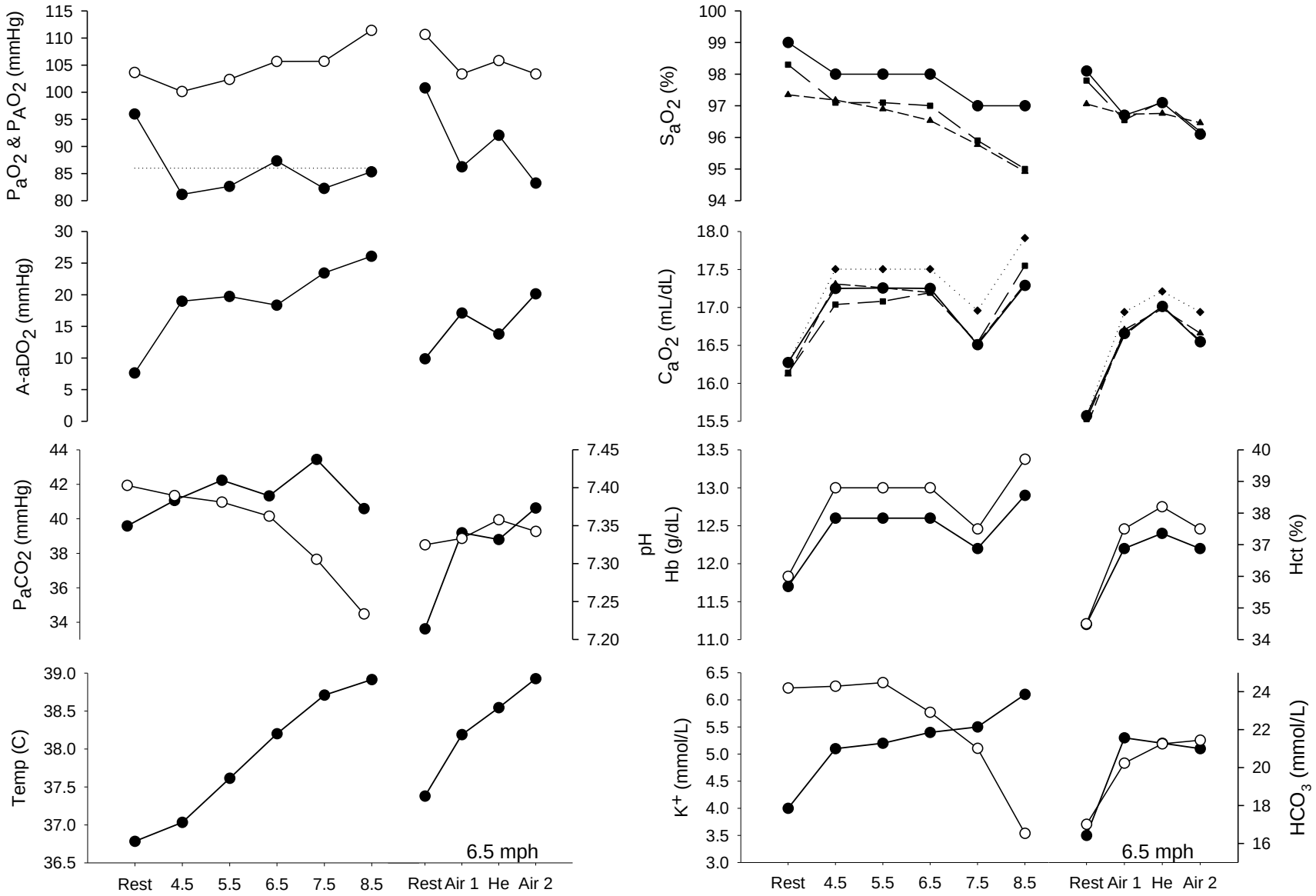


Figure 85- KM, respiratory mechanics.

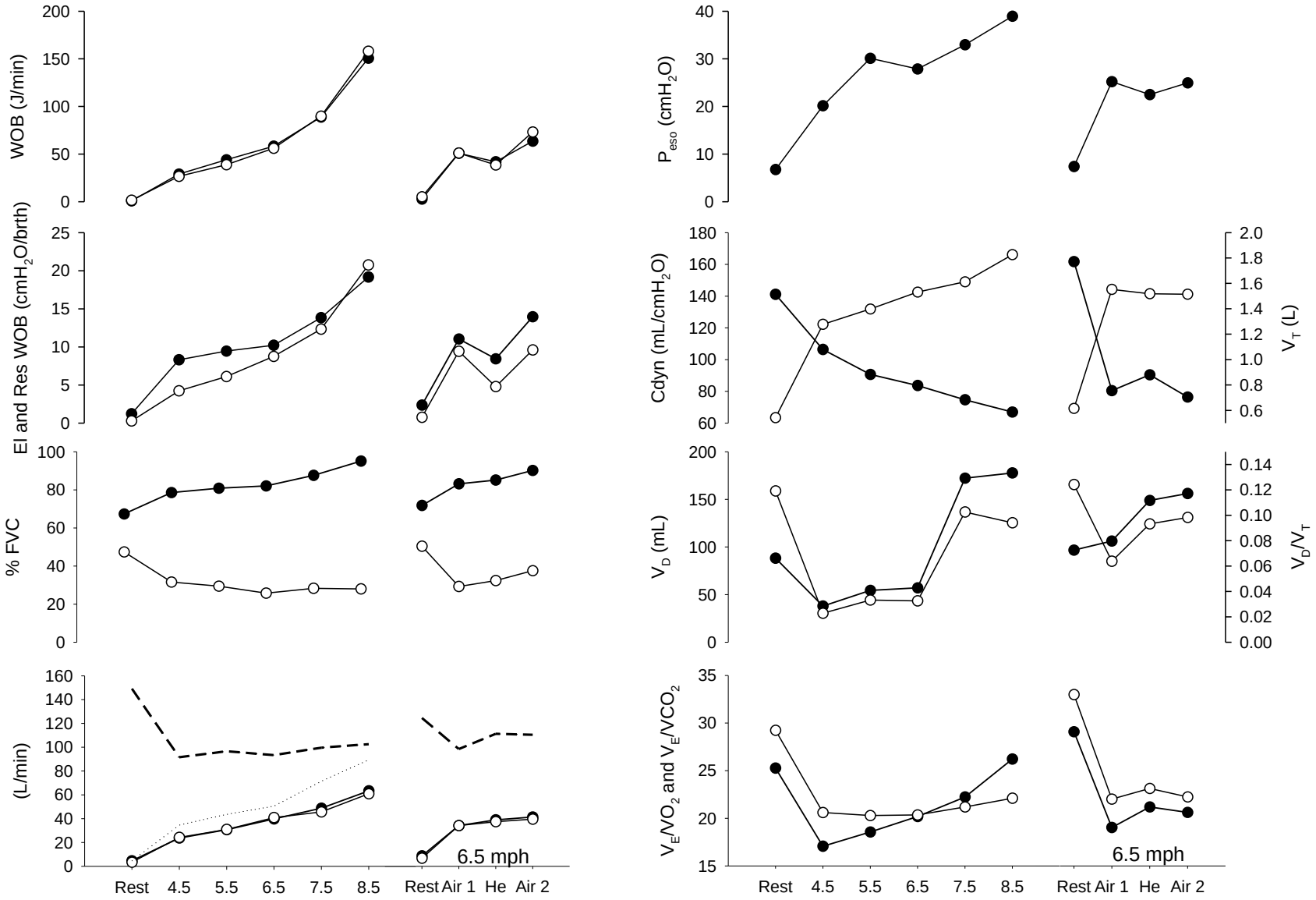


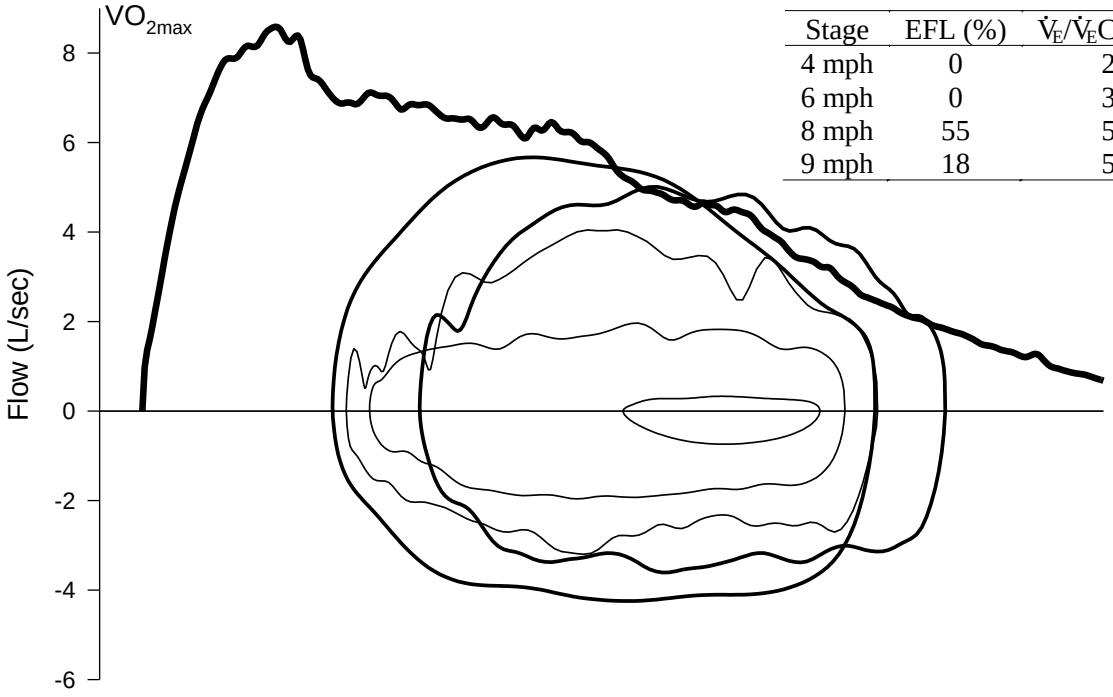
Figure 86- KS, MEFV curve and descriptors.

Subject KS- Hockey/Gymnastics. 10-15hrs/wk. 5-6x

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
21	168	67	23.7	4.26	107	31.74	0.15	-124

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.65	54	4.05	94	1.11	2.4	45	18	32



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4 mph	0	20
6 mph	0	34
8 mph	55	54
9 mph	18	54

Figure 87- KS, arterial blood gas.

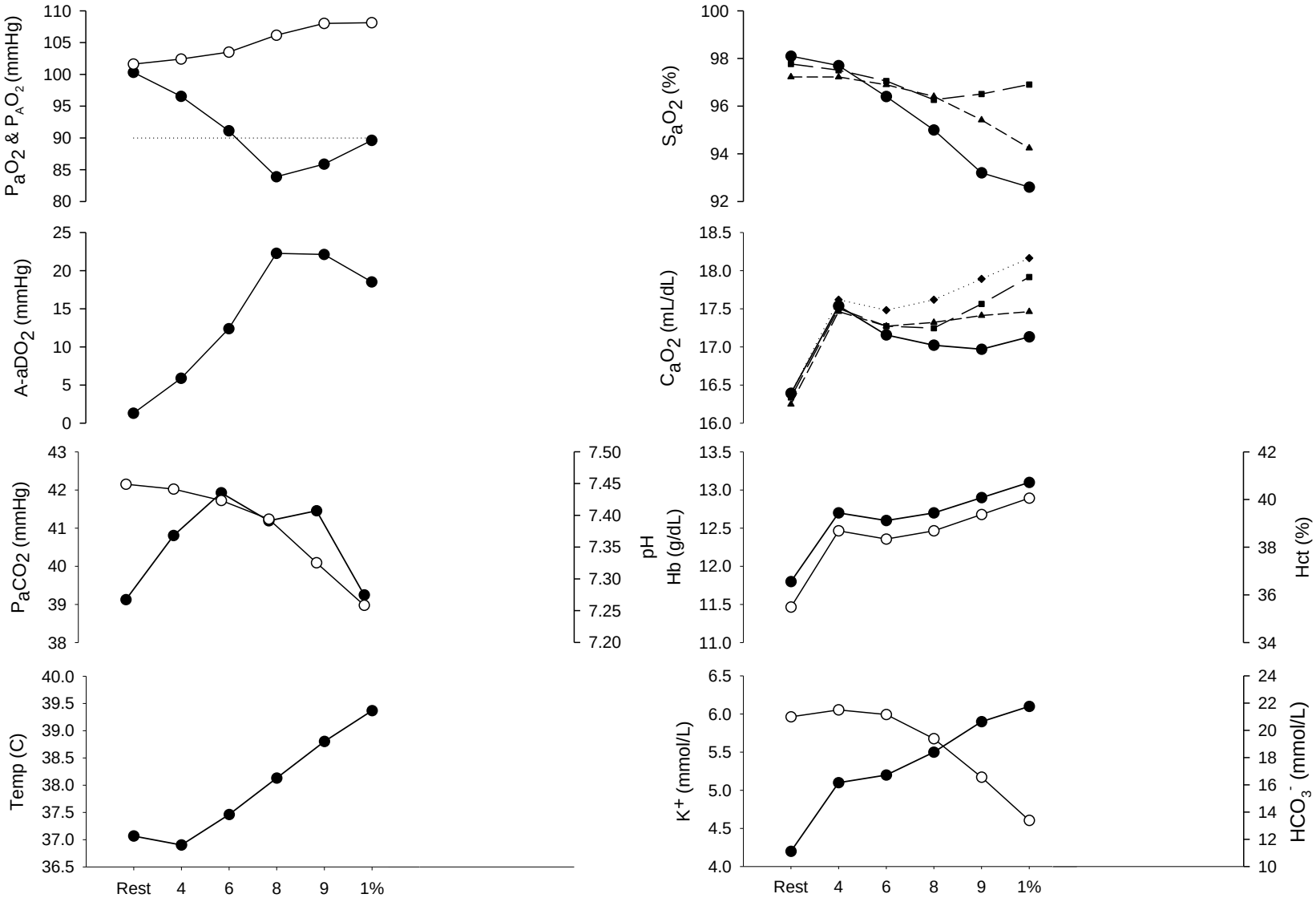


Figure 88- KS, respiratory mechanics.

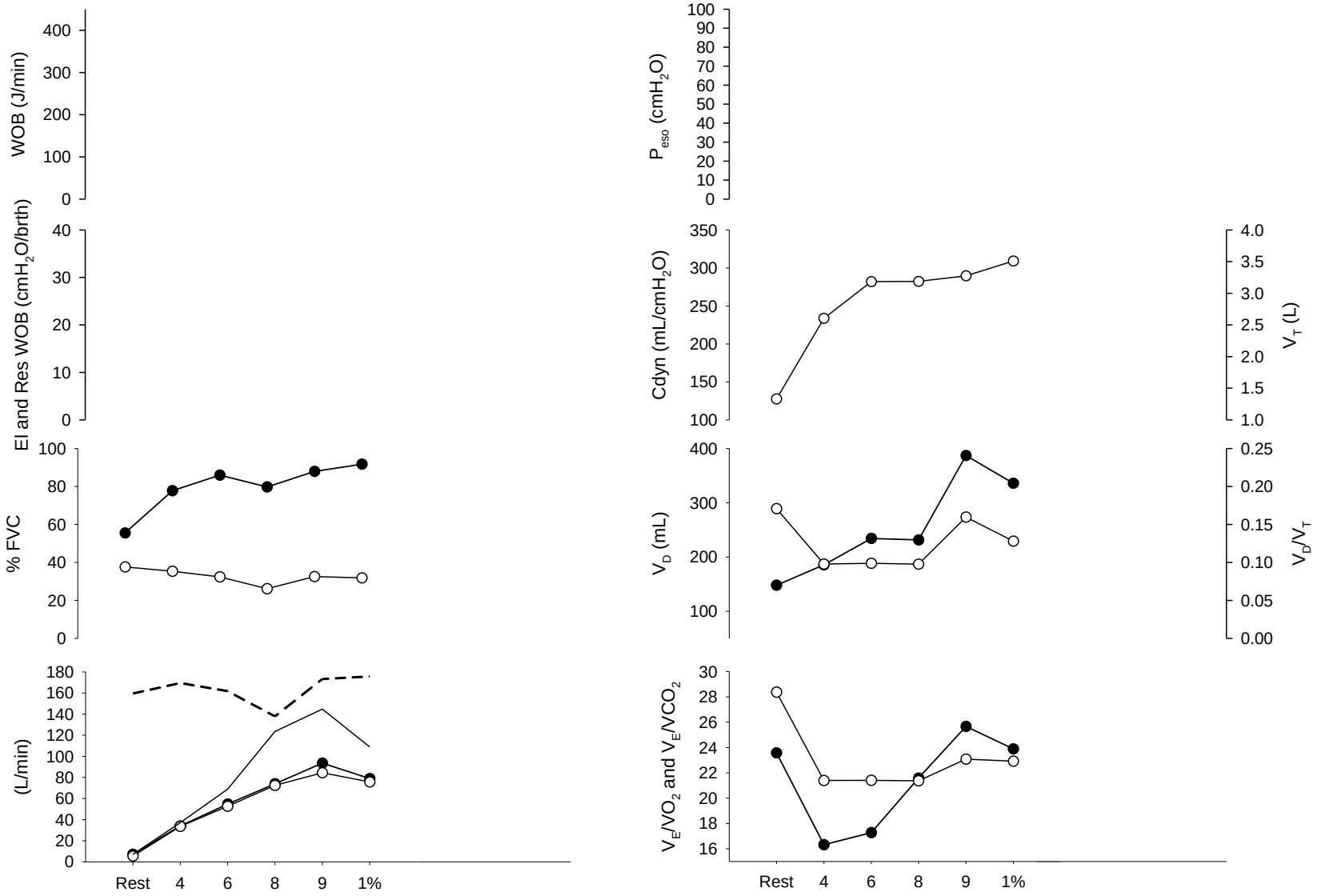


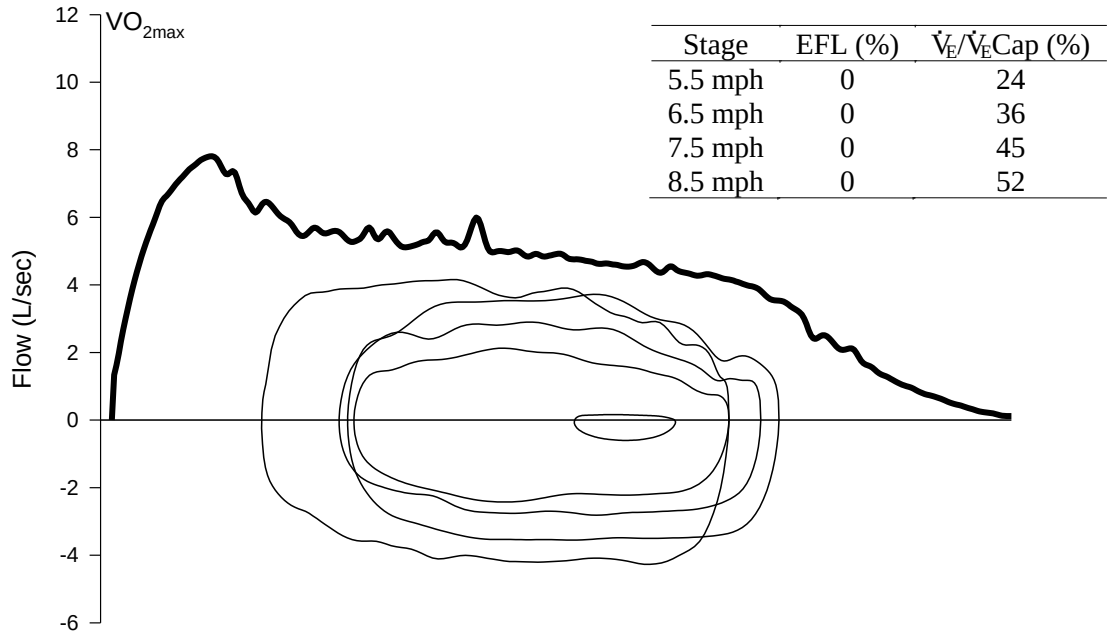
Figure 89-MB, MEFV curve and descriptors.

Subject MB- Triathalon training. 8-16hrs/wk (daily). Competes internationally (Ironman)

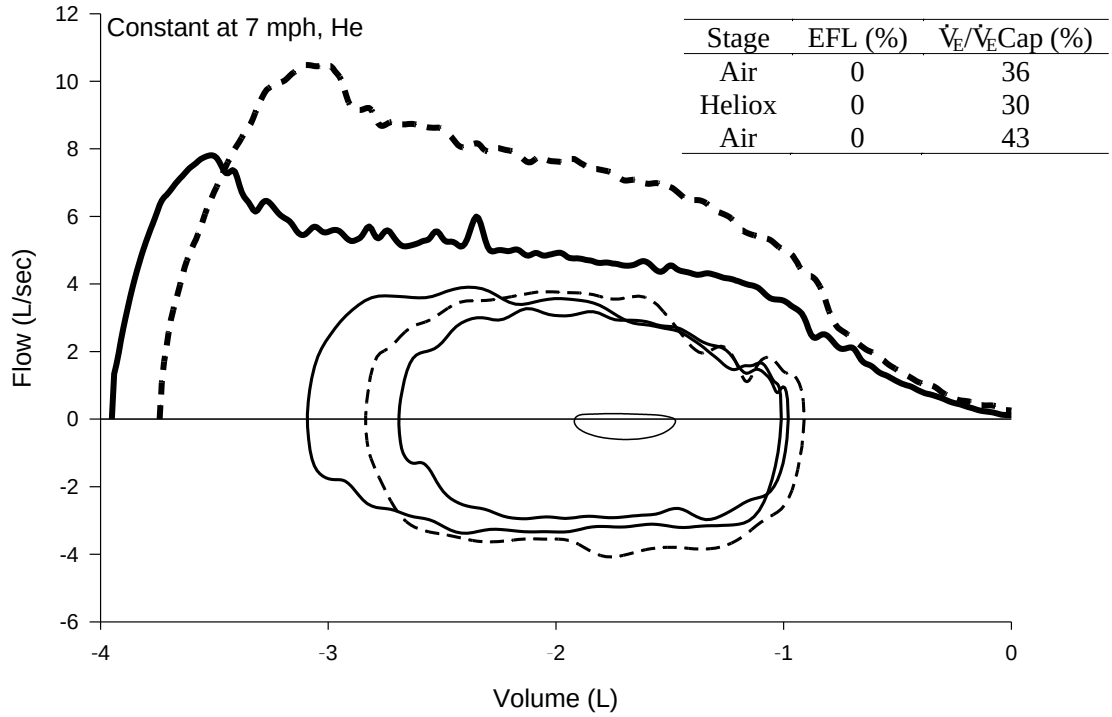
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
42	169.5	52	18.1	3.99	112	25.57		-113

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.21	62	3.3	87	1.13	2.2	46	0	31



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
5.5 mph	0	24
6.5 mph	0	36
7.5 mph	0	45
8.5 mph	0	52



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	36
Heliox	0	30
Air	0	43

Figure 90- MB, arterial blood gases.

