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Altitude Physiology Research Laboratory: Equipment and Setup

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Final Report

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16. Abstract

This document describes the testing systems and data collection equipment used by the Environmental Physiology Research Team of the Civil Aerospace Medical Institute in the performance of their research activities addressing human safety in civil aviation operations.

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"Space Cowboys"

1.0 Laboratory Introduction

The Federal Aviation Administration's (FAA) Altitude Physiology Research Laboratory (APRL) is located at the Civil Aerospace Medical Institute (CAMI) in Oklahoma City, under the charge of the Protection & Survival Research Branch of the Aerospace Medical Research Division of CAMI. Altitude Physiology Research Laboratory personnel perform highly specialized physiological research to provide evidence supporting safety in aviation. This research focuses on the physiological impact to the human element in the system, posed by participation in aviation and aerospace travel. The results of this research may indicate that more restrictive or more relaxed regulations are necessary, in order to maintain the level of safety in aerospace travel, without adding an unacceptable level of risk. This allows the FAA to more readily adapt to and encourage new and innovative technologies, while preserving the safety of humans in the aerospace system.

Figure 1: APRL "Space Cowboys", preparing the FAA for the future of Aerospace Travel

Advances in the air traffic control infrastructure, aerospace vehicular designs, avionics, and medicine may all lead to additional requests for APRL research. Questions regarding the environmental impact of aerospace travel or other flight safety concerns during changing or extreme environmental conditions may lead to requests for research from APRL scientists. For example, they have been requested to investigate concerns such as the impact of programs to control aircraft noise, operations in volcanic fallout conditions, and to assist in determining the efficiency of bolus-delivery of oxygen or the impact of low-flow oxygen systems in hypoxic-hypoxia recovery.

The APRL supports the FAA's safety mission by helping to balance the risks of aerospace travel against the need and desire for new innovations and increased efficiency. The results of this research allow the FAA to balance its guidance and regulatory framework and to maintain our safety culture without sacrificing innovative opportunities.

Historically, APRL personnel have conducted research related with and around a physical condition known as hypoxic-hypoxia, which is low oxygen content in the blood via gas diffusion through the lungs. Blood oxygen saturation (denoted SaO_2) is the standard physiological element traditionally measured to determine the safety of aviation and aerospace operations. The risk to human health associated with low SaO_2 is significant under normal circumstances, where persistence of a SaO_2 below minimum levels will damage the vital organs of the body, including the heart and the brain. However, human cognitive function can be significantly impaired at SaO_2 levels above and with a shorter duration than would be expected to cause permanent damage to vital organs. This cognitive impairment may pose a significant risk to human health and safety when experienced by someone who is actively piloting an aircraft or aerospace vehicle. For these reasons, most APRL research involves the monitoring of SaO_2 levels and measuring human performance under varying environmental conditions.

Figure 2 provides an illustration showing some of the areas to monitor or examine for functional changes associated with human performance degradation or physiological reactions to exposure to reduced SaO_2.

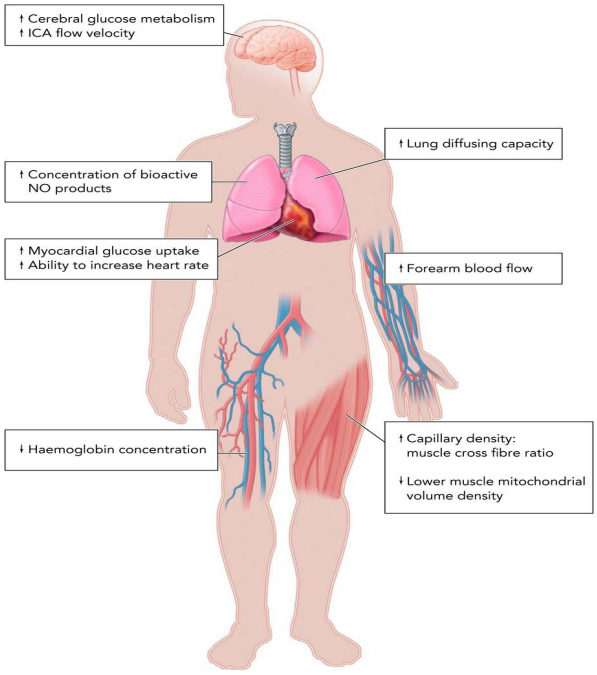

Figure 2: Illustration showing some of the functional areas of the human body to monitor for physiological changes