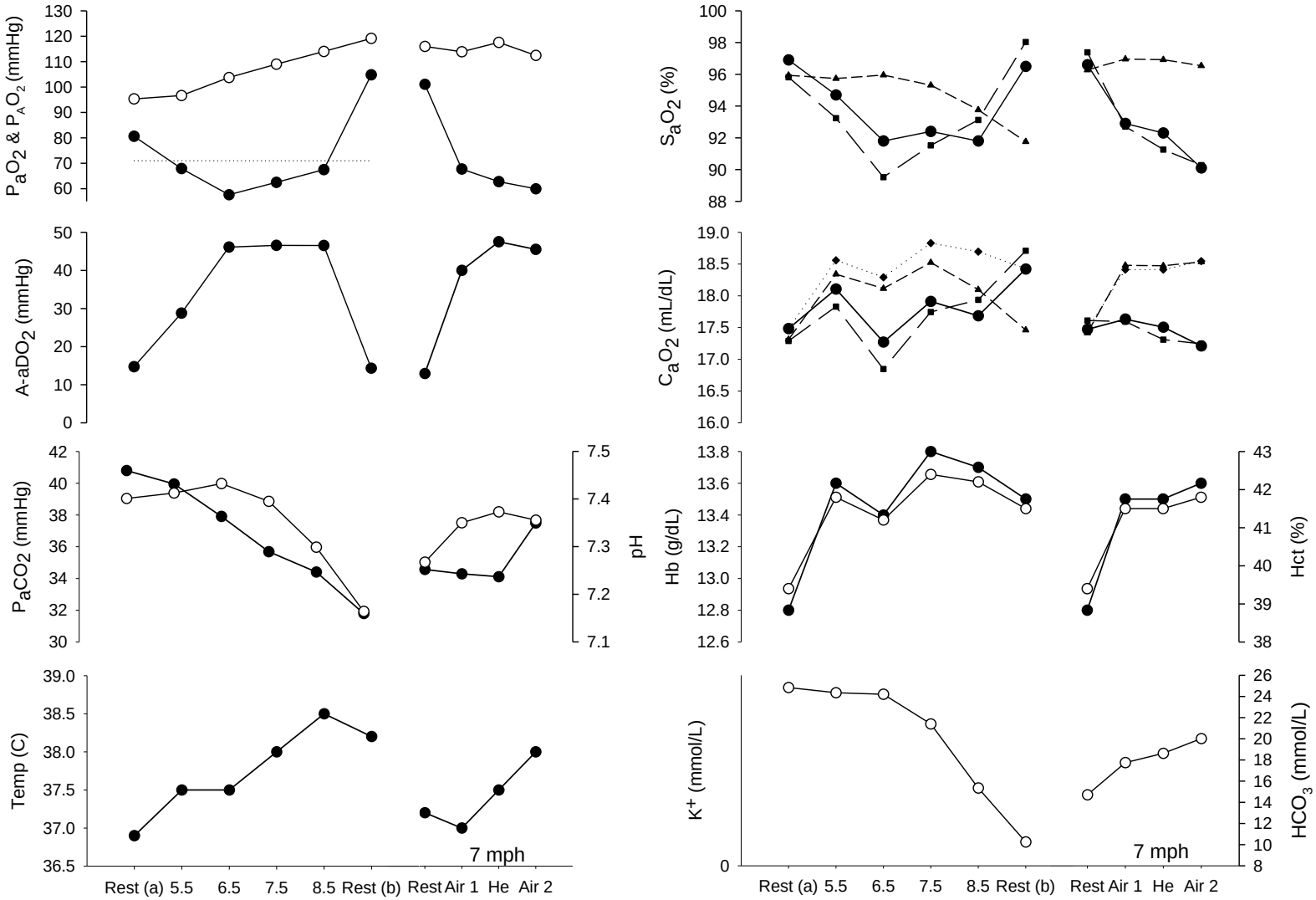


Figure 91- MB, respiratory mechanics.

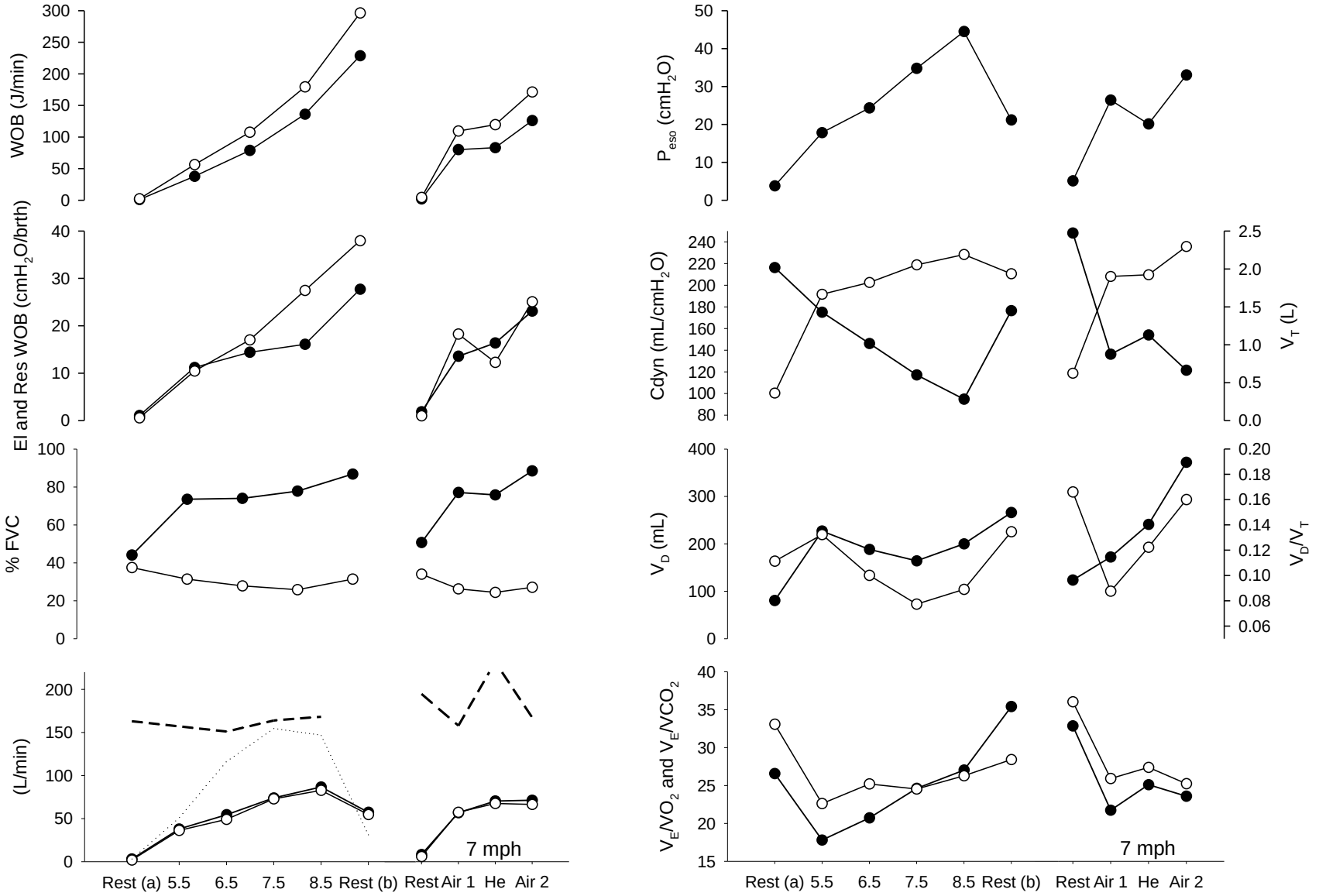


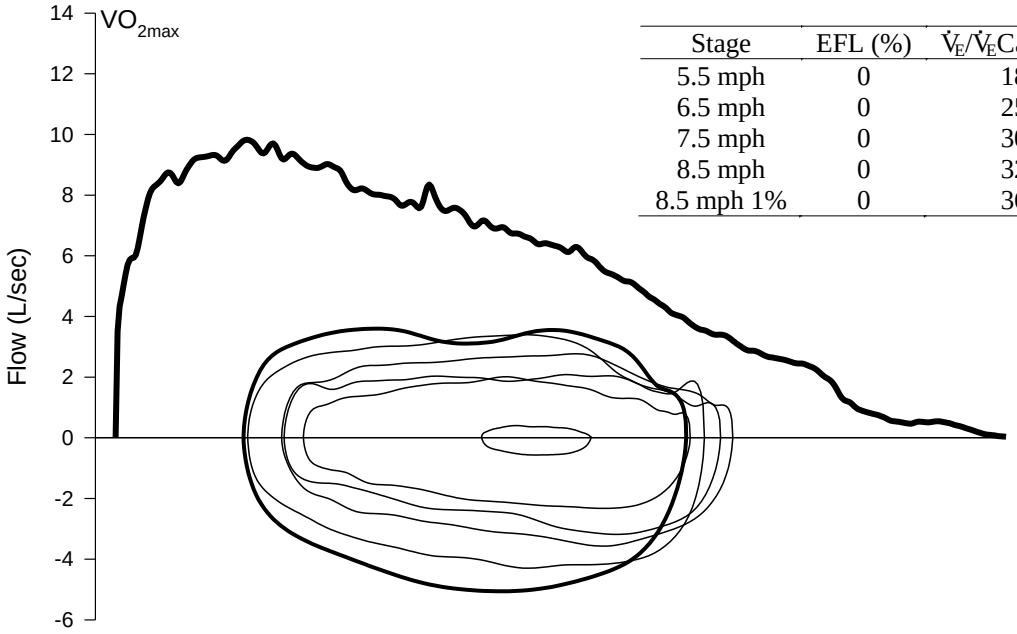
Figure 92- MF, MEFV curve and descriptors.

Subject MF- Run (Varsity). 2hr/2x/wk. Multivitamen, Iron Supplements

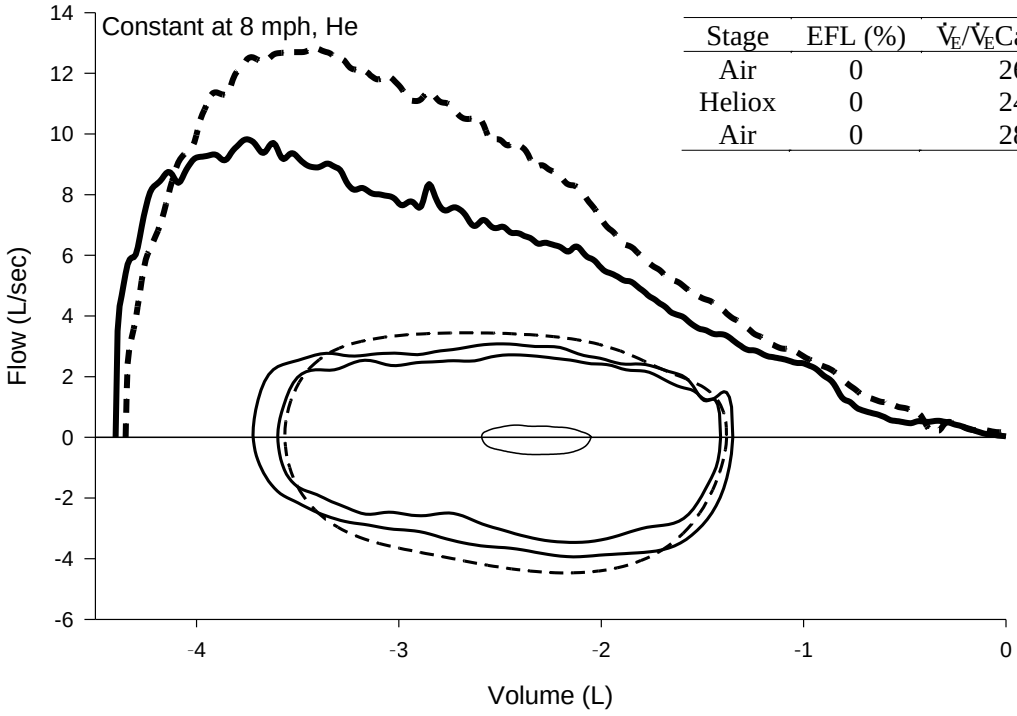
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
19	179	71.3	22.3	4.46	98	26.64	0.18	-74

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.54	50	3.91	89	1.11	2.4	44	0	36



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
5.5 mph	0	18
6.5 mph	0	25
7.5 mph	0	30
8.5 mph	0	32
8.5 mph 1%	0	36



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	26
Heliox	0	24
Air	0	28

Figure 93- MF, arterial blood gases.

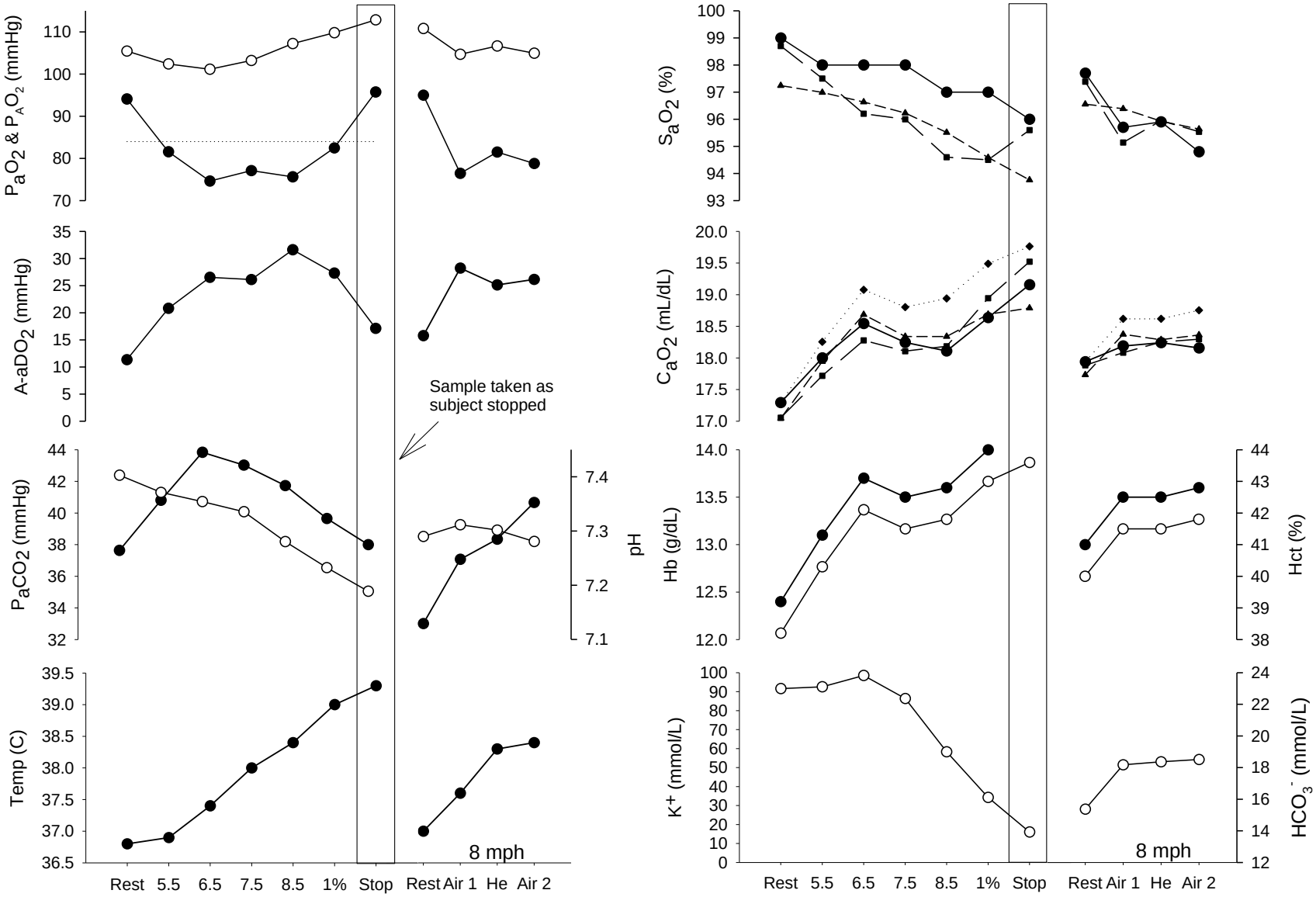


Figure 94- MF, respiratory mechanics.

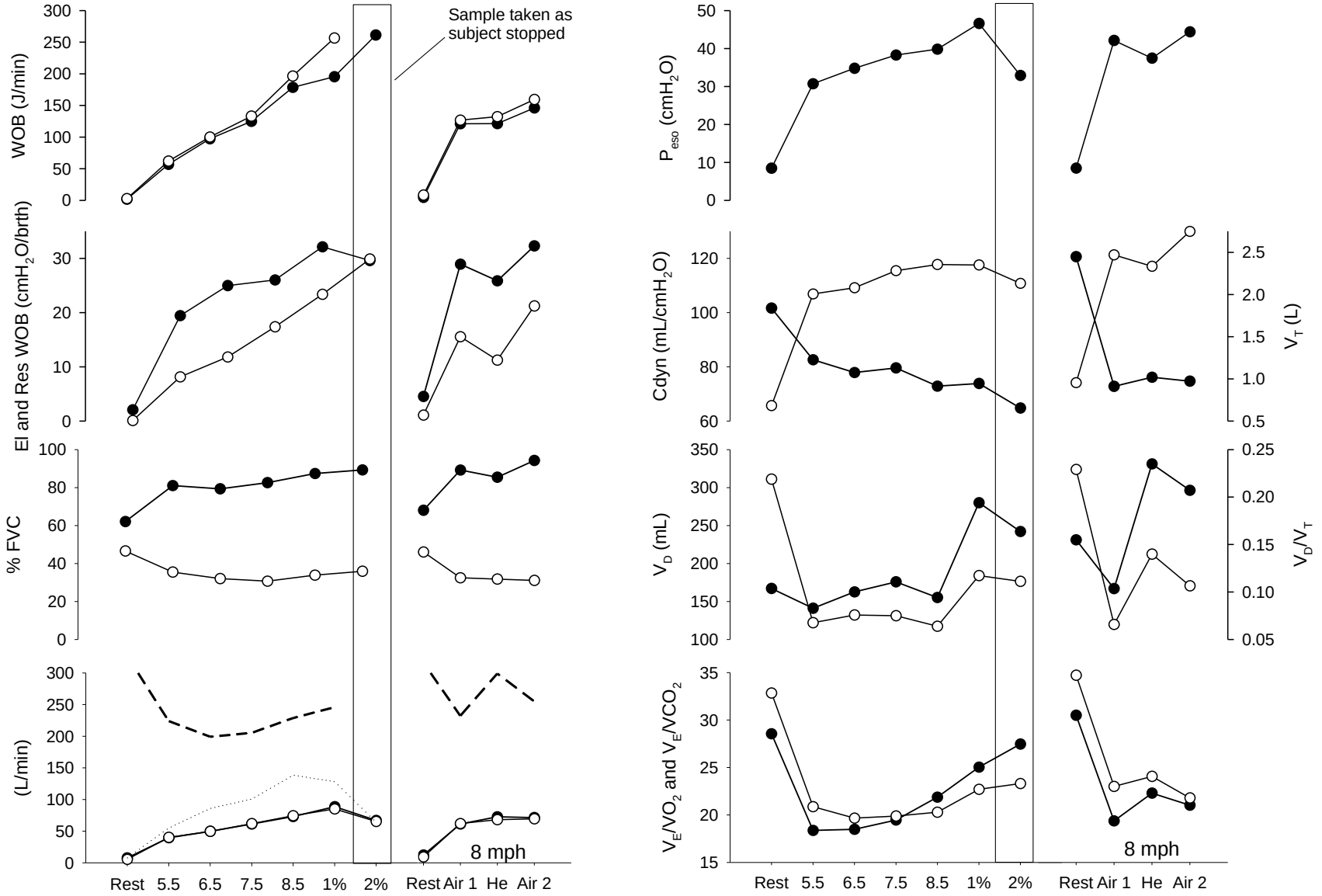


Figure 95- MG, MEFV curve and descriptors.

Subject MG- Run (Rec) ~30min. 2-3x/wk

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
28	161	48	18.5	3.67	105	20.61	0.27	-86

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
1.87	39	1.90	58	1.02	1.68	41	0	36

Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4 mph	0	11
5 mph	0	23
6 mph	0	33

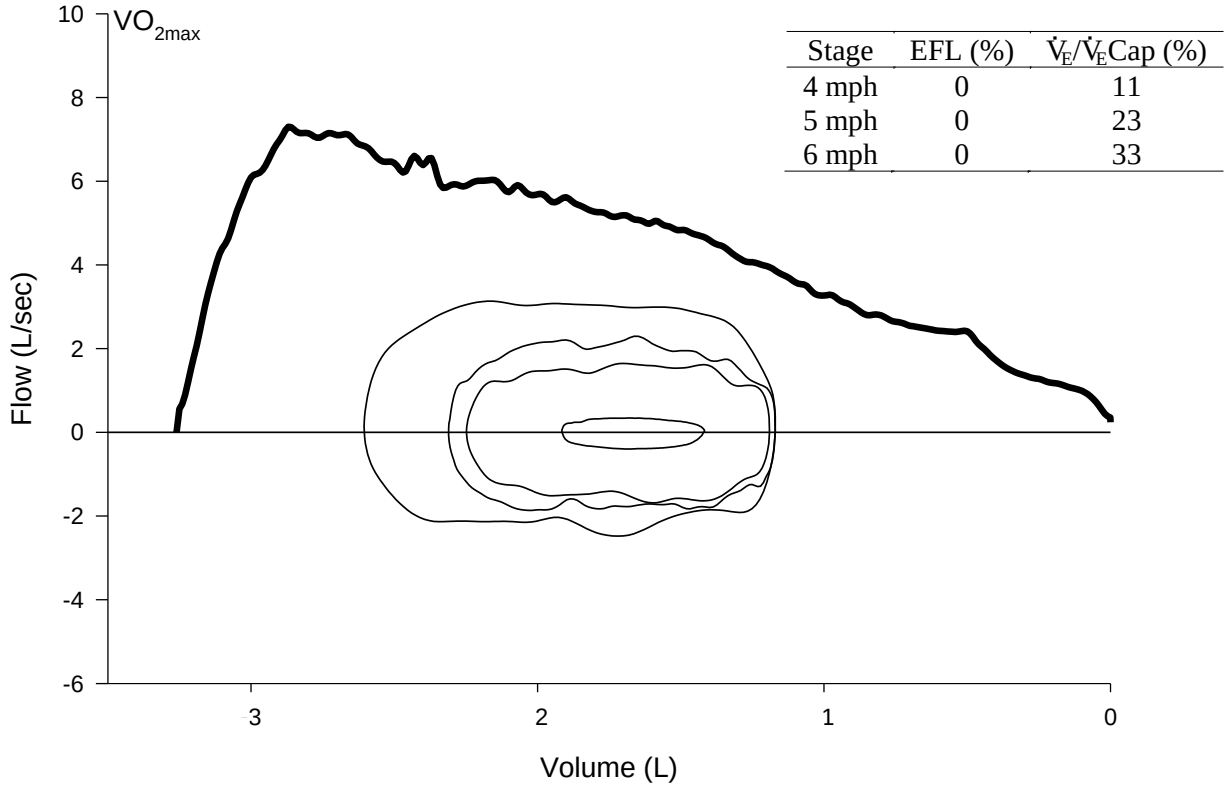


Figure 96- MG, arterial blood gases.

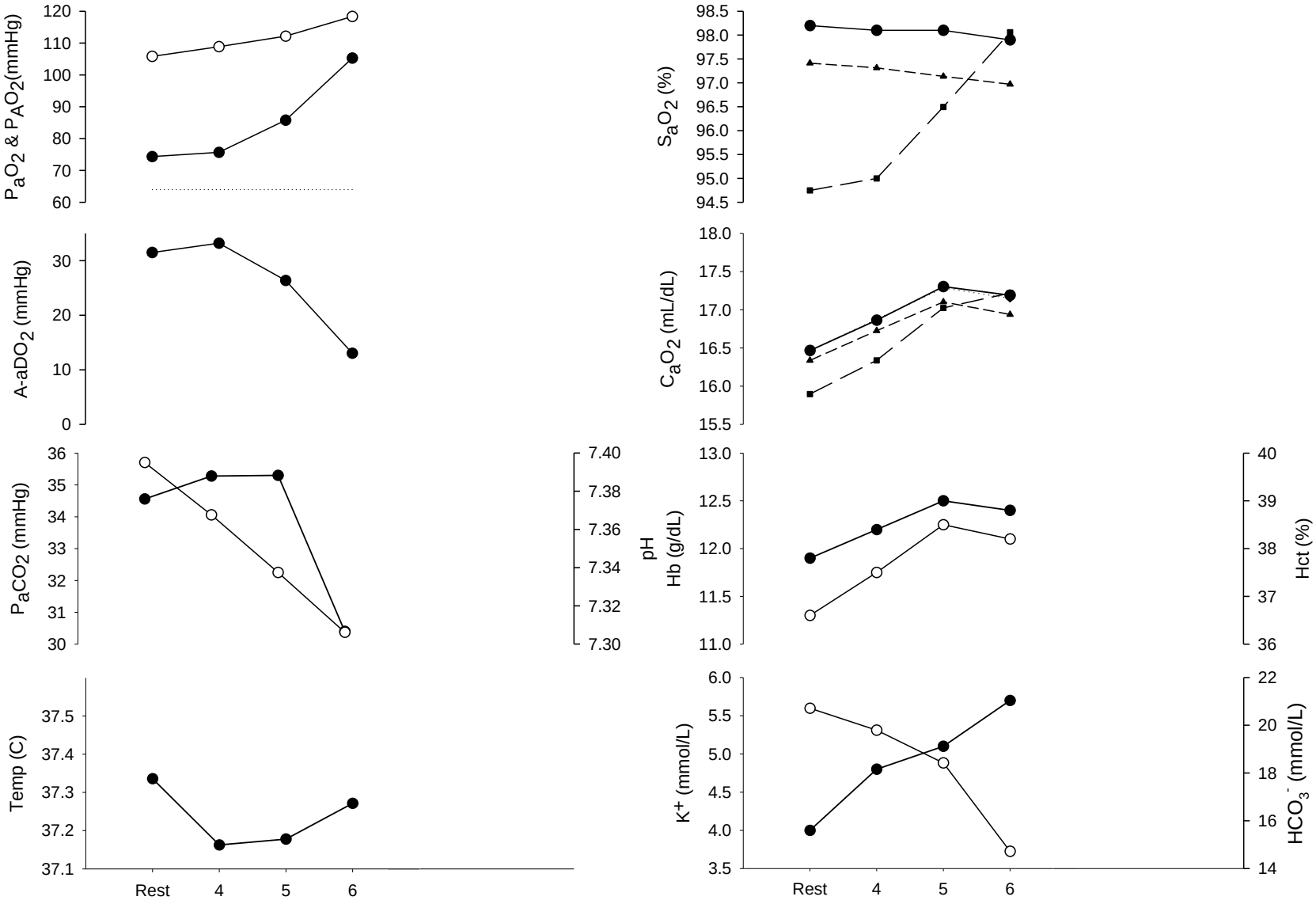


Figure 97- MG, respiratory mechanics.

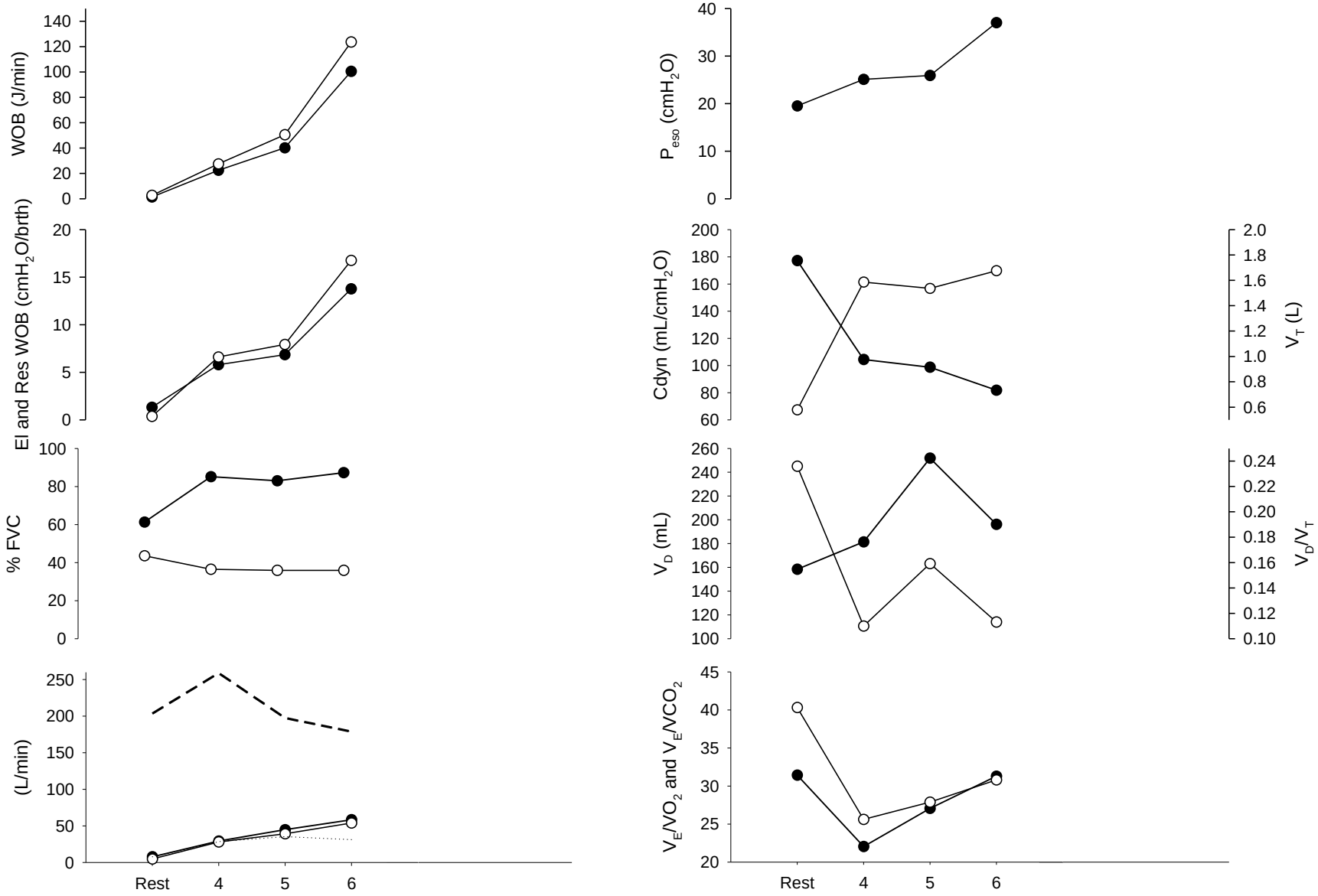


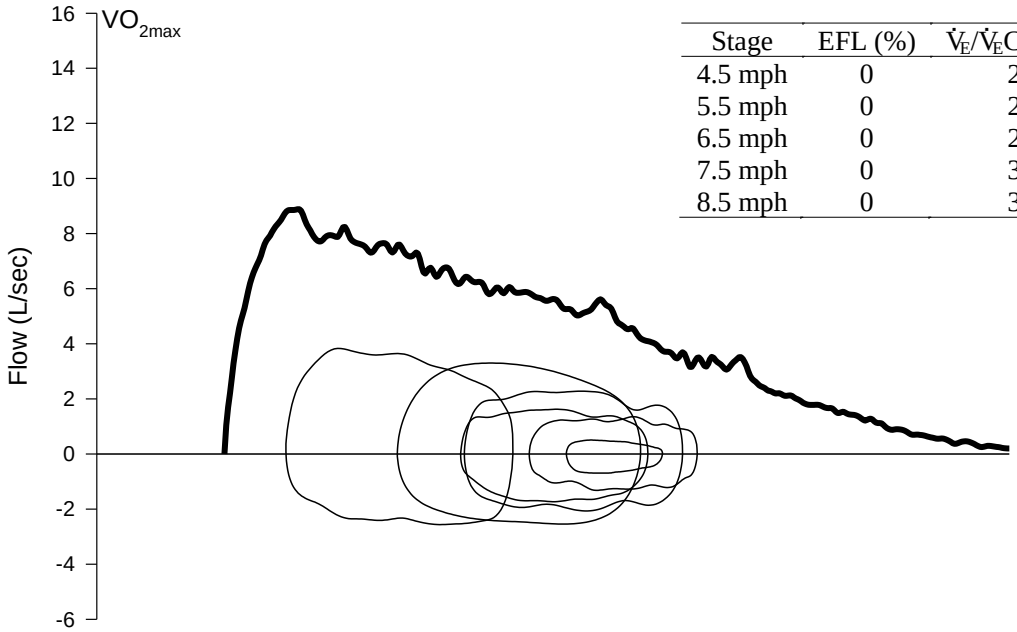
Figure 98- MM, MEFV curve and descriptors.

Subject MM- Road/Mt Bike, Yoga. 1-6hr/daily (10-12hrs/wk)

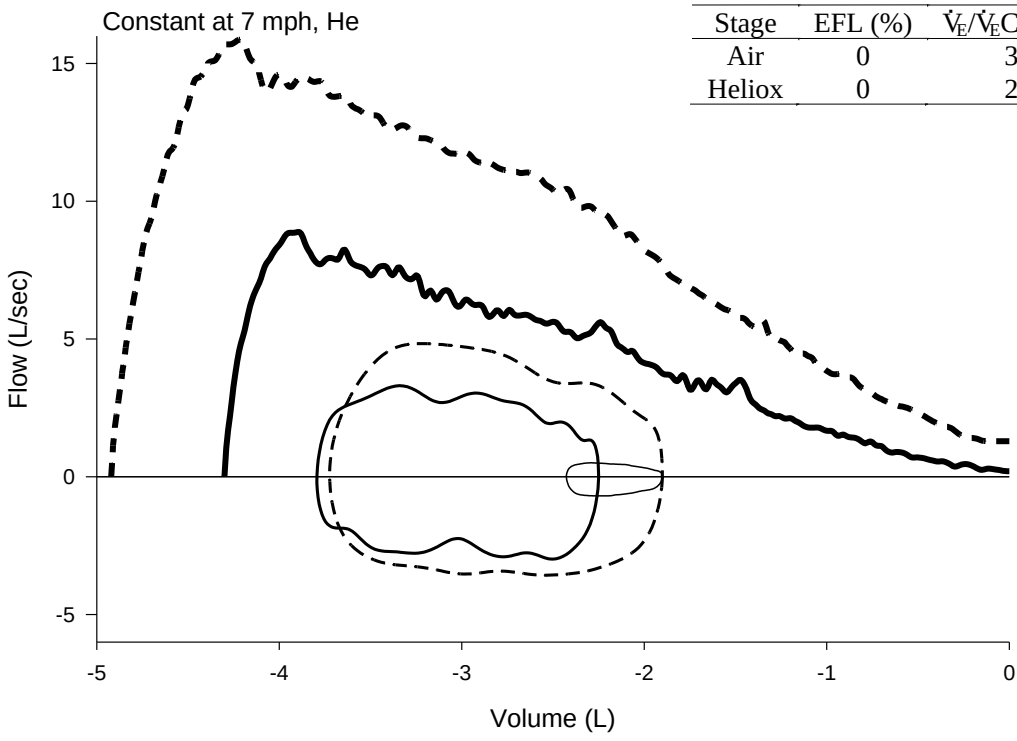
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
31	173	72	24.1	4.74	120	32.11	0.22	-95

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.23	45	3.52	73	1.09	1.4	61	0	63



Stage	EFL (%)	$\dot{V}_E/\dot{V}_ECap$ (%)
4.5 mph	0	20
5.5 mph	0	21
6.5 mph	0	29
7.5 mph	0	31
8.5 mph	0	32



Stage	EFL (%)	$\dot{V}_E/\dot{V}_ECap$ (%)
Air	0	31
Heliox	0	24

Figure 99- MM, arterial blood gases.

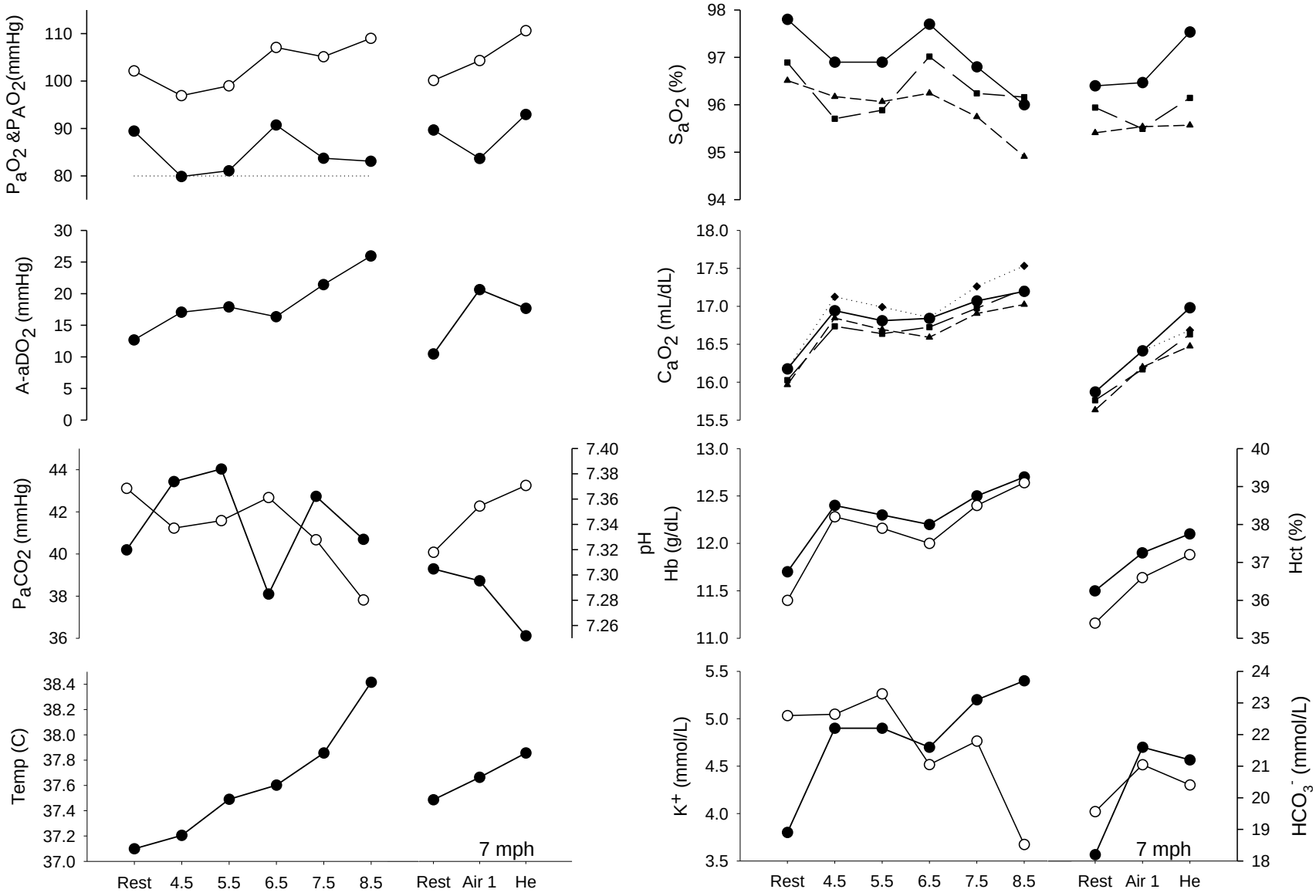


Figure 100- MM, respiratory mechanics.

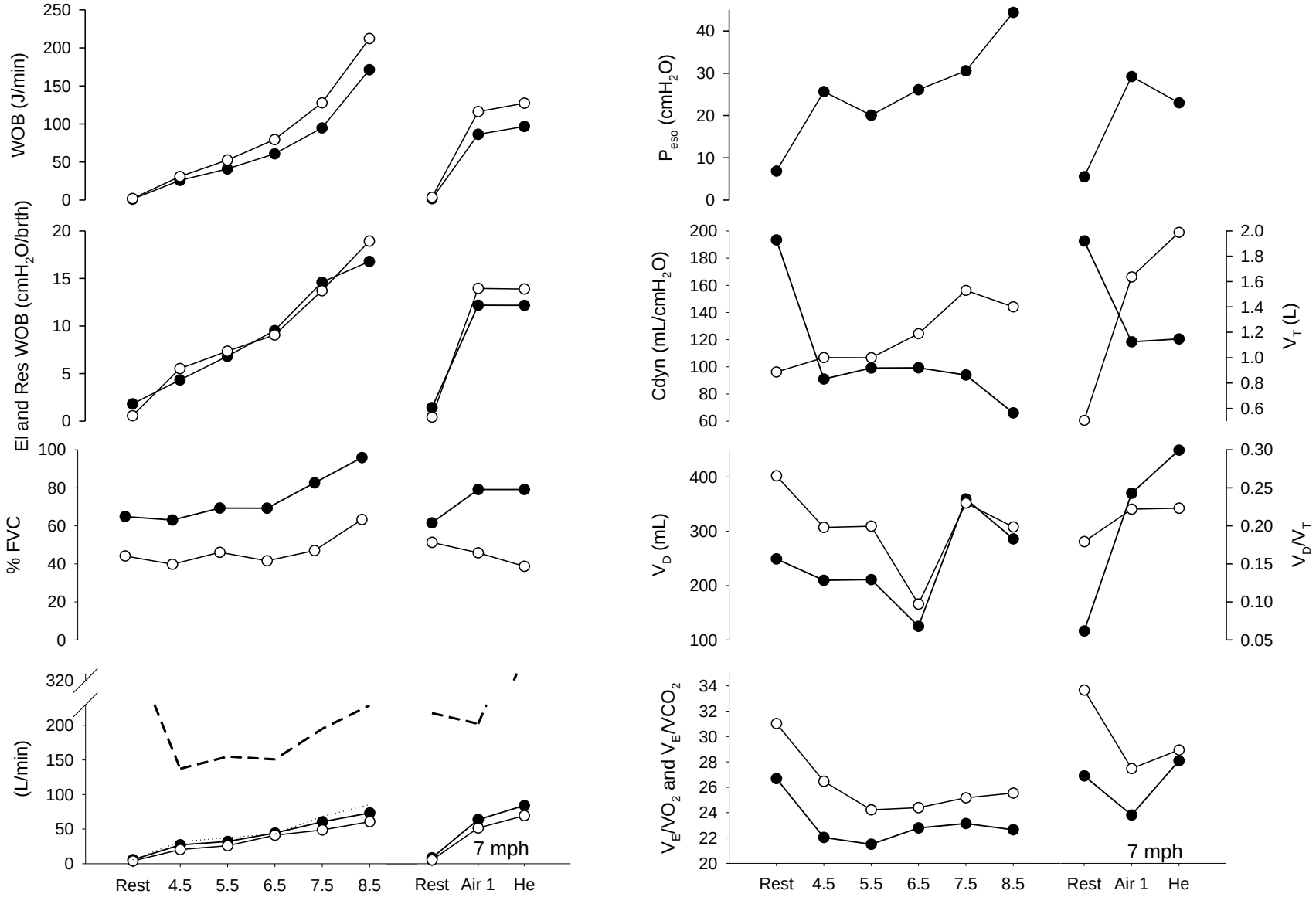


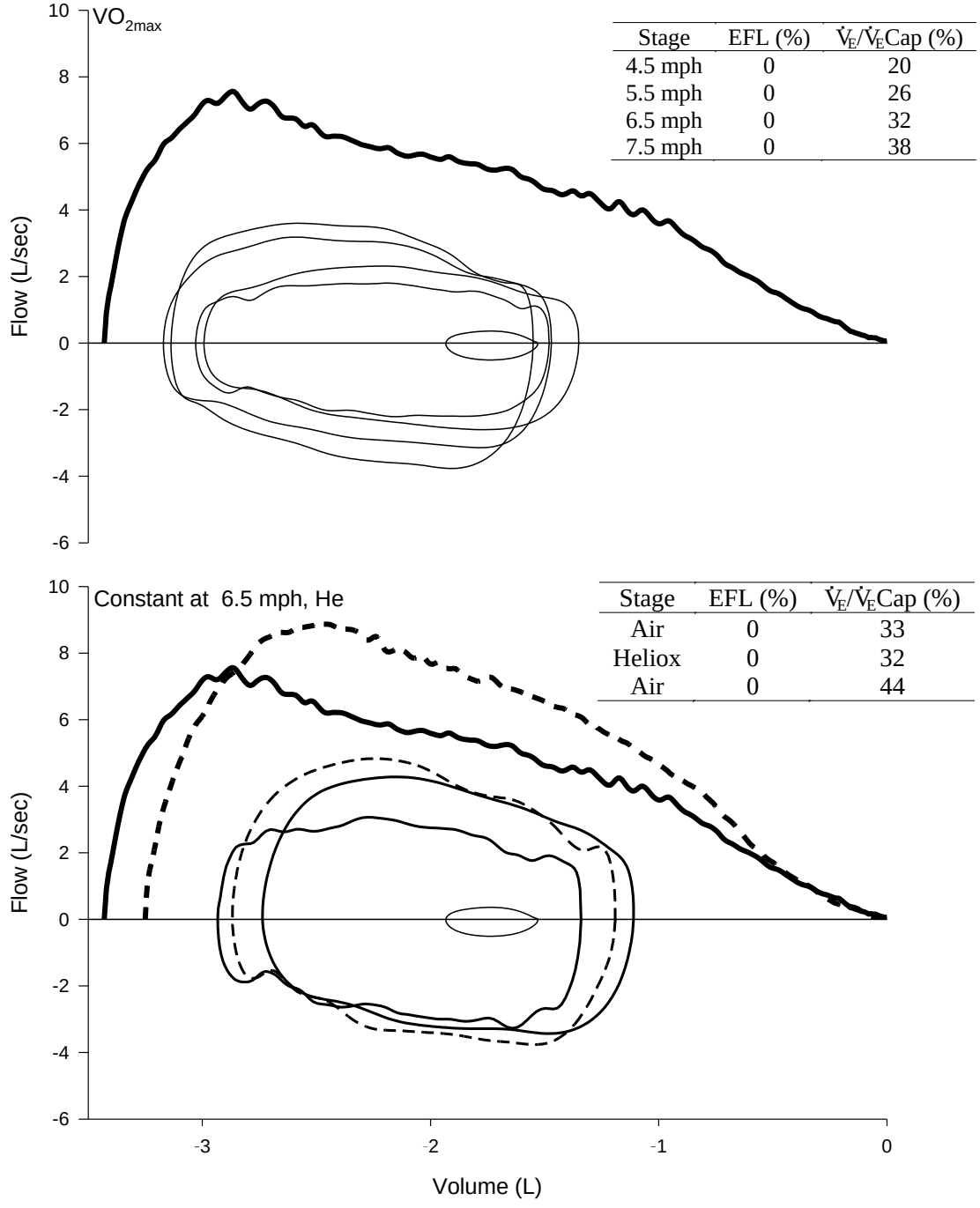
Figure 101- NN, MEFV curve and descriptors.

Subject NN- Big Run/Bike (Rec). 45mi/3-4x/wk.

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
32	165	65	23.9	3.54	99	37.33		-76

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.93	45	3.38	75	1.15	1.6	56	0	45



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4.5 mph	0	20
5.5 mph	0	26
6.5 mph	0	32
7.5 mph	0	38

Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	33
Heliox	0	32
Air	0	44

Figure 102- NN, arterial blood gases.