Mitigating the risks associated with low SaO_2 seems simple. When traveling in high-altitude environments where there is a chance of becoming hypoxic by not having enough oxygen to breathe, just provide high-concentrations of oxygen to people and they should be fine. This line of thought leads to an expectation that the science to mitigate this risk should have been settled and documented through testing long ago. In practice, there are still many unanswered questions with regard to hypoxia and hypoxic onset, and technological advancements offer opportunities for additional research to see if they can provide additional information or efficiencies in this area.

Much of the early research into the physiological effect of high altitude aerospace and aviation travel was done with primates, and many interesting questions were answered through this research. These results have been documented and used to improve aerospace flight safety. Figure 3 shows a picture of one of the early test subjects.

Figure 3: One of the early test subjects for SaO_2 research

After data was collected via animal studies on the safety of high altitude human flight, physiological studies were undertaken on humans to investigate new and innovative methods of oxygen-delivery. Figure 4 shows an example of how creative the original physiological researchers had to be to collect data. Here, a steady-state respiratory subject's breath is captured in a hot-air balloon to undergo analysis back in the laboratory where it will be analyzed to quantitatively discern gas-composition during exercise at ground level. They are at approximately 9,000 feet above Mean Sea Level (MSL) and the subject is breathing in air from his surrounding environment, metabolizing it, and expelling the byproducts. Many airmen flying at 9,000 feet above MSL or Flight-Level (FL) 90 experience mild symptoms of hypoxia significantly affecting night-vision which has been linked to runway, approach, and landing mishaps. The FAA investigates such mishaps, and the conditions under which they arise, so that scientists can focus on why such mishaps occur and suggest mitigations so they are less likely to occur in the future.

Figure 4: Experimental design example for physiological research

As aviation technology improved, the demand for humans to fly at higher altitudes increased. This, in turn, increased the need for physiological research to protect the passengers and crew on-board higher altitude flights, and to improve their comfort.

Figure 5: Technological advances and innovations lead to additional research to ensure continuity of safety

Performance can degrade rapidly as a person becomes hypoxic, and research has shown that it can degrade significantly without the knowledge of the person whose state has been altered. While this is a concern for passengers and aircrew alike, the risk is much greater when pilots become hypoxic. Pilots pose a greater risk since they are more likely to crash an airplane while their performance is compromised. This risk is managed by training pilots to recognize hypoxic onset, and requiring they use supplemental oxygen when flying above certain flight levels. Figures 6 and 7 below show examples of devices meant to supply only the amount of oxygen needed by the user, which were tested through research funding from the FAA at the APRL facilities.

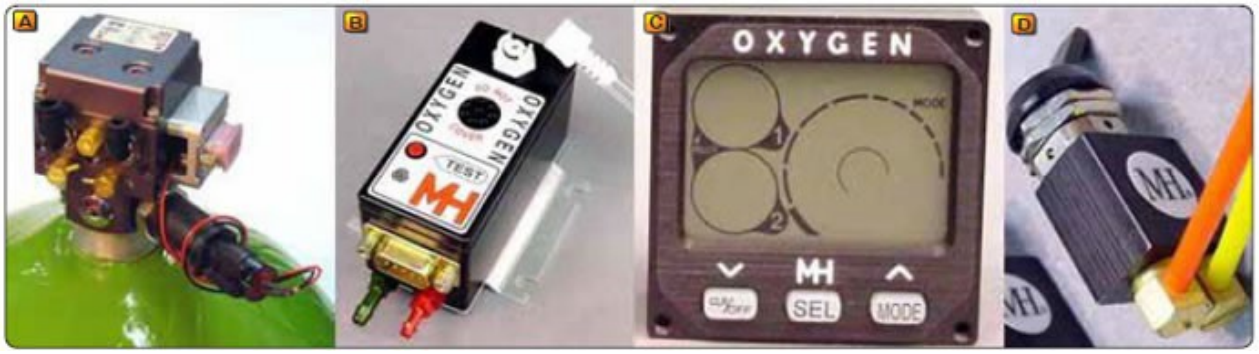

Figure 6: The key components of a built-in electronic pulse demand oxygen metering system: (A) electronic regulator, (B) oxygen station distributer unit, (C) common/display unit, (D) emergency bypass switch