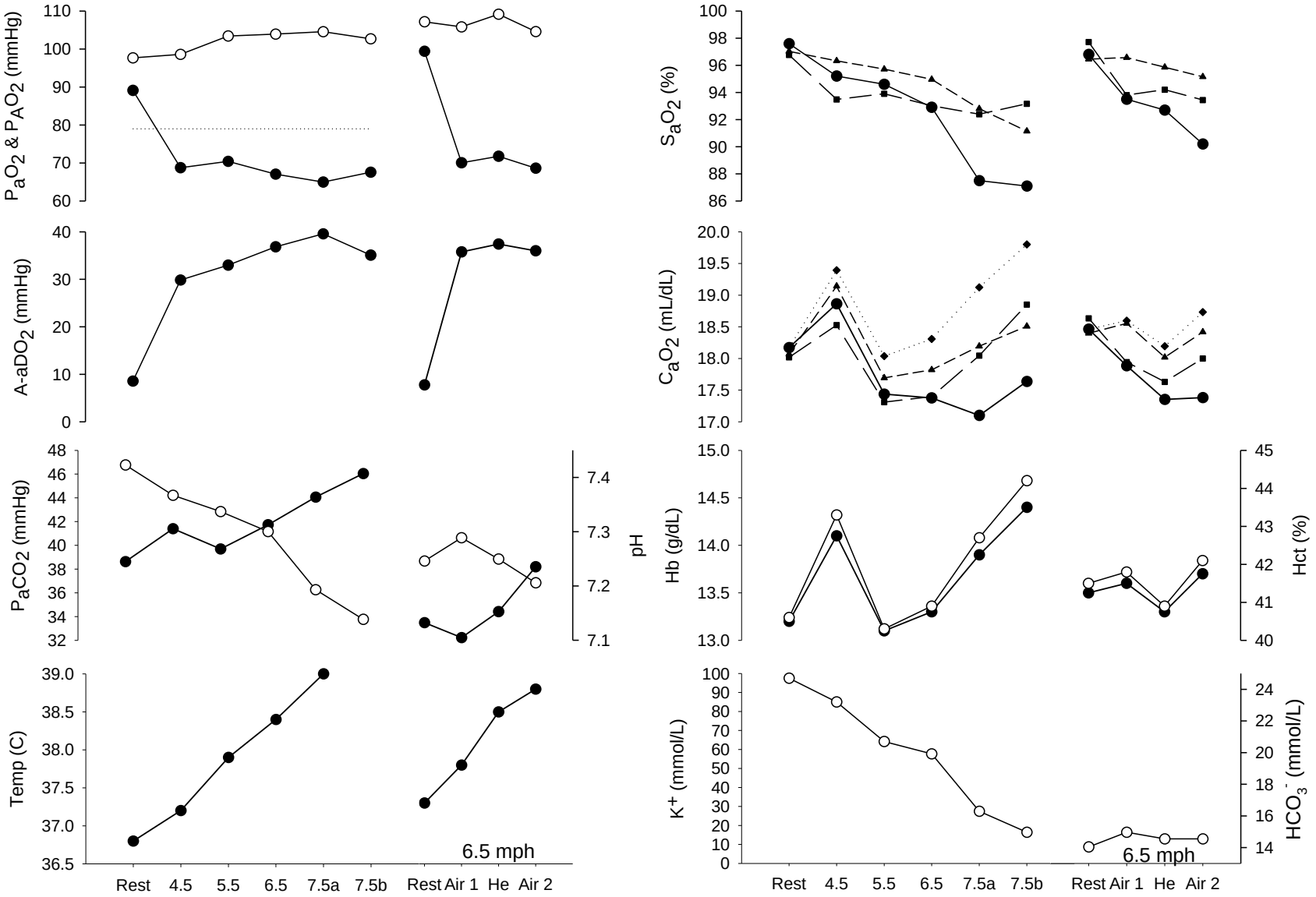


Figure 103- NN, respiratory mechanics.

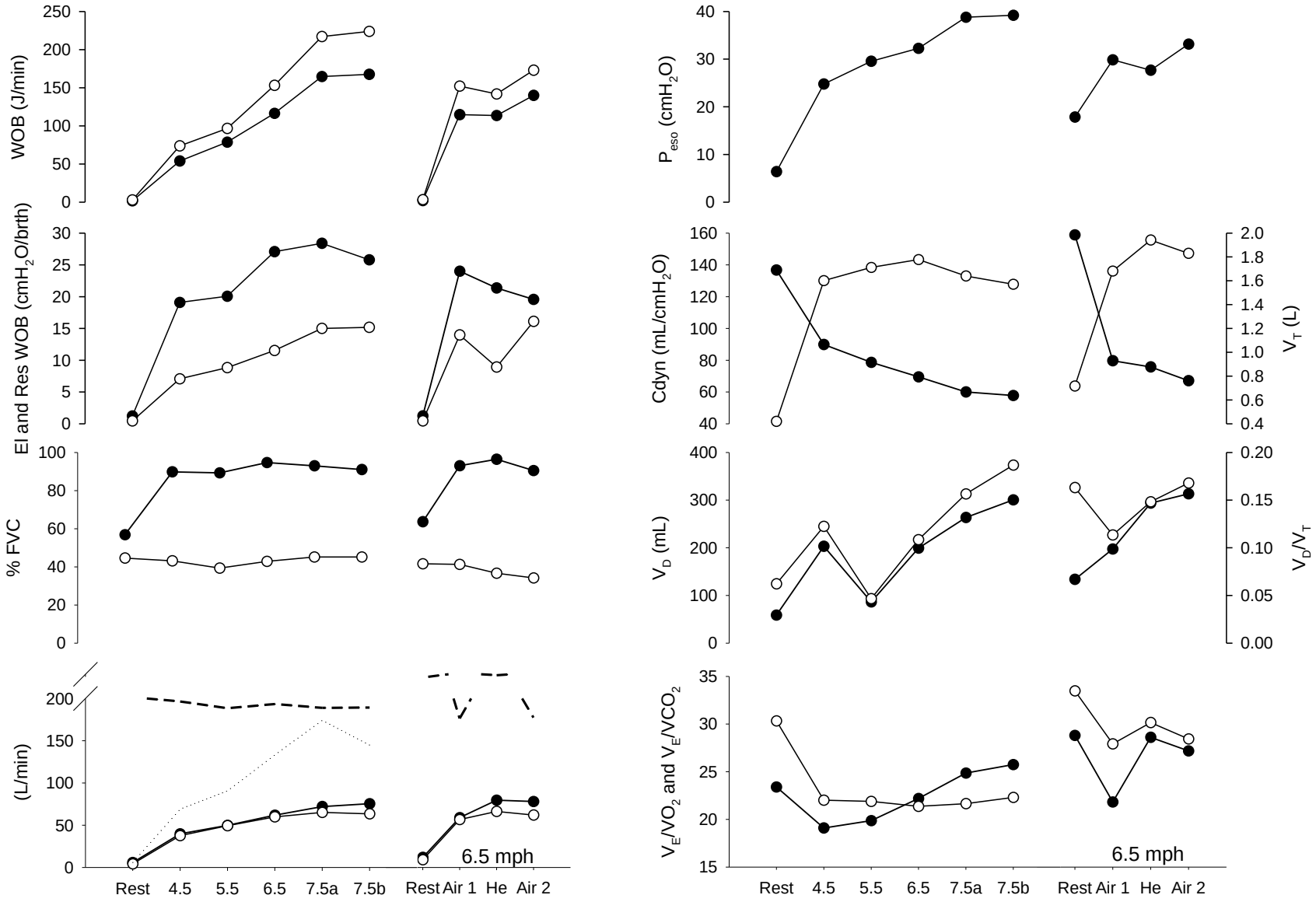


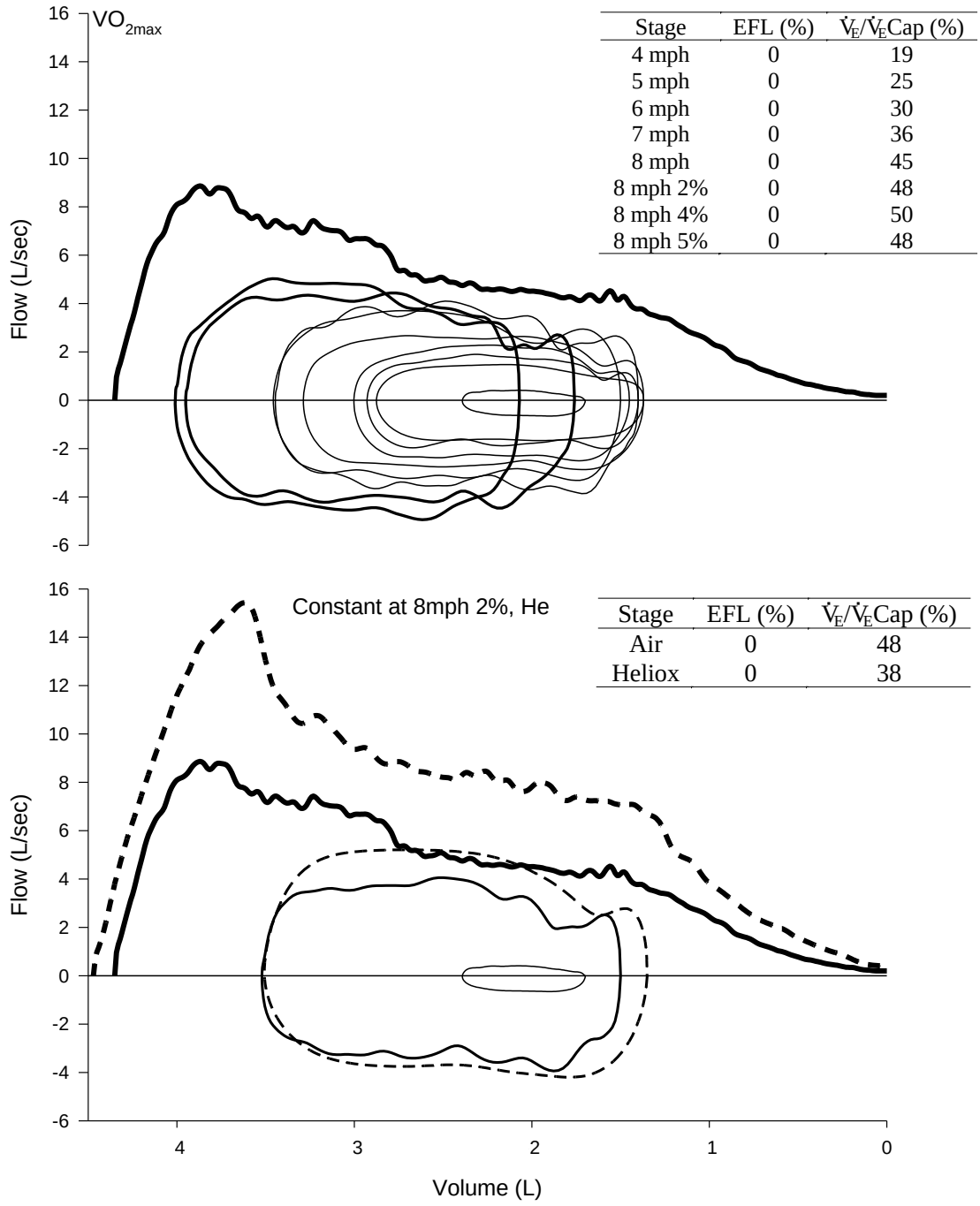
Figure 104- NW, MEFV curve and descriptors.

Subject NW- Biking/Cyling/Climbing. 1hr/3-5x week

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
31	168	60	21.3	4.41	118	26.52	0.19	-118

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.43	57	3.59	99	1.05	2.1	55	0	48



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4 mph	0	19
5 mph	0	25
6 mph	0	30
7 mph	0	36
8 mph	0	45
8 mph 2%	0	48
8 mph 4%	0	50
8 mph 5%	0	48

Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	48
Heliox	0	38

Figure 105- NW, arterial blood gases.

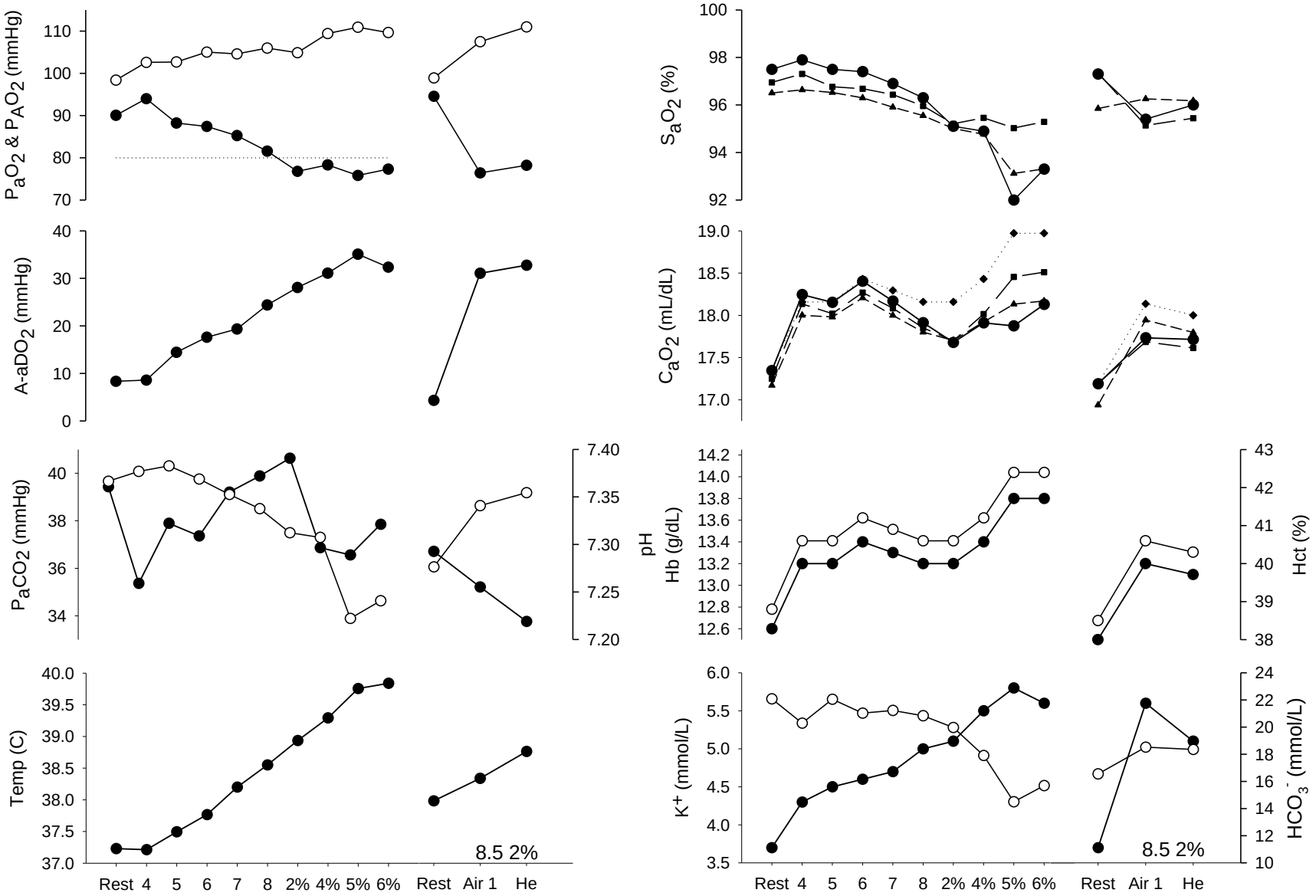


Figure 106- NW, respiratory mechanics.

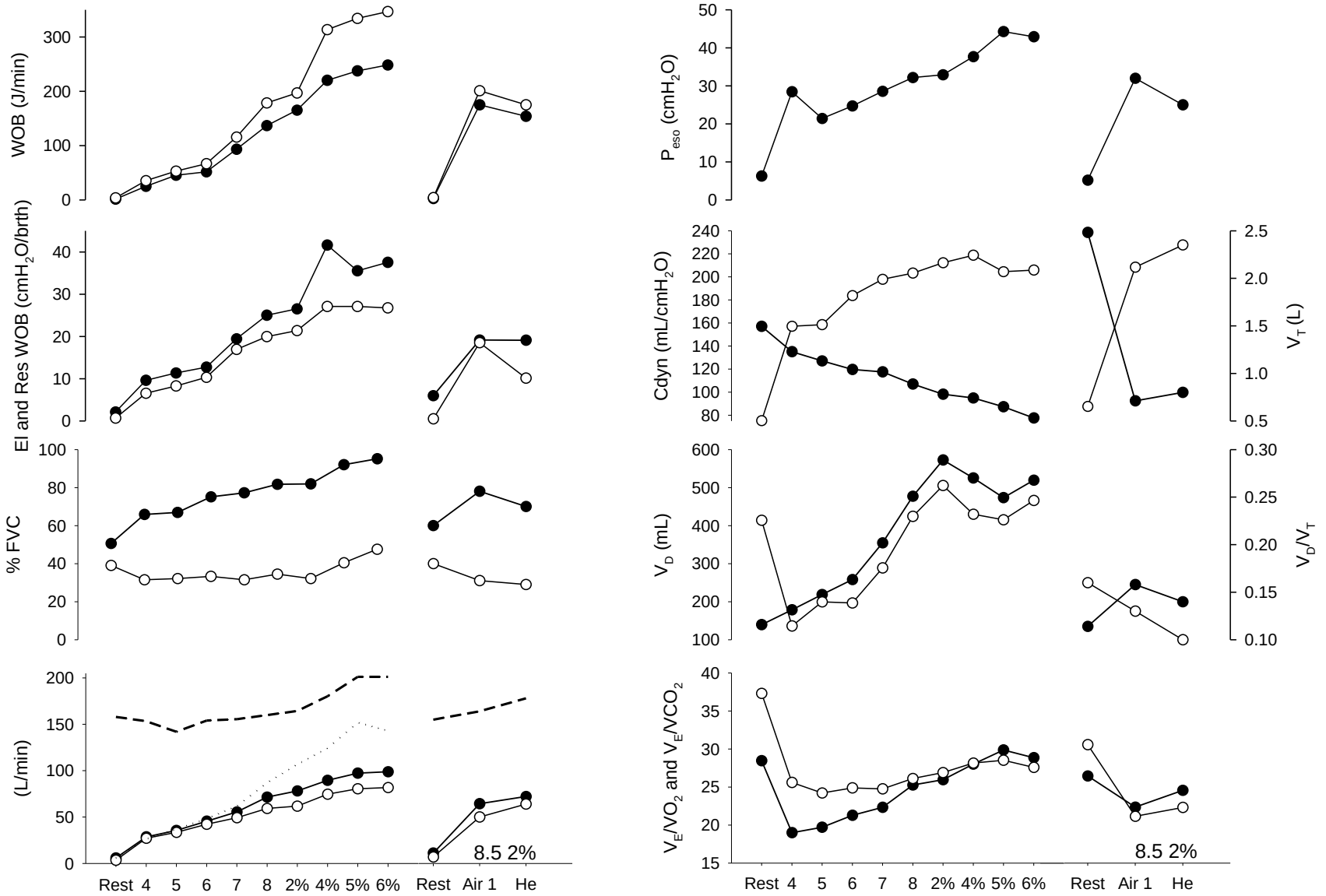


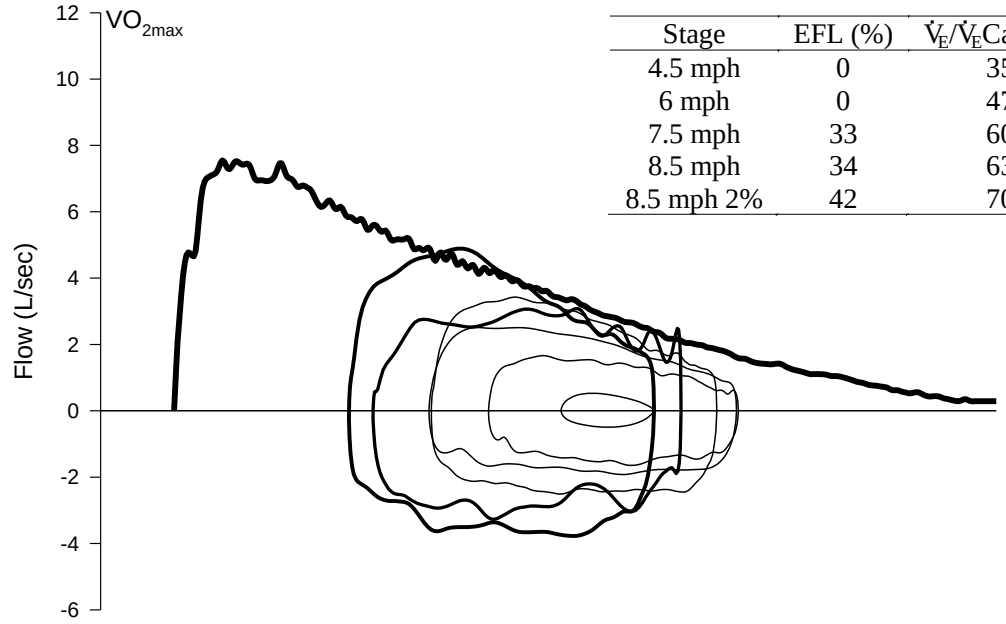
Figure 107- PH, MEFV curve and descriptors.

Subject PH- Run/Cyle Recreational. 30-90min/3-5x week

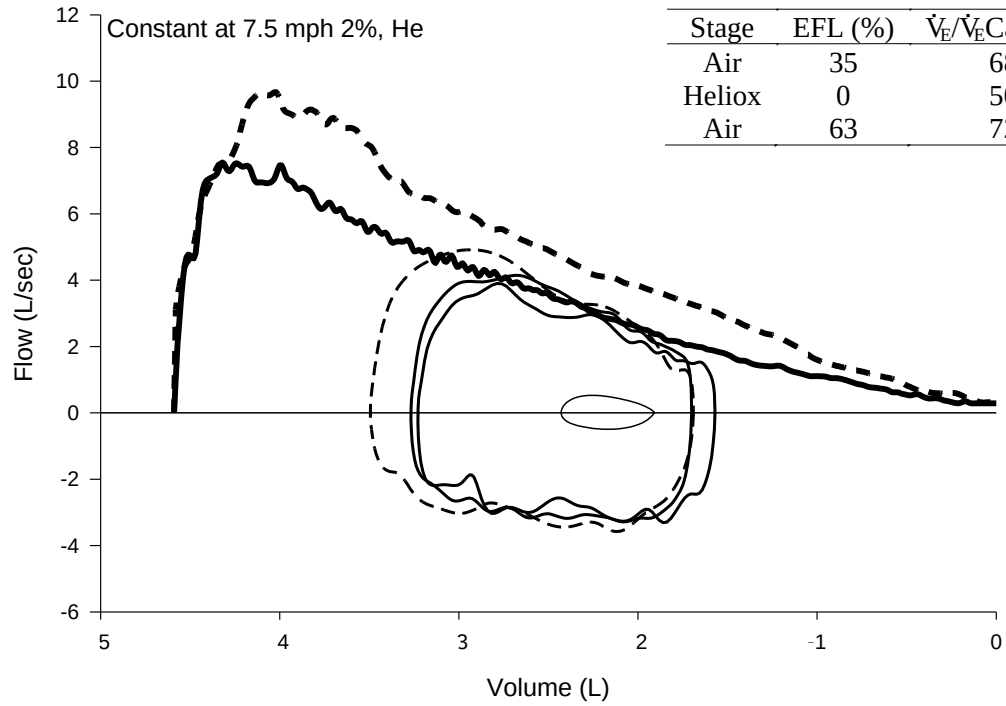
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
22	173	71	23.7	4.79	114			-75

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.12	44	3.34	87	1.11	1.71	59	42	42



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4.5 mph	0	35
6 mph	0	47
7.5 mph	33	60
8.5 mph	34	63
8.5 mph 2%	42	70



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	35	68
Heliox	0	50
Air	63	72

Figure 108- PH, arterial blood gases.

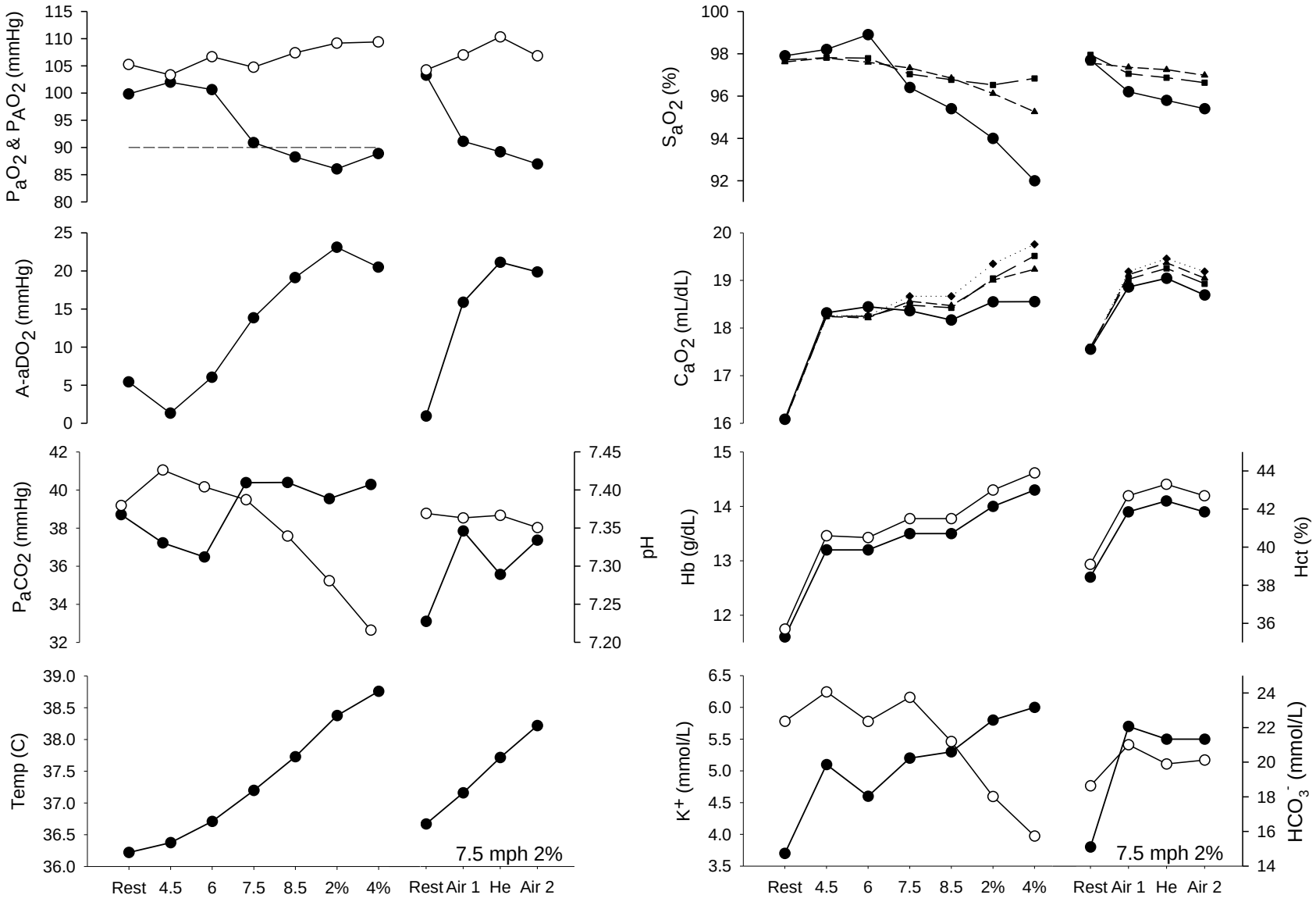


Figure 109- PH, respiratory mechanics.

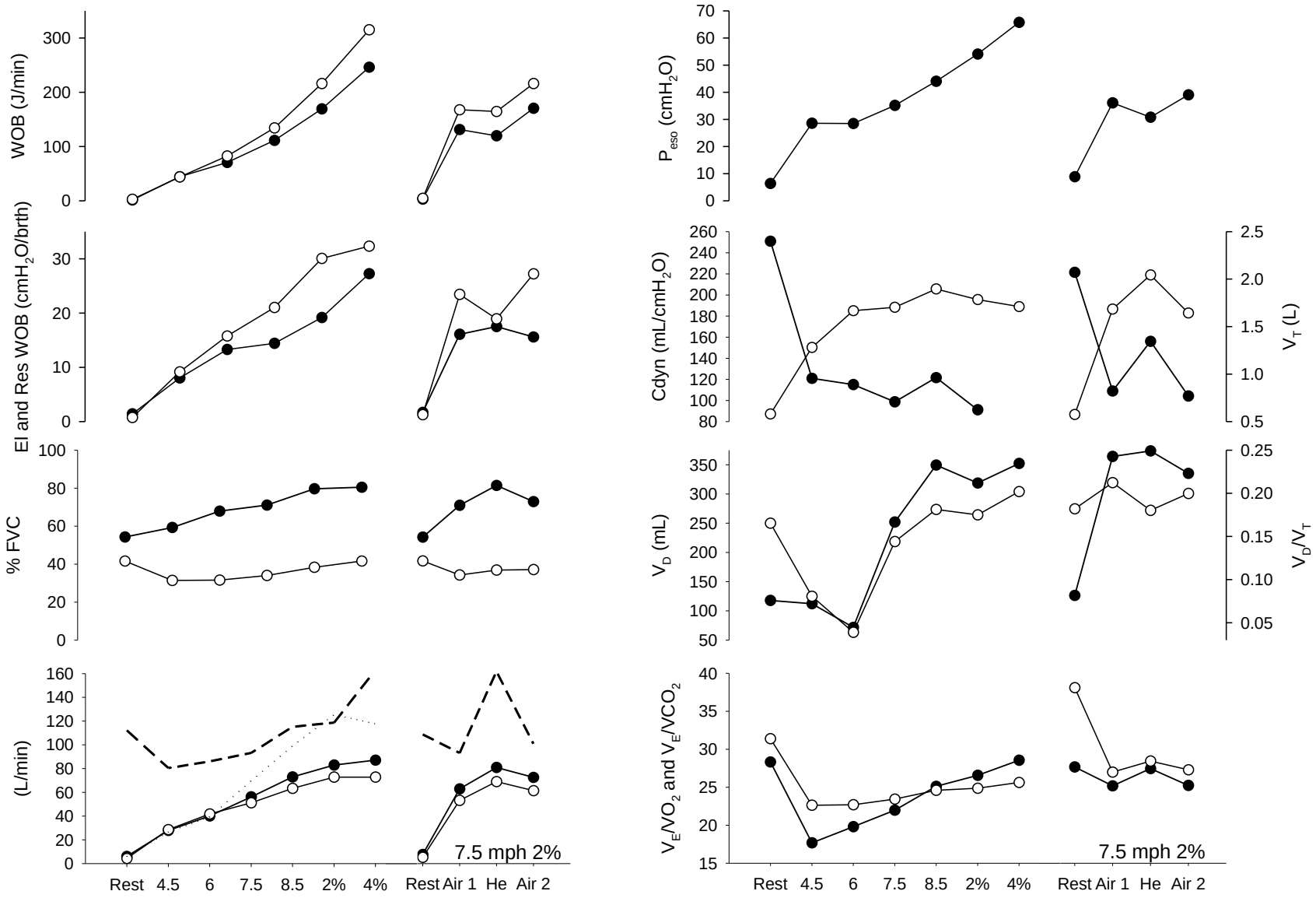


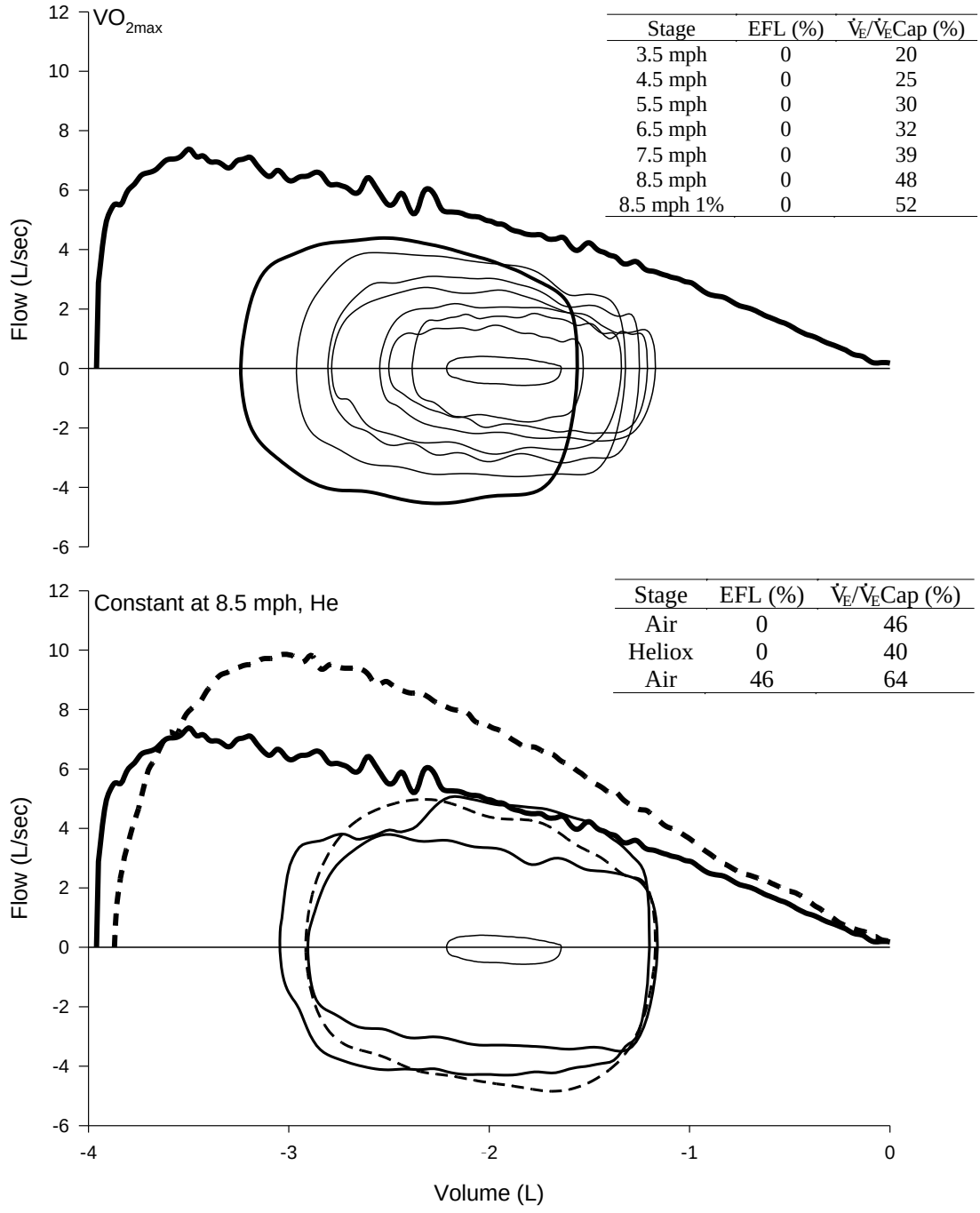
Figure 110- RB, MEFV curve and descriptors.

Subject RB- Rugby. 3hrs/5x/wk

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
19	161	60.2	23.2	4.17	111	26.84	0.19	-105

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.39	56	3.90	98	1.15	1.8	65	0	39



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
3.5 mph	0	20
4.5 mph	0	25
5.5 mph	0	30
6.5 mph	0	32
7.5 mph	0	39
8.5 mph	0	48
8.5 mph 1%	0	52

Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	46
Heliox	0	40
Air	46	64

Figure 111- RB, arterial blood gases.

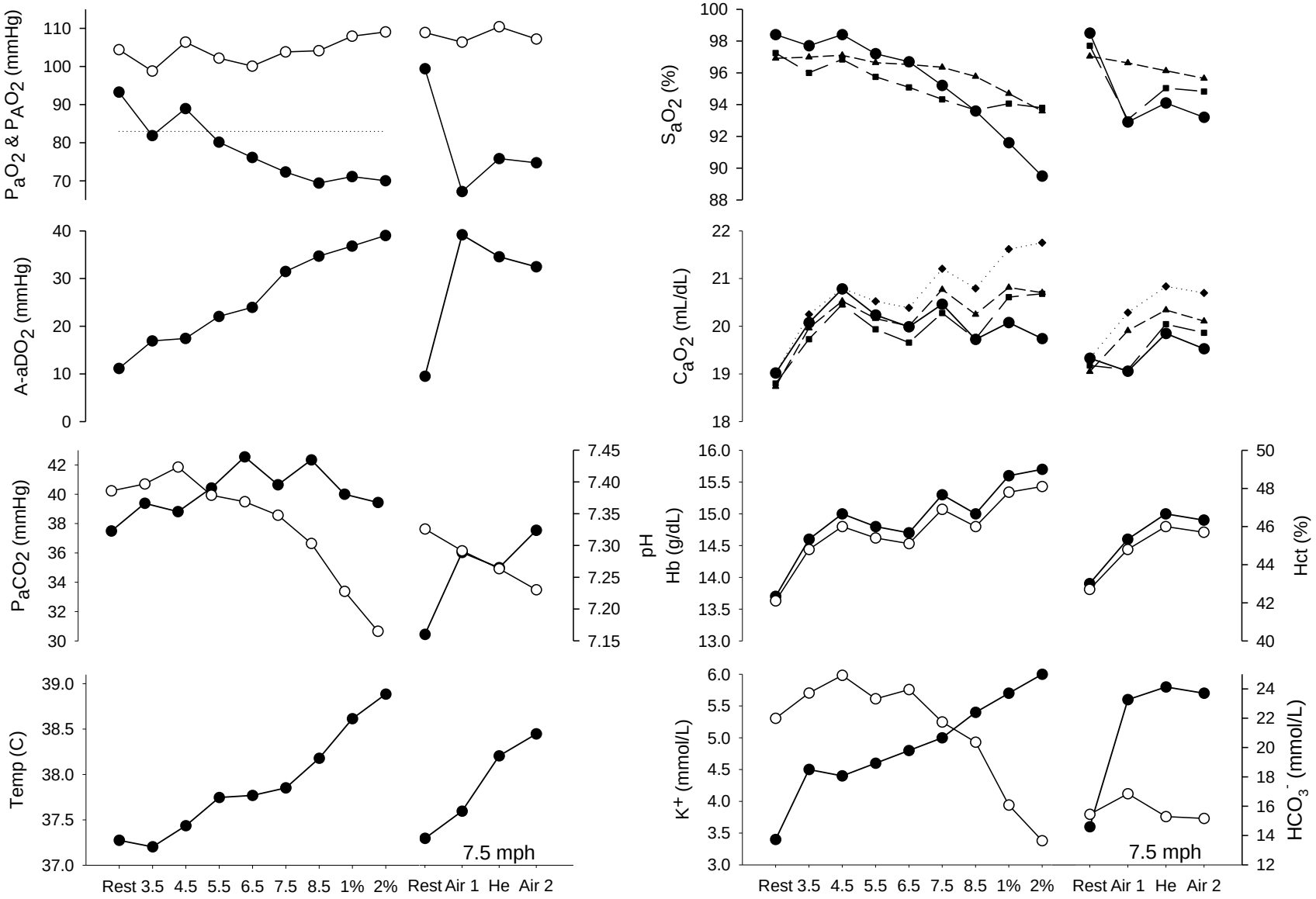


Figure 112- RB, respiratory mechanics.

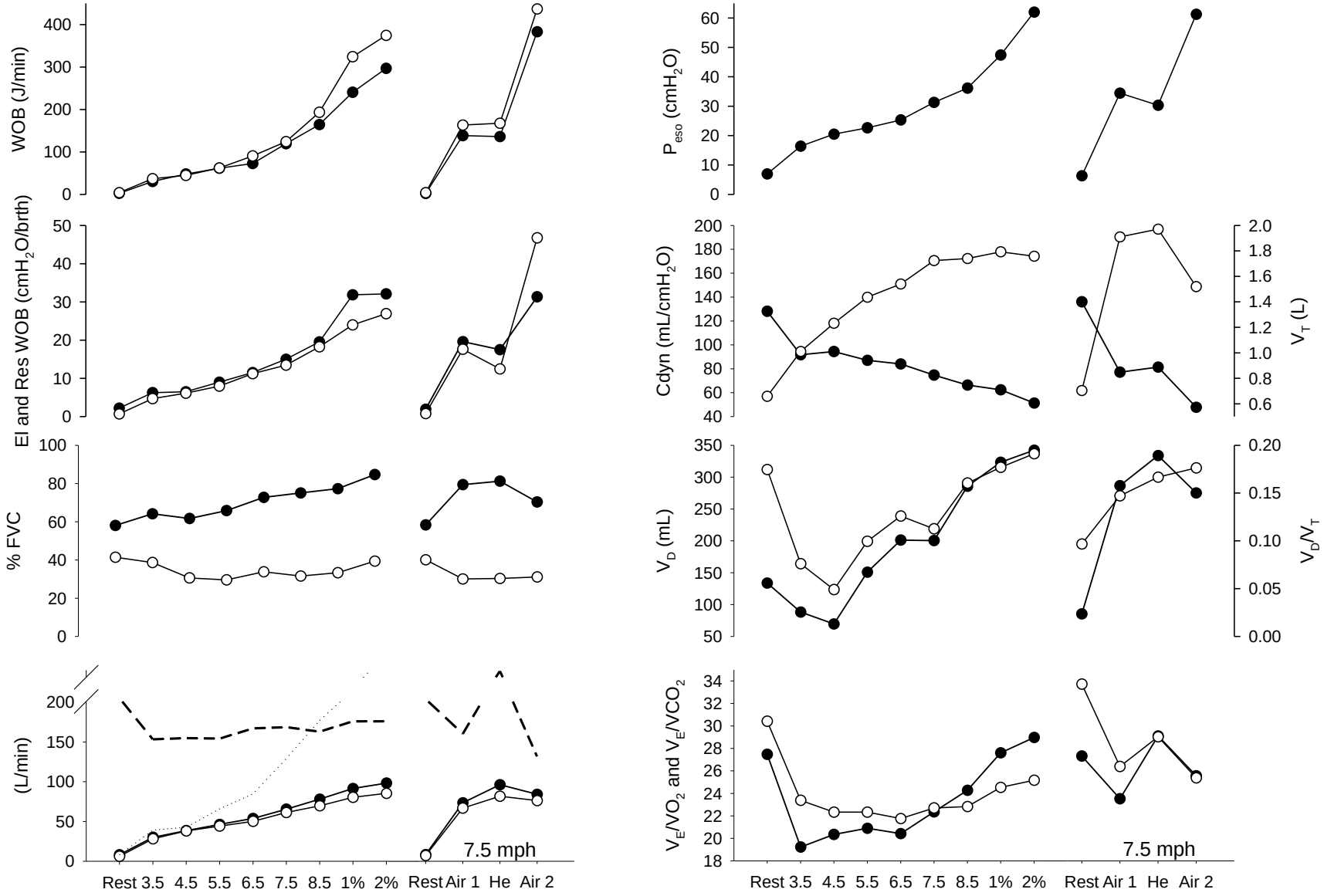


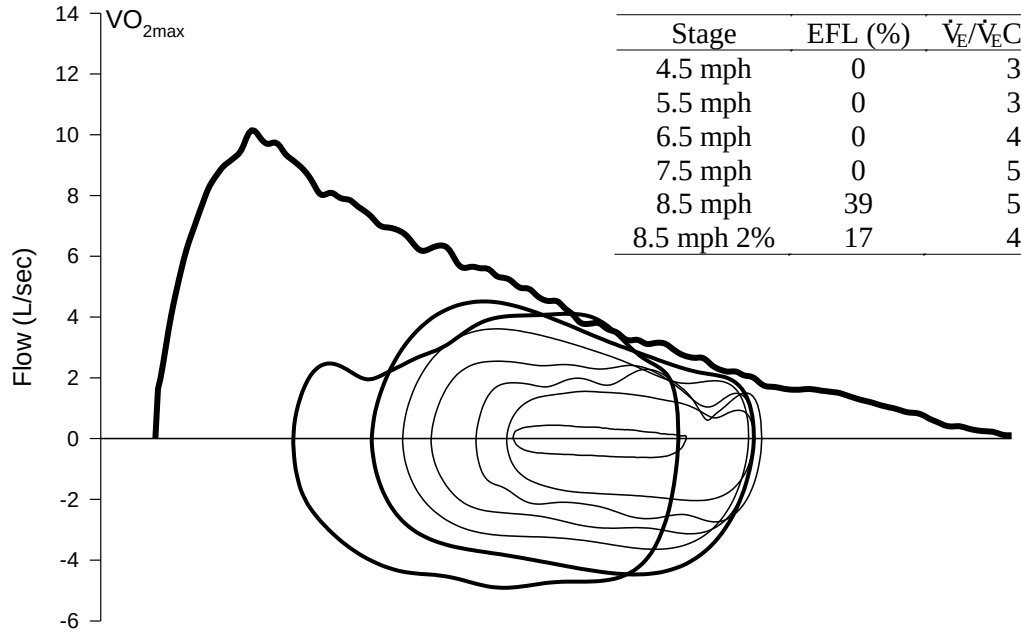
Figure 113- SD, MEFV curve and descriptors.

Subject SD- Competitive Rope Skipping, Run/Cycle (Rec). 1-2hr/4-6x wk

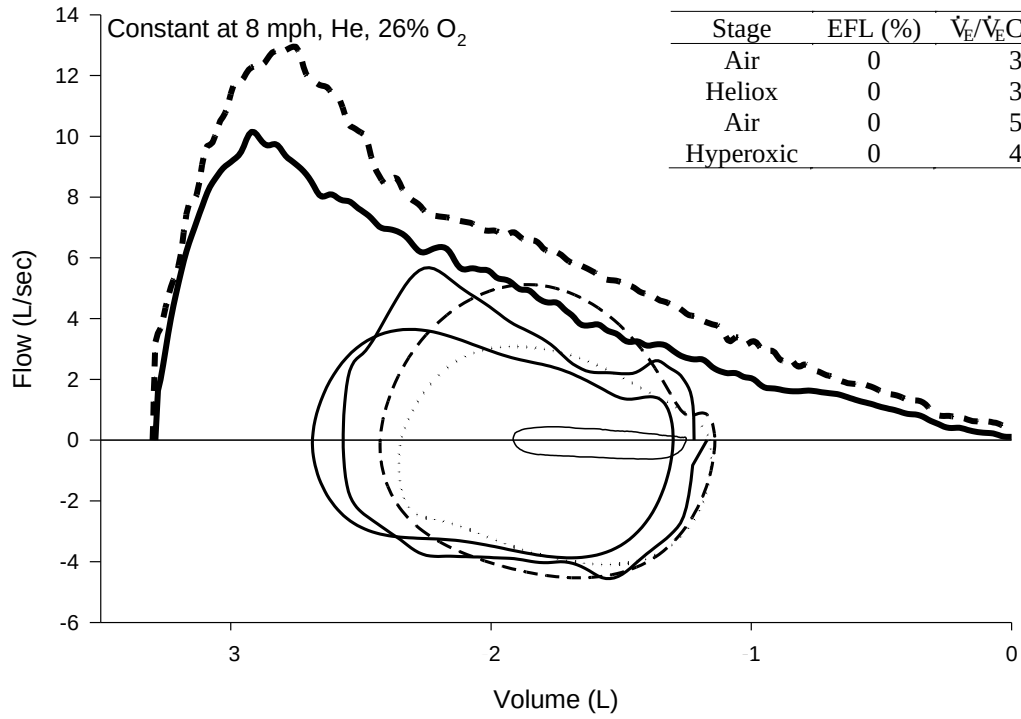
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
26	163	62	23.3	3.46	95	29.09	0.16	-134

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.90	47	3.20	86	1.1	1.6	62	17	39



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4.5 mph	0	34
5.5 mph	0	33
6.5 mph	0	45
7.5 mph	0	52
8.5 mph	39	53
8.5 mph 2%	17	40



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	39
Heliox	0	39
Air	0	53
Hyperoxic	0	49

Figure 114- SD, arterial blood gases.