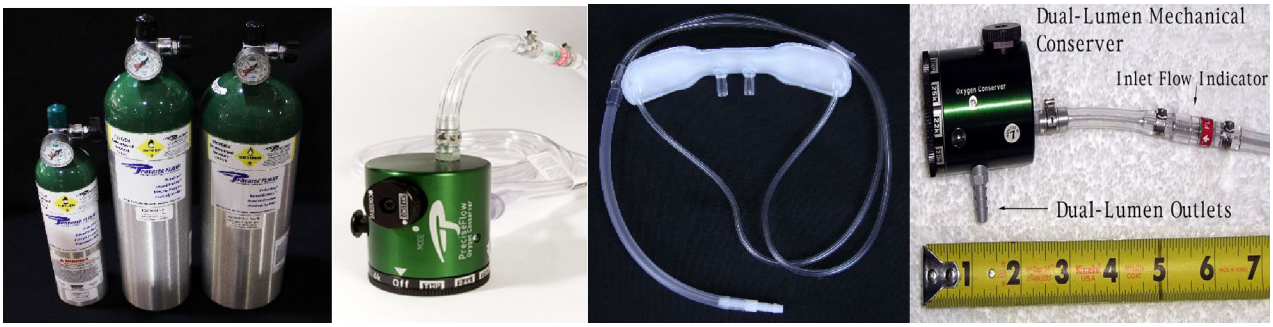

Figure 7: Second example of an oxygen metering system tested in the APRL

These devices were developed, as many are continually developed, with the intention of providing cost savings to aircraft operators through reducing the weight, space, and cost associated with the amount of supplemental oxygen that must be carried on-board aviation flights. The amount of oxygen that must be carried on aviation flights is determined by the amount thought to be necessary to protect the health and safety of passengers and aircrew if a rapid decompression event were to occur during their scheduled flight. These reductions would increase the efficiency of the operators using them, which would lead to an increase in profit margins.

Altitude Physiology Research Laboratory personnel conduct physiology research using noninvasive state of the art technology to identify the minimal amount of supplemental oxygen that operators can carry to ensure that aircrew and passengers enjoy safe operation and passage while travelling in the national airspace system. We deliver experimental design, develop research protocol approved by the FAA's Institutional Review Board for the protection of human volunteer research subjects, fabricate experimental apparatus, and generate data files for analysis. Our scientists interpret this data, providing conclusions and/or recommendations to external stakeholders and in research publications. Figure 8 shows a physiological monitoring setup connecting to one of our test subjects. In this particular setup, we were measuring electroencephalogram (EEG), transcranial blood flow, deep vein oximetry, respiration via breath-by-breath (BxB) analysis, blood pressure (BP), carbon dioxide (CO_2), pulse oximetry (SaO_2) and hematocrit. Measurements were recorded during simulated flights, and in some cases hematological specimens were drawn prior, during, and post exposure to simulated normobaric altitudes in excess of 34,000 ft. above MSL.