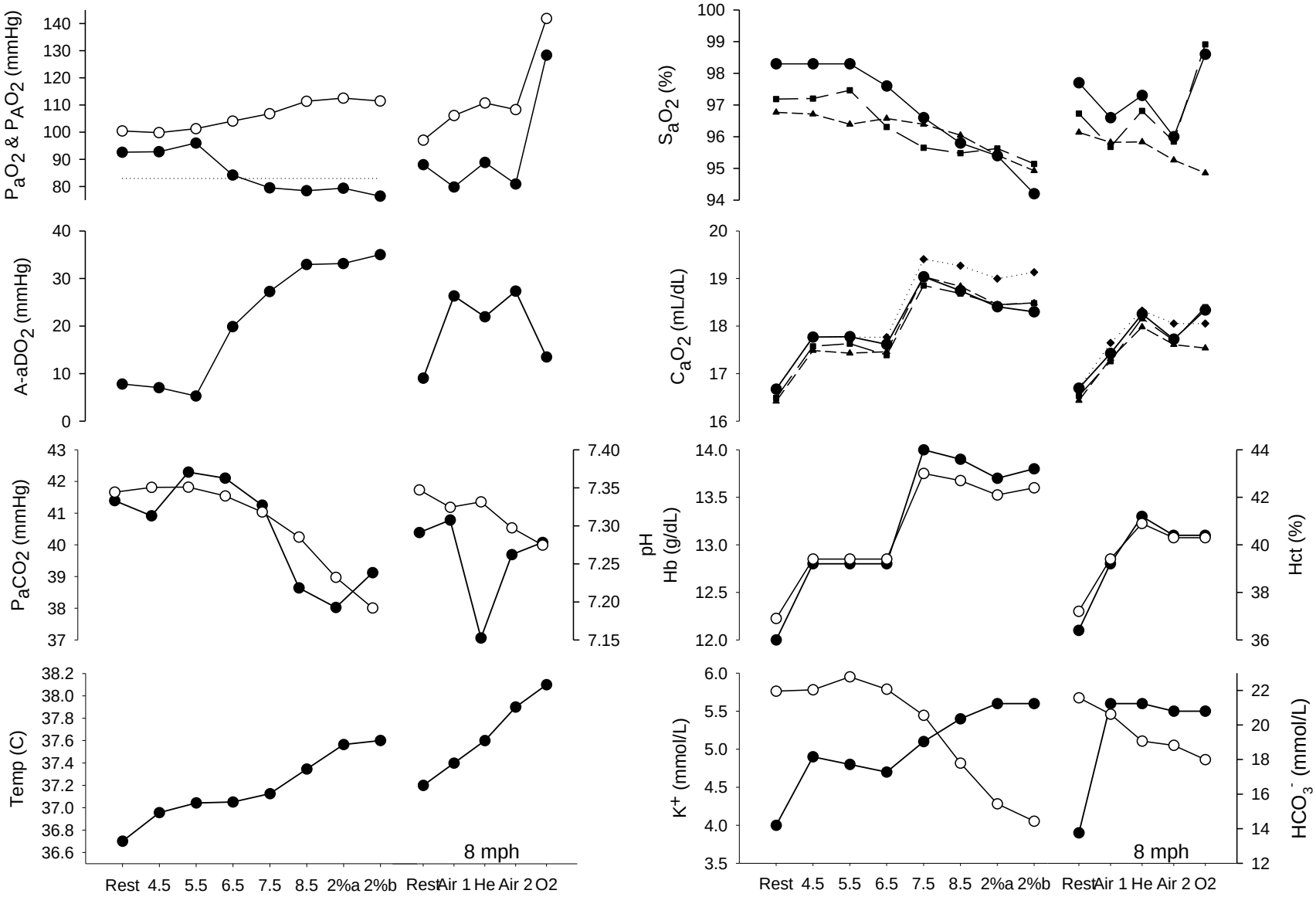


Figure 115- SD, respiratory mechanics.

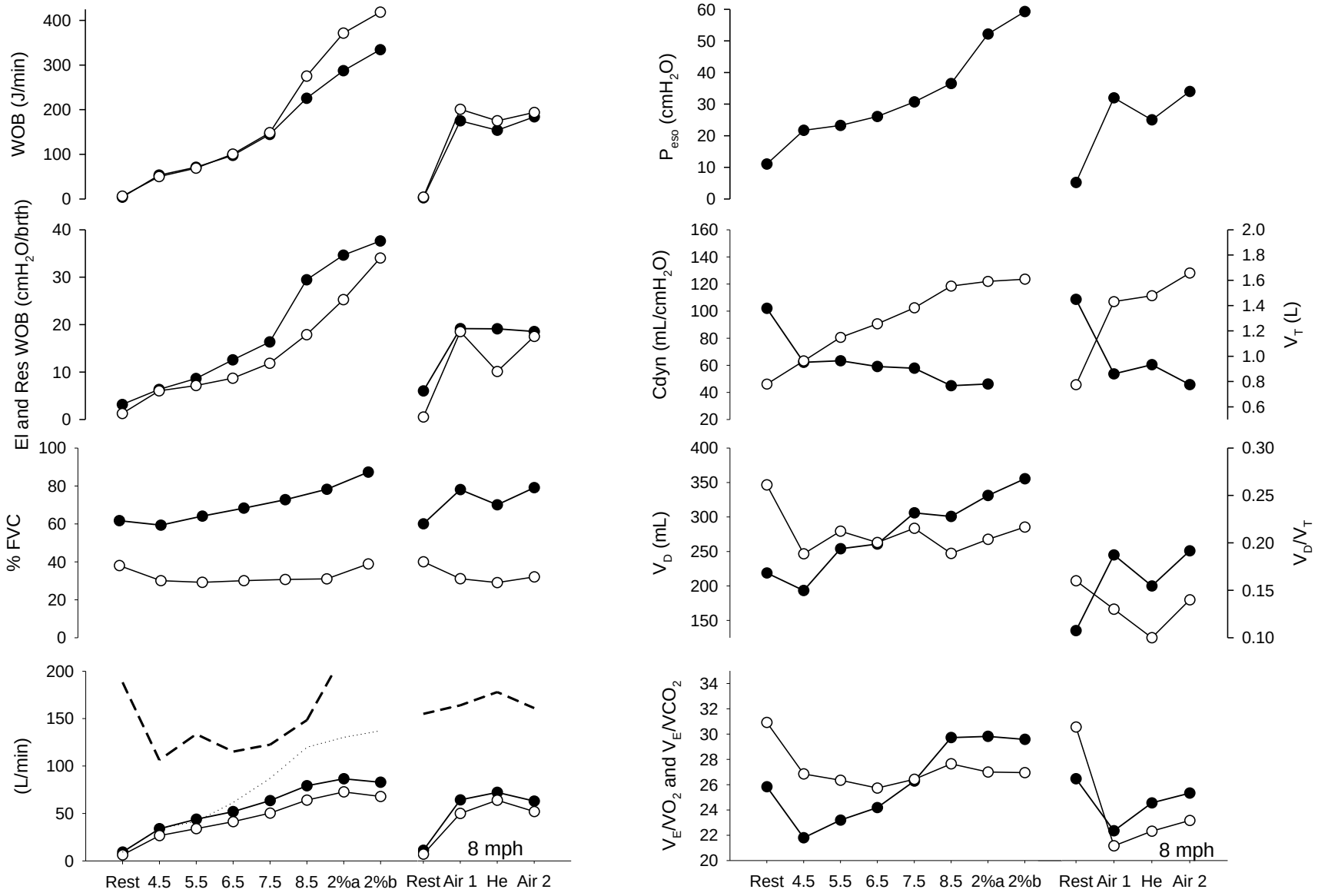


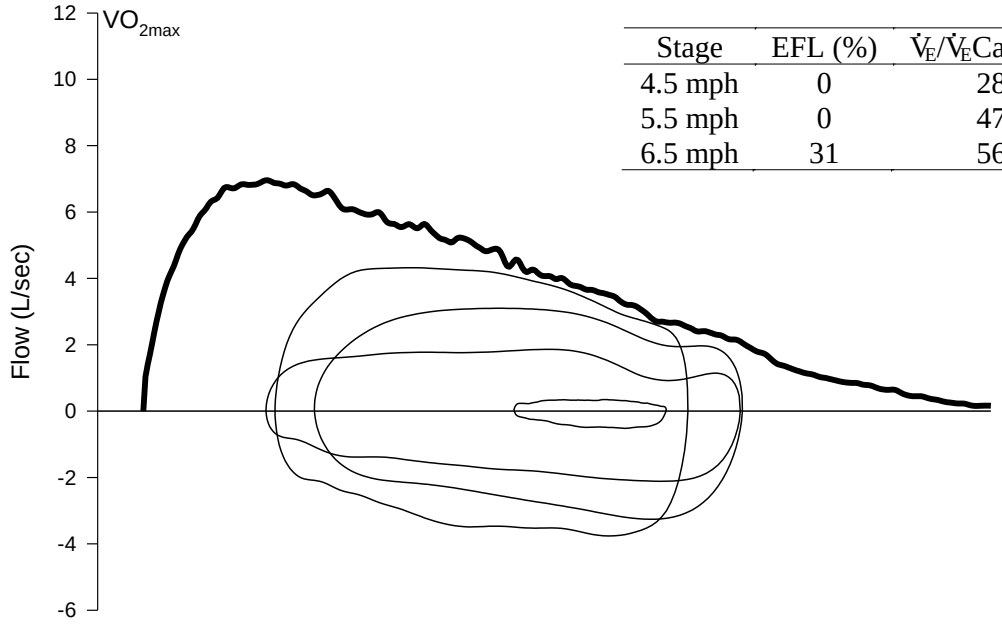
Figure 116- SL, MEFV curve and descriptors.

Subject SL- Cardio/Weights. 1hr/2-3x/wk

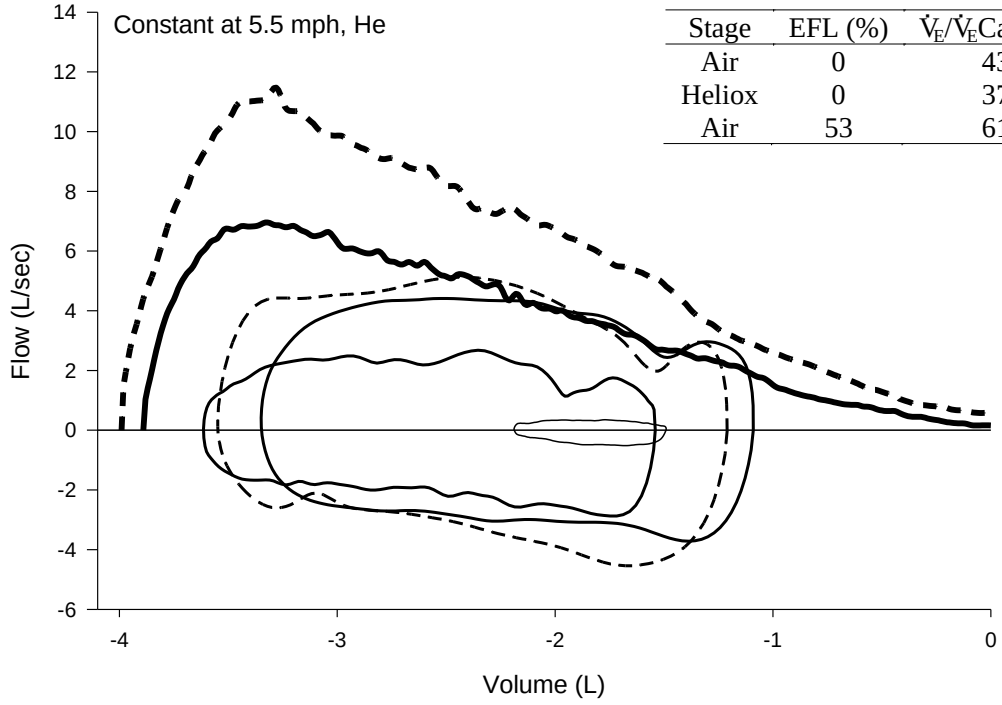
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
27	166	74.1	26.9	3.78	101	25.52	0.11	-109

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.96	40	3.2	78	1.15	2.1	44	31	36



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4.5 mph	0	28
5.5 mph	0	47
6.5 mph	31	56



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	43
Heliox	0	37
Air	53	61

Figure 117- SL, arterial blood gases.

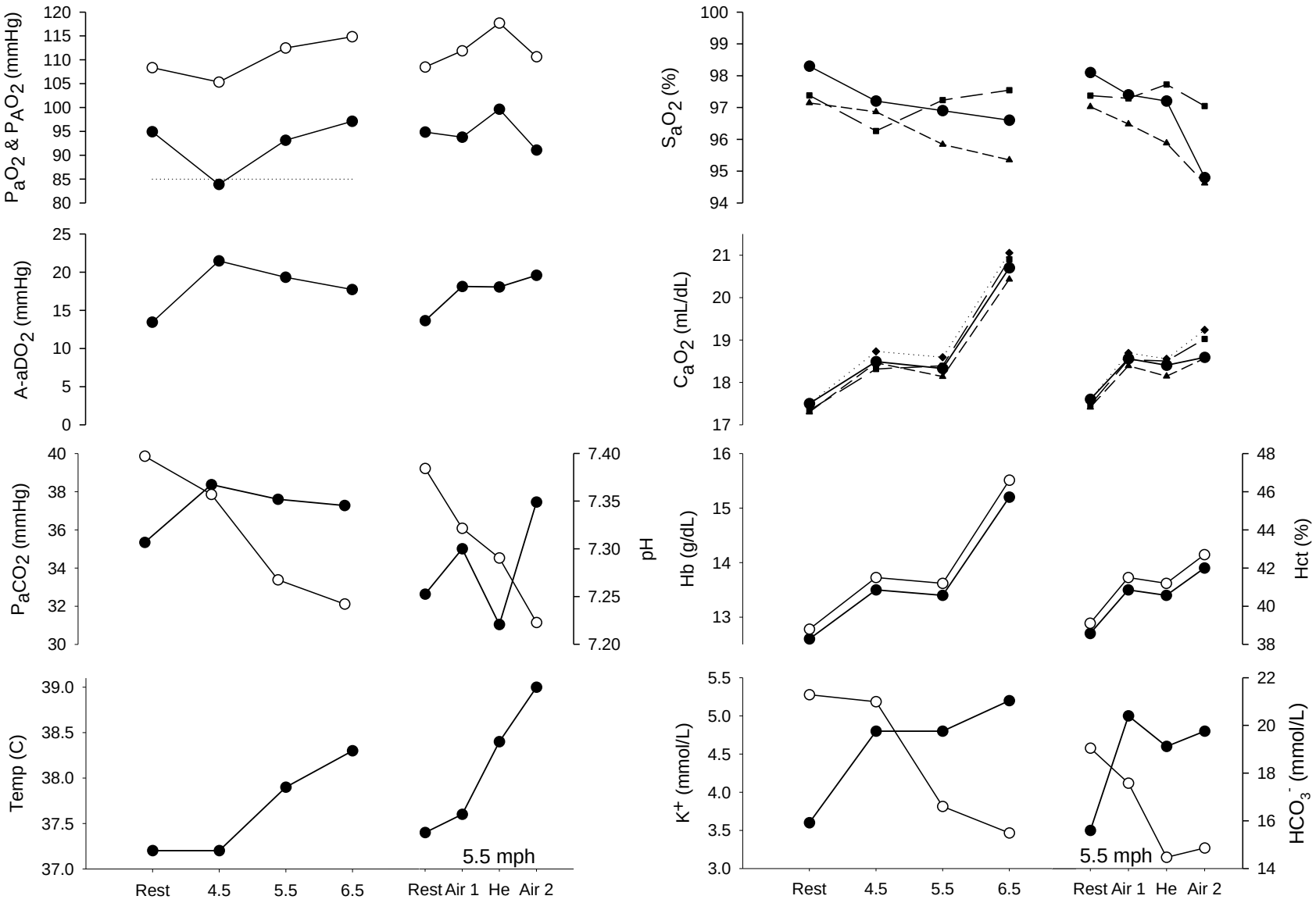


Figure 118- SL, respiratory mechanics.

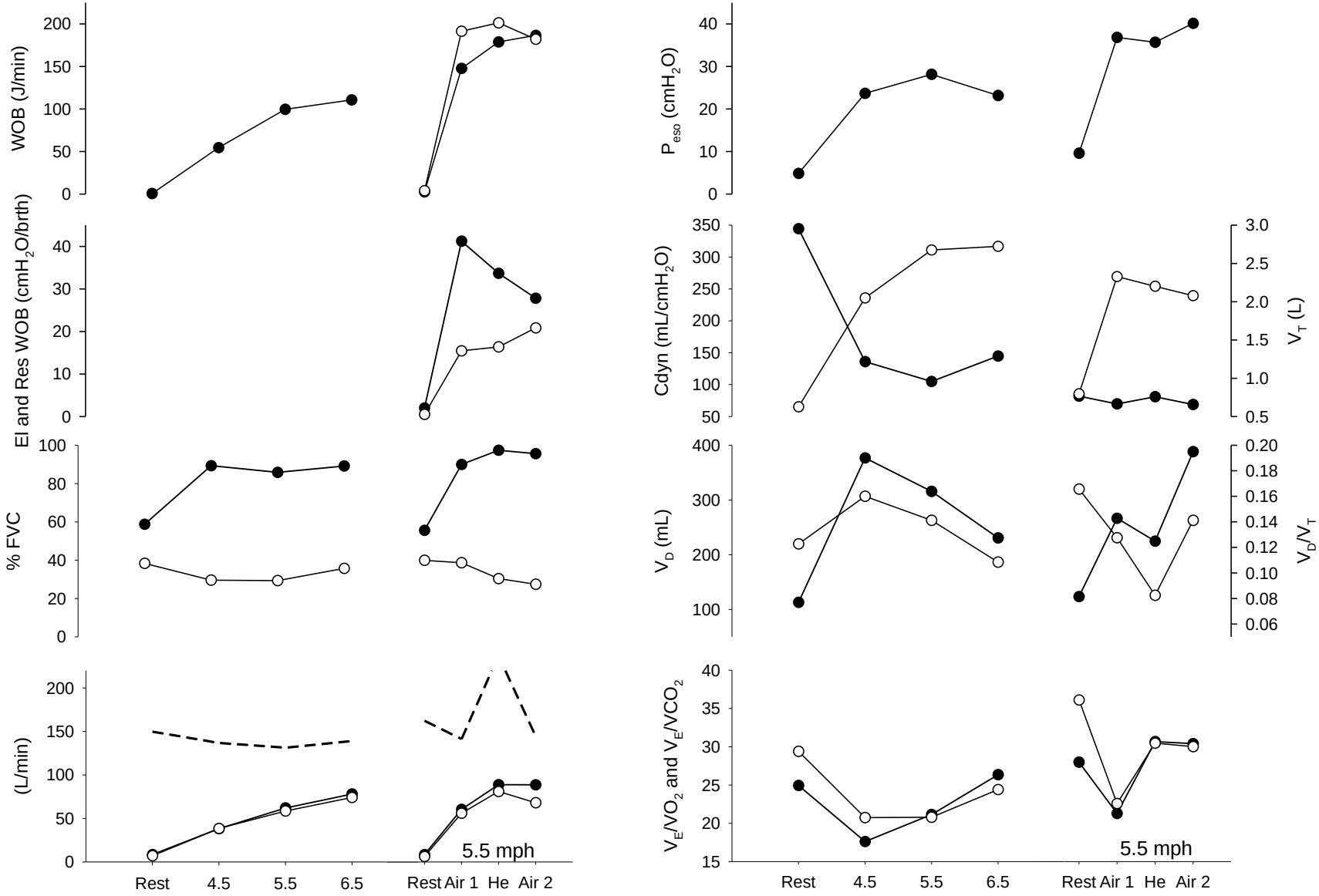


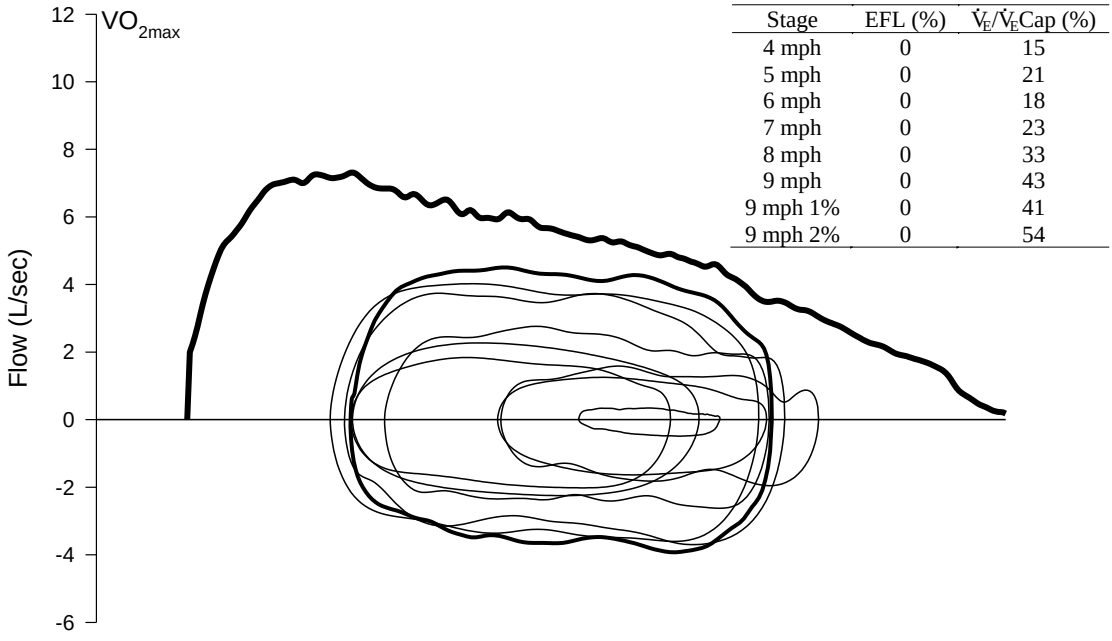
Figure 119- SS- MEFV curve and descriptors.

Subject SS- Running. 30-60min 5x/wk

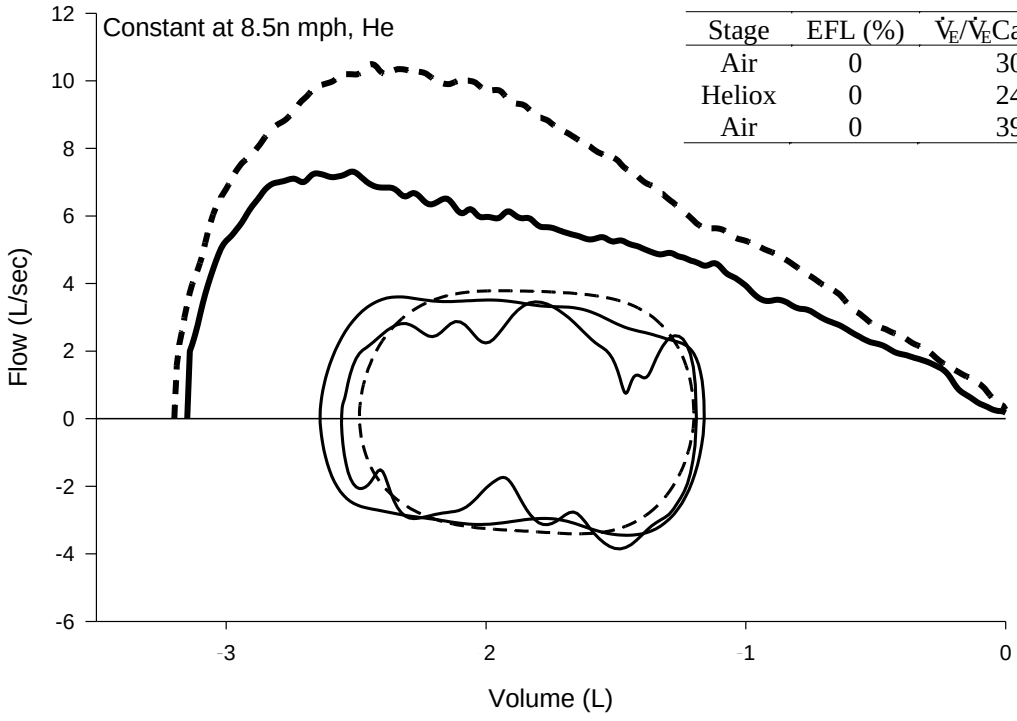
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
32	169	56	19.6	3.84	102	26.03	0.28	-93

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.93	52	3.12	89	1.1	1.73	59	0	29



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4 mph	0	15
5 mph	0	21
6 mph	0	18
7 mph	0	23
8 mph	0	33
9 mph	0	43
9 mph 1%	0	41
9 mph 2%	0	54



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	30
Heliox	0	24
Air	0	39

Figure 120- SS, arterial blood gases.

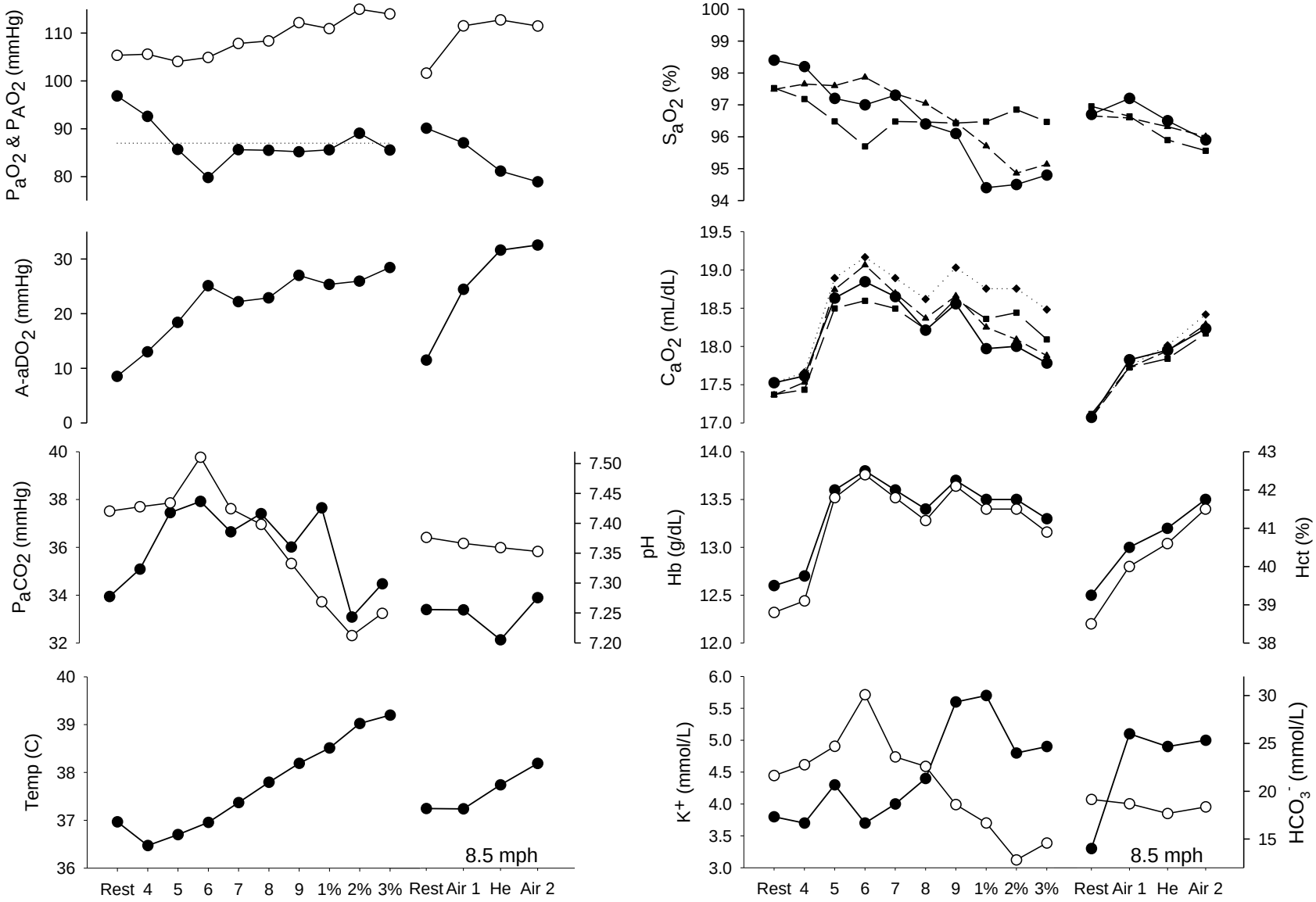


Figure 121- SS, respiratory mechanics.

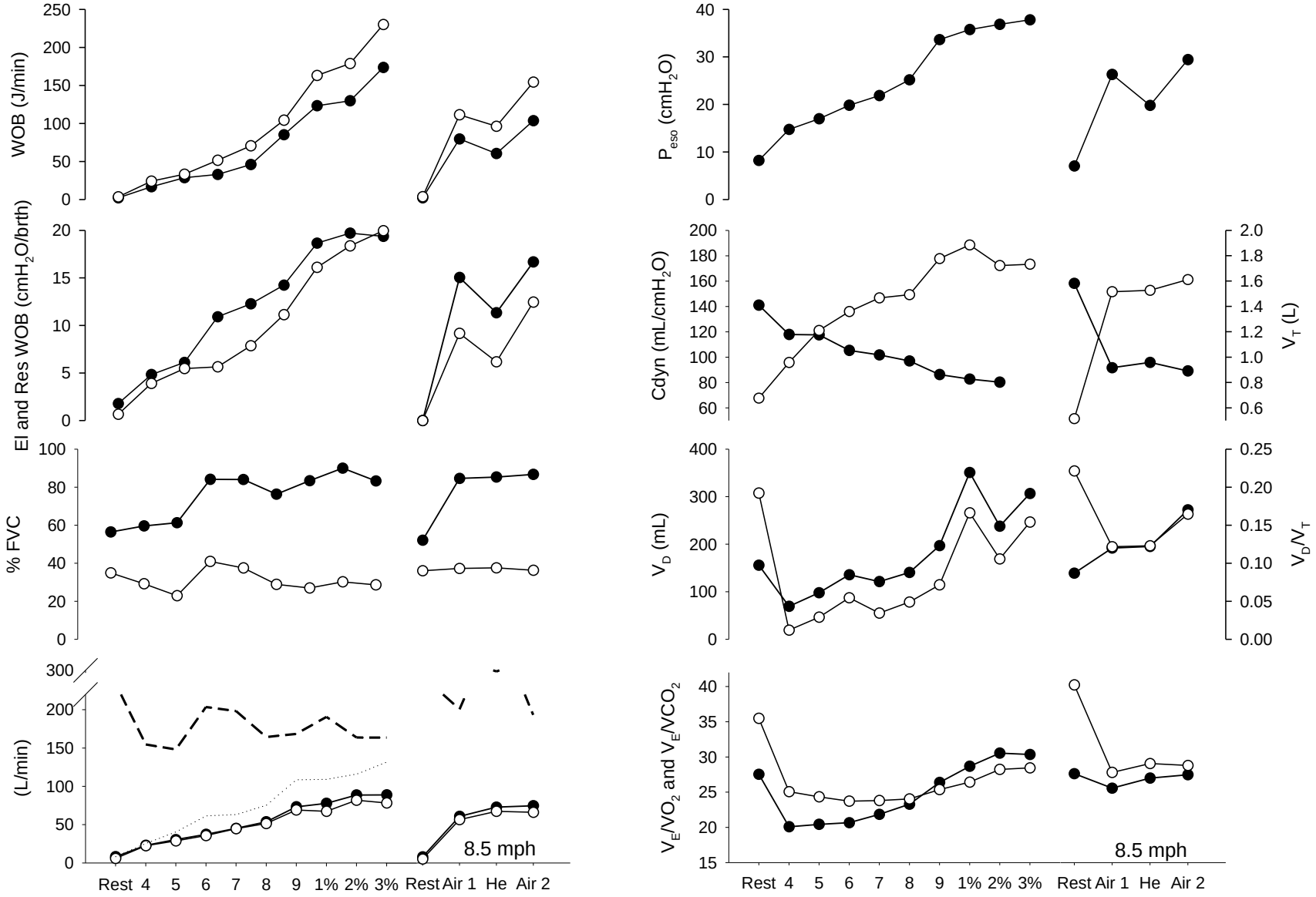


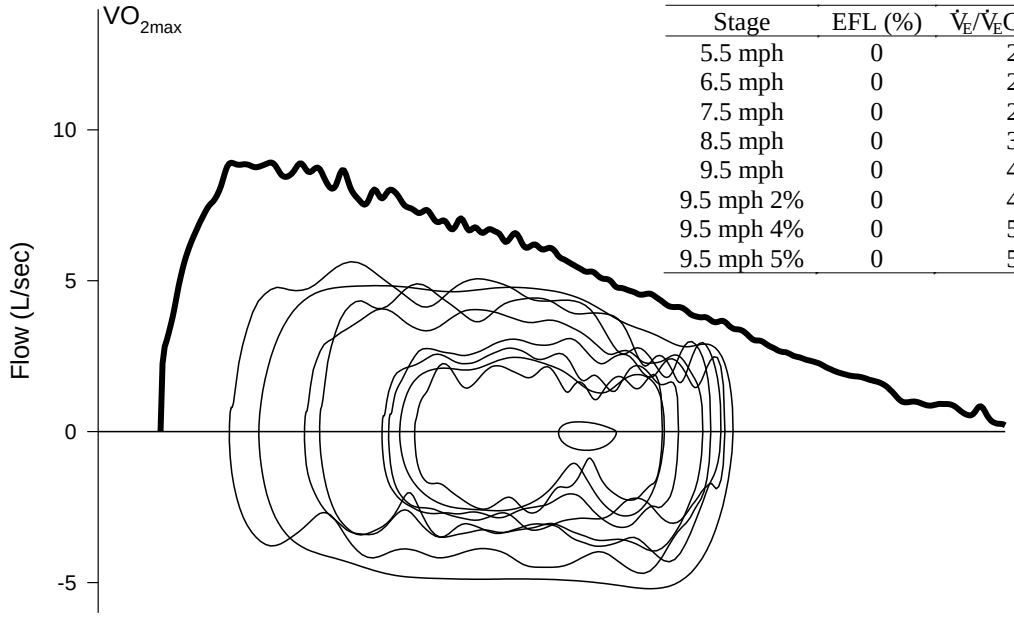
Figure 122- SW (Jun), MEFV curve and descriptors.

Subject SW (JUN)- Run/Swim/Bike/Weights. 1.5hrs 6x/wk. DAY 1

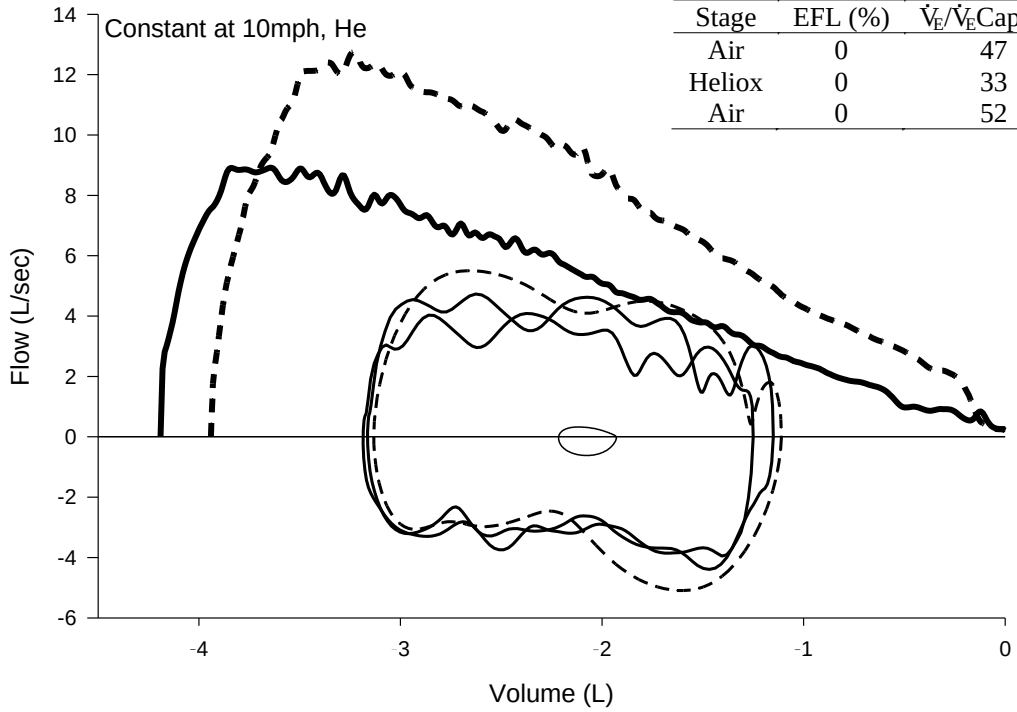
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
26	174	57.8	19.1	4.63	112	29.24	0.25	-90

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.43	59	3.72	112	1.08	2.5	53	0	32



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
5.5 mph	0	20
6.5 mph	0	24
7.5 mph	0	28
8.5 mph	0	37
9.5 mph	0	40
9.5 mph 2%	0	45
9.5 mph 4%	0	50
9.5 mph 5%	0	57



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	47
Heliox	0	33
Air	0	52

Figure 123- SW (Jun), arterial blood gases.

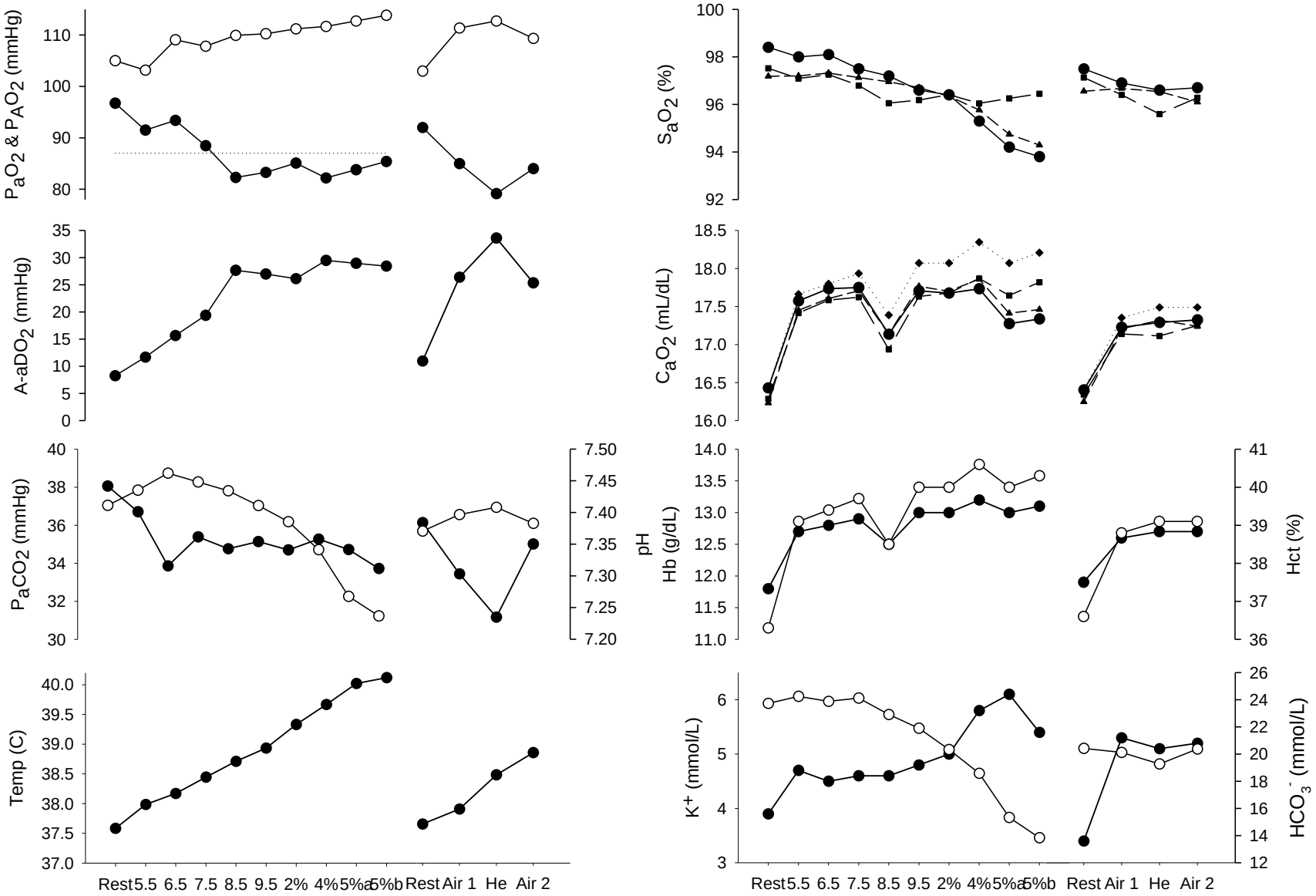


Figure 124- SW (Jun), respiratory mechanics.

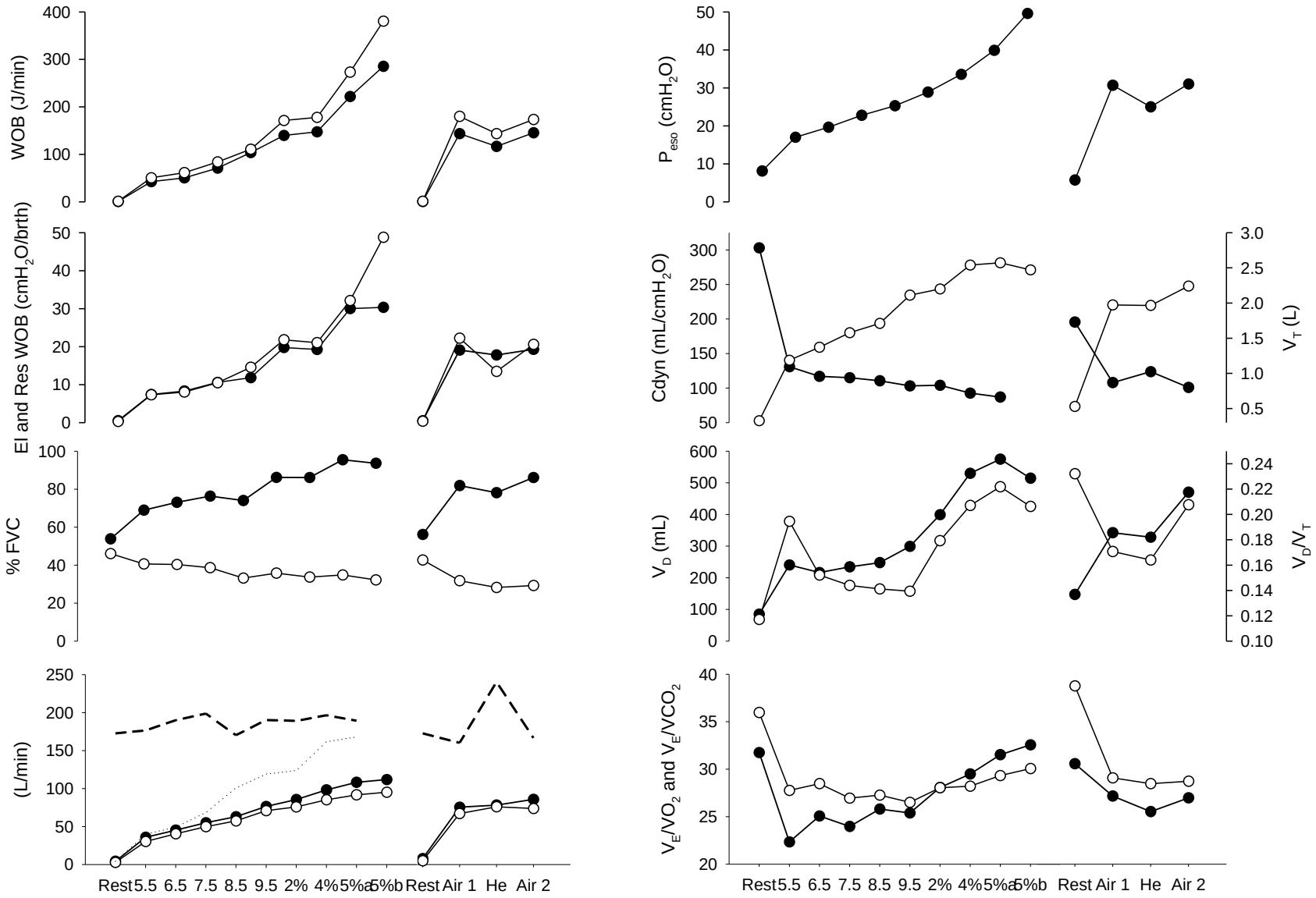


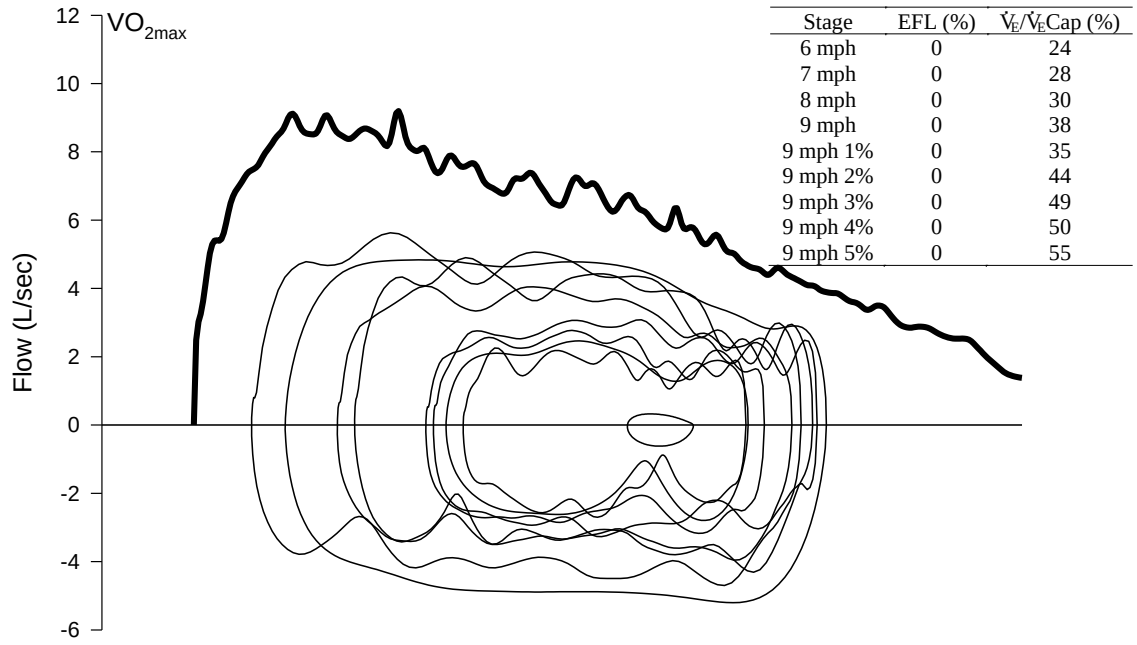
Figure 125- SW (Nov), MEFV curve and descriptors.

Subject SW NOV- Run (Varsity, 5000m),Swim,Bike,Weight. 1.5hrs 6-7x/wk. DAY 2

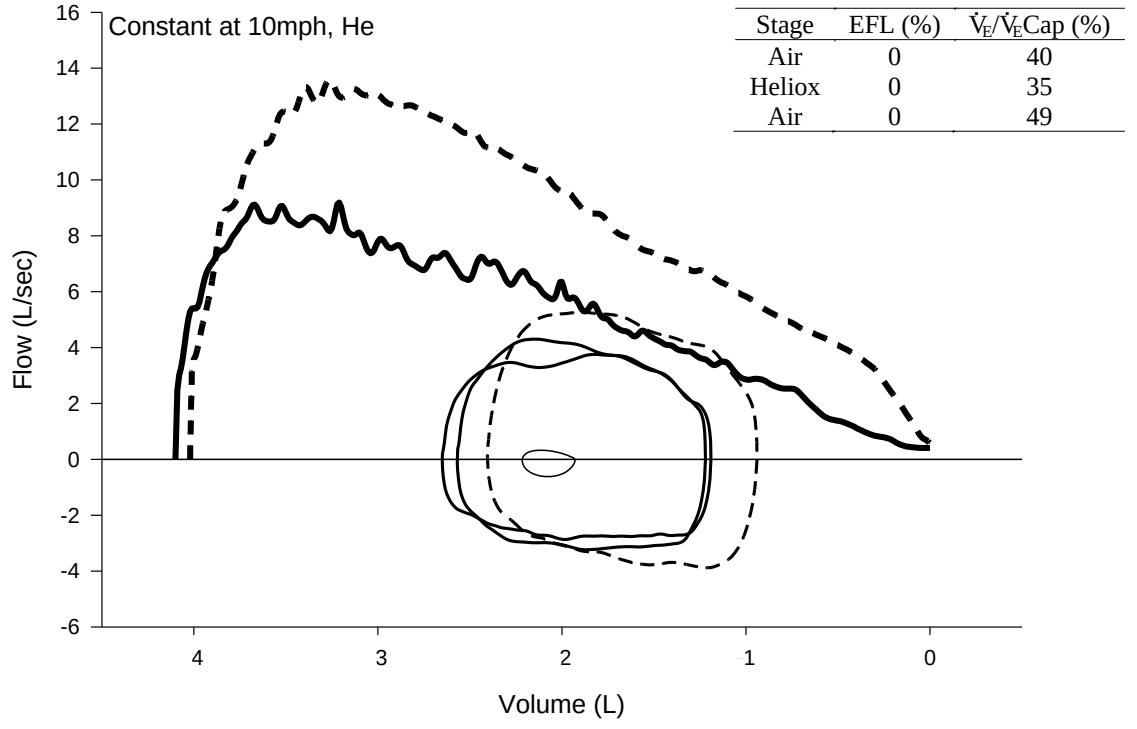
Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
26	174	56.8	18.8	4.57	110	27.69	0.25	-72

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
3.82	67	4.16	114	1.09	2.58	51	0	31



Stage	EFL (%)	$\dot{V}_E/\dot{V}_ECap$ (%)
6 mph	0	24
7 mph	0	28
8 mph	0	30
9 mph	0	38
9 mph 1%	0	35
9 mph 2%	0	44
9 mph 3%	0	49
9 mph 4%	0	50
9 mph 5%	0	55



Stage	EFL (%)	$\dot{V}_E/\dot{V}_ECap$ (%)
Air	0	40
Heliox	0	35
Air	0	49

Figure 126- SW (Nov), arterial blood gases.

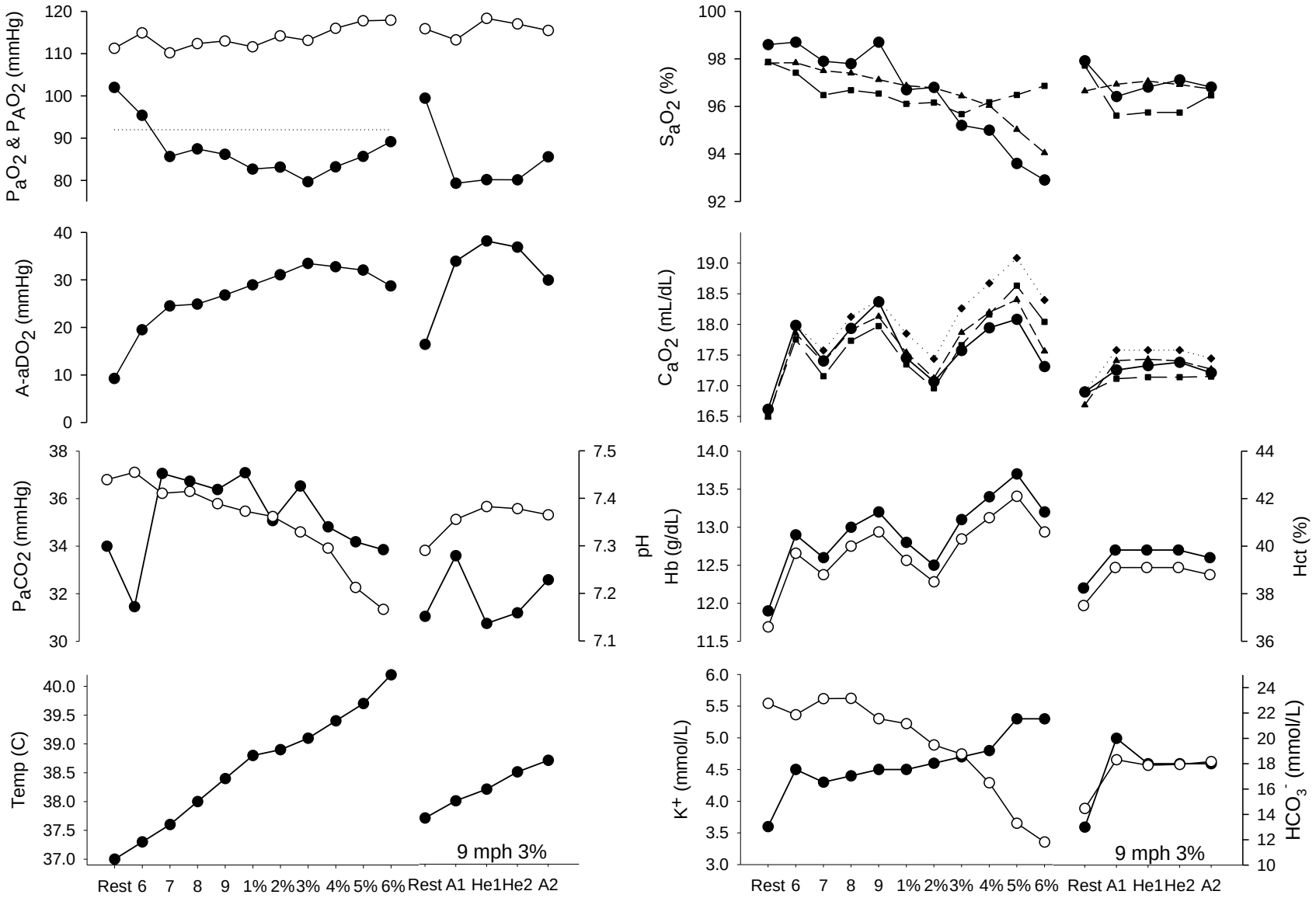


Figure 127- SW (Nov), respiratory mechanics.

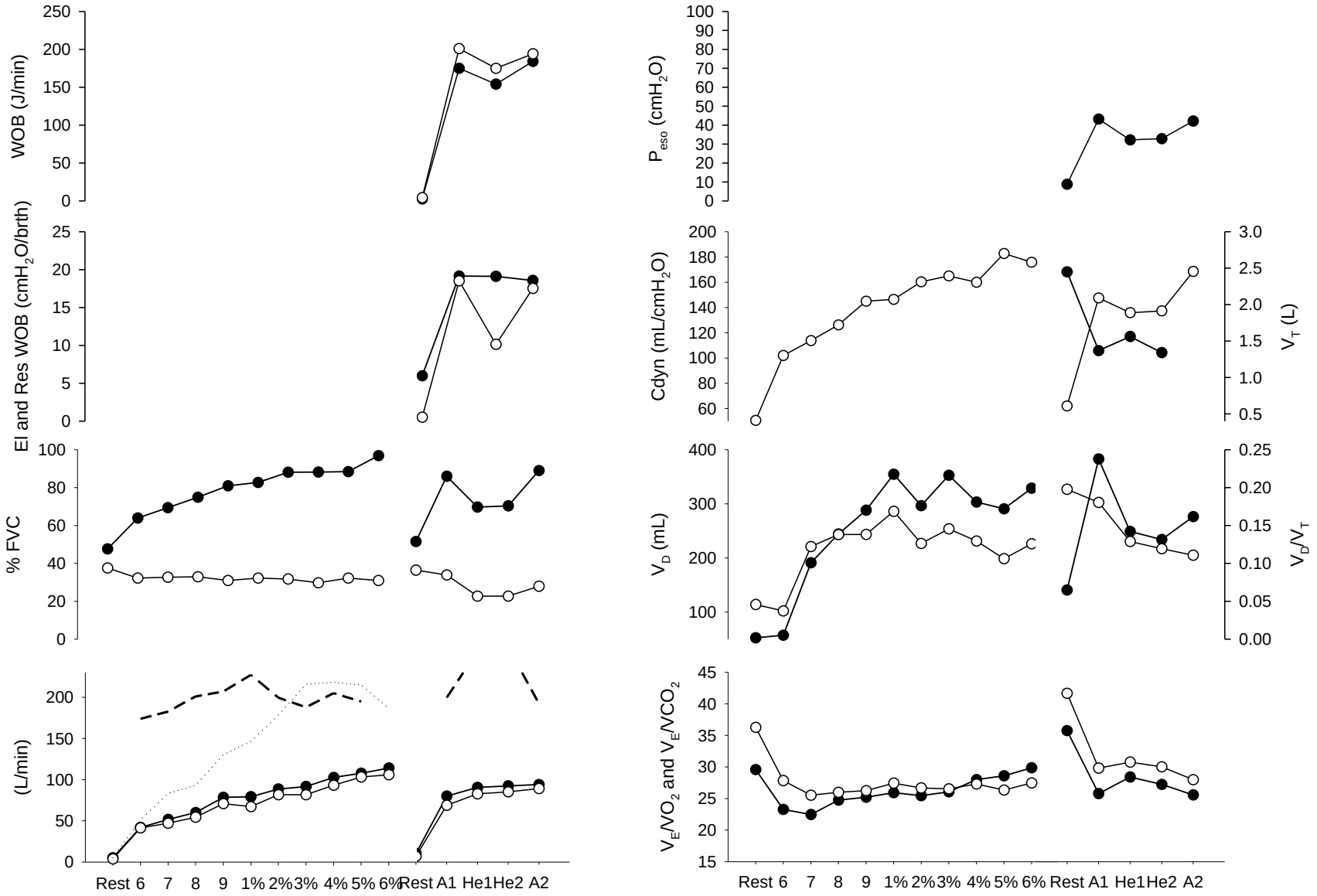


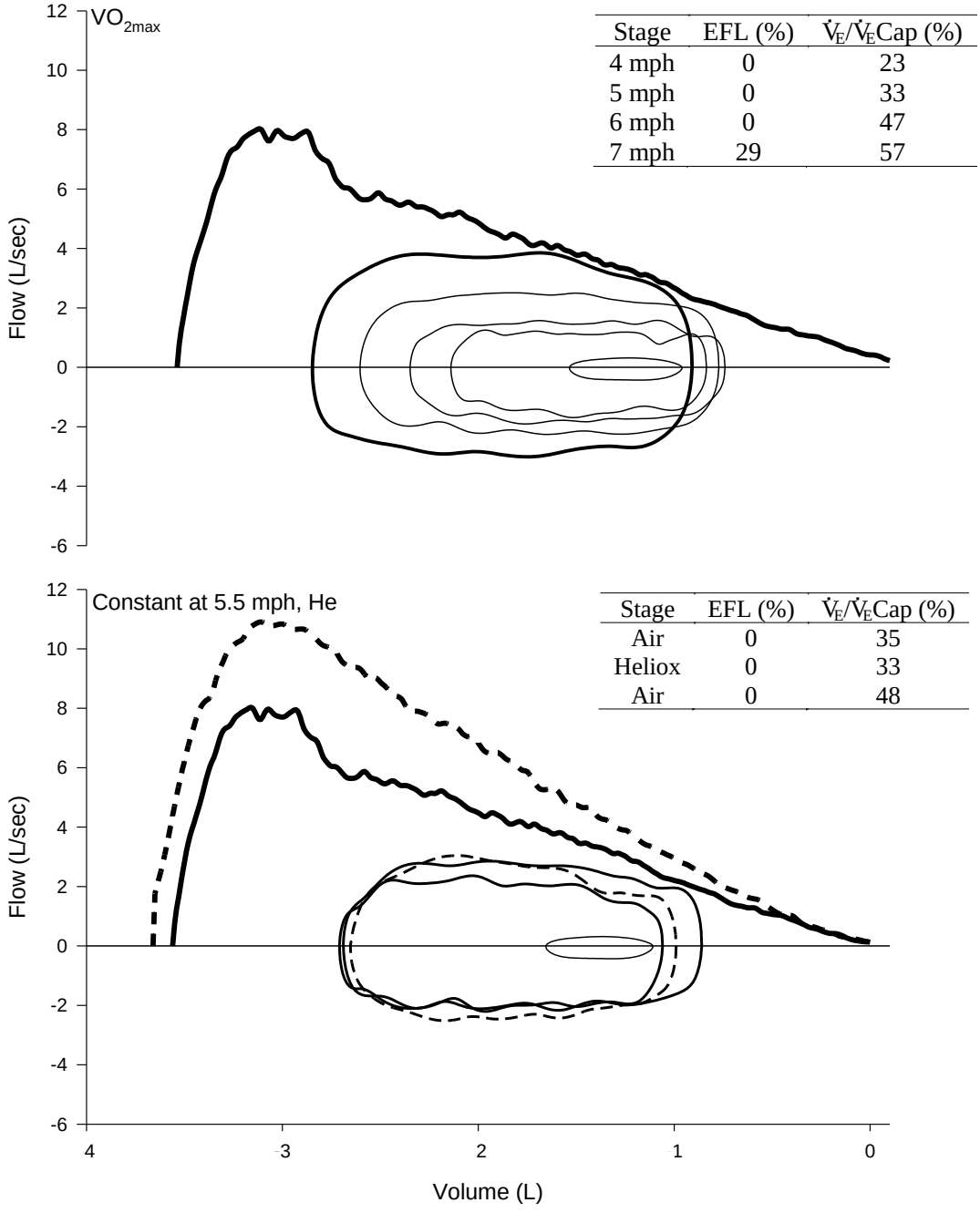
Figure 128- VW, MEFV curve and descriptors.

Subject VW- Yoga, Softball. 2hrs 3x/wk.

Age	Height	Weight	BMI	FVC	FVC	DLCO	Dysanapsis	MIP
yr	cm	kg	kg/m^2	L	%	mL/min/mmHg		cmH_2O
29	168	69.1	24.5	3.94	104		0.18	-112

Peak exercise, 10 mph, 5% grade

$\dot{V}O_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	RER	V_T	Fb	EFL	EELV
L/min	mL/kg/min	L/min	L/min		L	bpm	%	% FVC
2.47	35.7	3.00	75	1.23	2.0	44	0	31



Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
4 mph	0	23
5 mph	0	33
6 mph	0	47
7 mph	29	57

Stage	EFL (%)	$\dot{V}_E/\dot{V}_E$Cap (%)
Air	0	35
Heliox	0	33
Air	0	48

Figure 129- VW, arterial blood gases

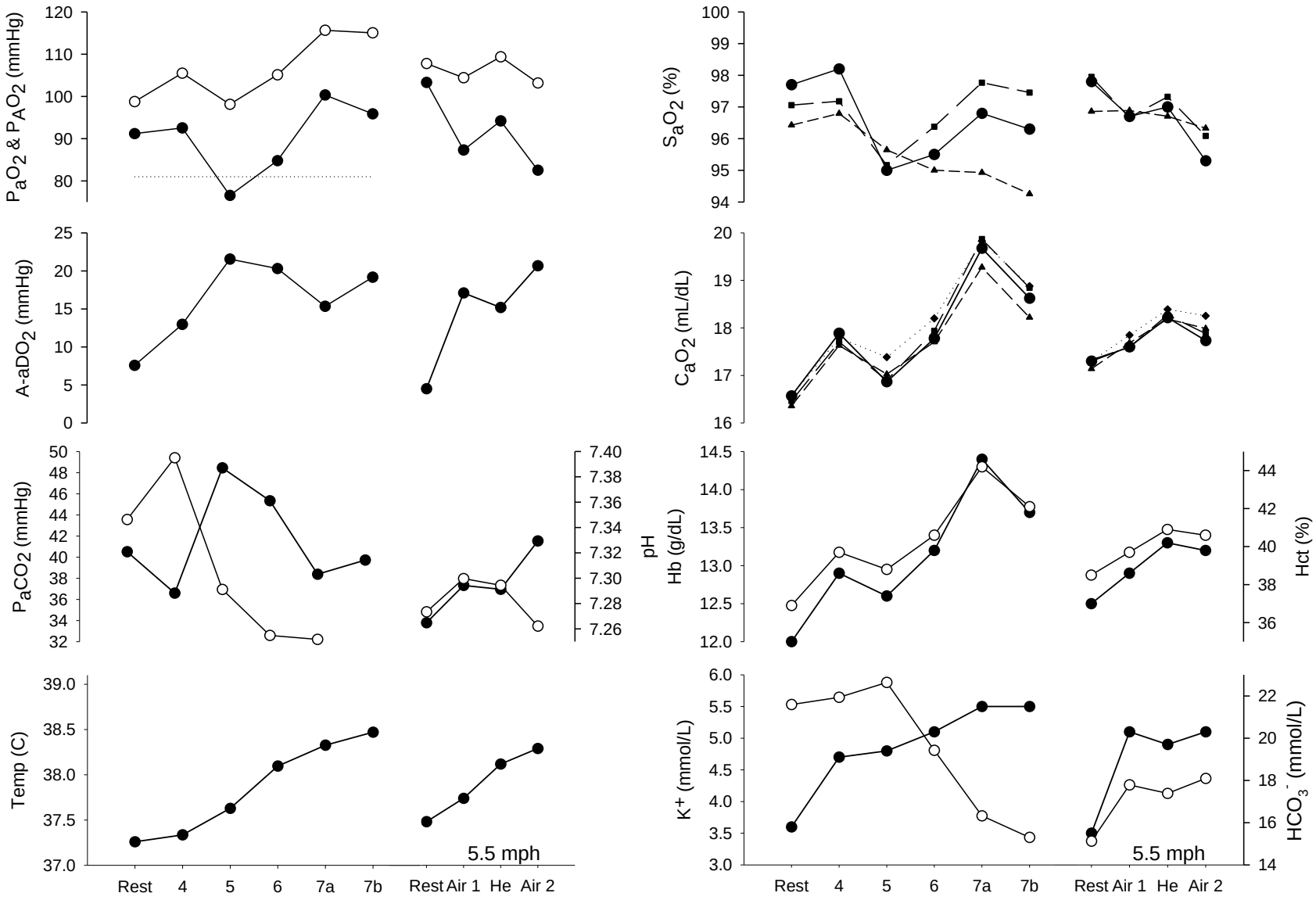
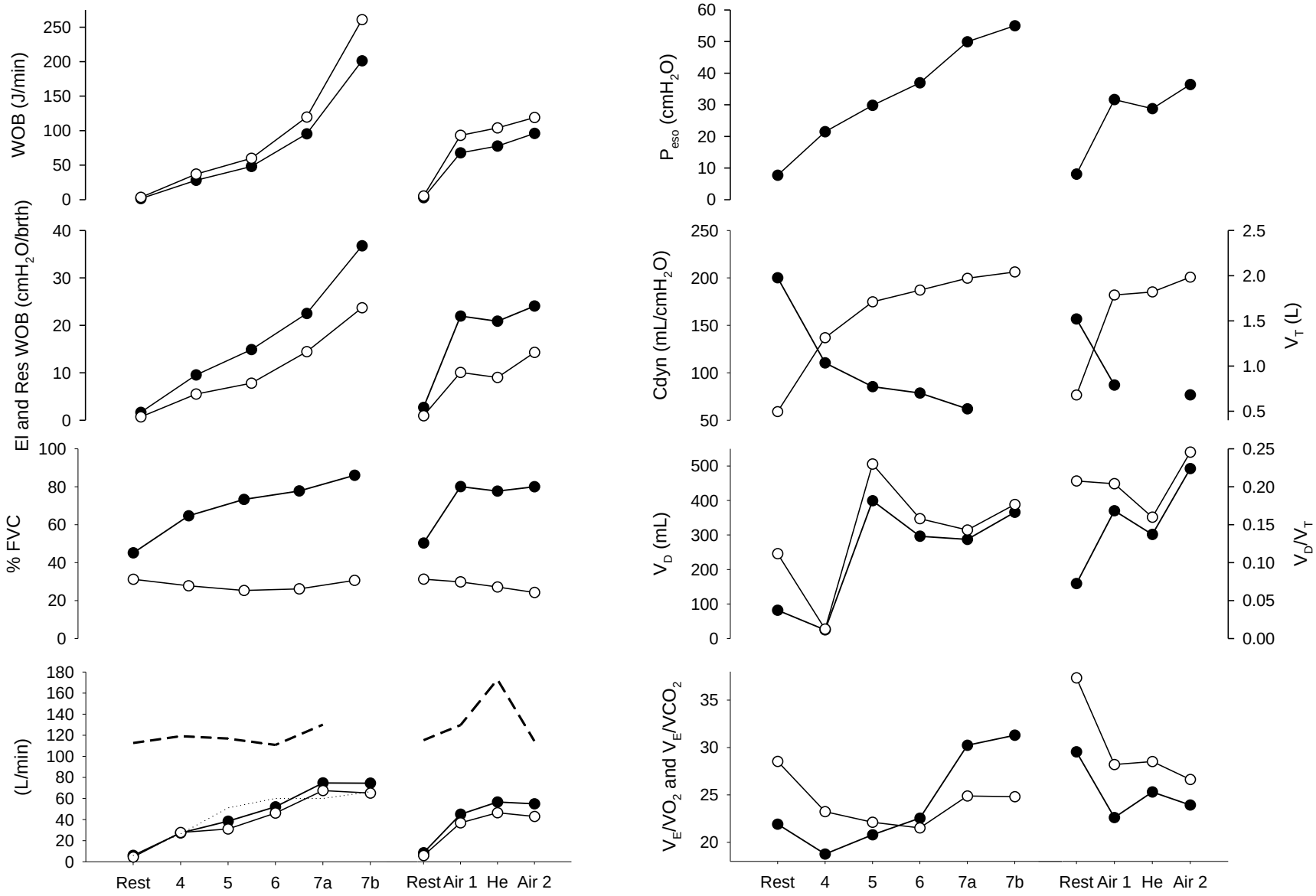


Figure 130- VW, respiratory mechanics



Appendix B: Questionnaire

Mechanical constraints in exercise induced arterial hypoxemia in young healthy women

Subject Identifier:

Medical History

1. Are you currently taking any medications (excluding oral contraceptives)?

   Please List: _____

2. Do you currently smoke? YES/NO

3. Are you a past smoker? YES/NO

4. When was the last time you had a cold? _____

5. Do you have asthma, other lung problems or significant illness? Please List:

_____

6. Have you had recent nasopharyngeal surgery? YES/NO

7. Do you have an ulcer or tumour in your oesophagus? YES/NO

8. Are you sensitive to local anaesthetics or if you have allergies to latex? YES/NO

9. Do you have a history of bruising easily or having blood clotting problems? YES/NO

10. Are you currently taking any anti-inflammatory medication? YES/NO

Physical Activity History

Type of Physical Activity: _____

Average Duration: _____

Average Frequency: _____