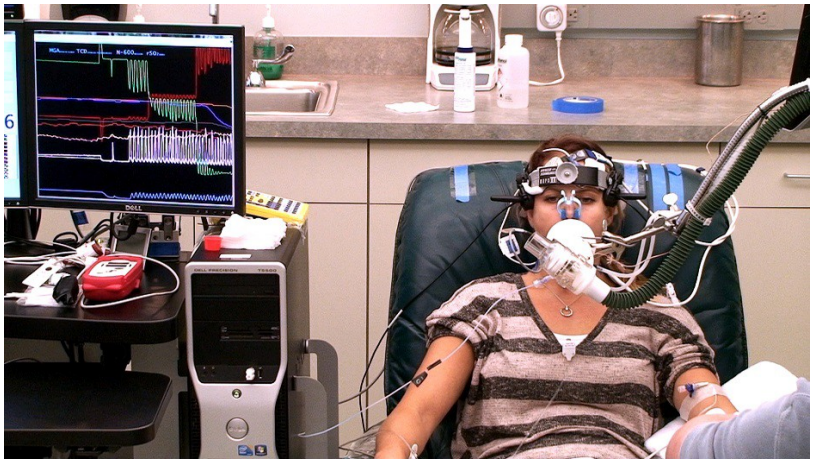

Figure 8: APRL Noninvasive Physiological Subject Monitoring

The devices used to monitor and collect data from our test subjects varies from project to project and has evolved over the years. However, there is one device used in the APRL consistently throughout the past quarter of a century. The MGA (medical gas analyzer) is used to accurately measure gas concentrations in room air, as well as the gas composition of the breath-by-breath inspirations and expirations of human test subjects.

2.0 APRL Physiological-Monitoring

Altitude Physiology Research Laboratory personnel routinely measure many parameters during research testing. The rationale for the monitoring and recording of the data serves dual purposes, some parameters are monitored to ensure the continued safety of the human test subjects and others are recorded to gather data from the test itself. Generally, data is gathered to detect any physiological changes that may indicate a change in the cognitive capabilities or performance of the test subjects. These parameters involve the process of breathing, characteristics of the blood and its flow through the tissues of the body, as well as information about the health or functioning of the brain during testing. Altitude Physiology Research Laboratory personnel collect physiological parameters as documented in this section and use the laboratory equipment listed when conducting research.

2.1 Measurement of inhaled atmospheric and/or end-tidal air composition

A Perkin-Elmer Medical Gas Analyzer, MGA-1100 (manufactured by PerkinElmer Life and Analytical Sciences, Inc. Waltham, MA) is used by research physiologists at APRL for near real-time, quantitative measurement of the percentages of atmospheric gases (Ar, N_2, O_2, CO_2, and H_2O). Research physiologists typically need to know the quantity of each of these gases present in the room air surrounding research subjects, as well as their percentages in the gas composition of the subject's inhaled and exhaled air. The measurement of other gases such as SF_6, a smoke mimicking non-toxic gas, and He_2 is optional, and its use in the experiment will be determined based upon the needs of the specific study. This recorded data will be compared to other data recorded while varying conditions as required by the study, such as testing to measure continuity of cognitive performance.

The capabilities of the MGA-1100 have made it the go-to device used by research physiologists at the APRL to measure the composition of both BxB and environmental atmospheric gases. The MGA-1100's ability to deliver quantitative values in near real-time allows temporal matching between different recorded data streams, thus allowing insight into possible correlation and possibly causality determination between different recorded events. Simultaneous multipoint sampling (SMS) allows monitoring of environmental gas compositions both inside and outside a pressure-vessel as well as inspired in vitro, tracheal inhalation and exhalation (end-tidal) gas compositions while the data is being displayed and/or recorded. This enables the comparison of various data streams recorded during testing, which provides flexibility in experimental designs and analysis capabilities. The MGA mass-spectrometers provide the capability for the APRL scientists to design experiments to determine if new, innovative, and more efficient equipment designs can provide an equivalent or better level of passenger safety when compared to legacy equipment options. This determination and subsequent recommendations are offered to aircraft designers and operators via regulatory requirements and other guidance provided by FAA.

The MGA-1100 can also record data at varying sample-rates, i.e. ~ 5Hz – 1KHz. This flexibility allows tailored data-analysis. The APRL's data acquisition (DAQ), visual monitoring, and subsequent recording of analog signals from all monitoring equipment is consolidated and displayed by configuring and using Laboratory Virtual Instrument Engineering Workbench (LabVIEW) by the National Instruments Corp., of Austin, TX.

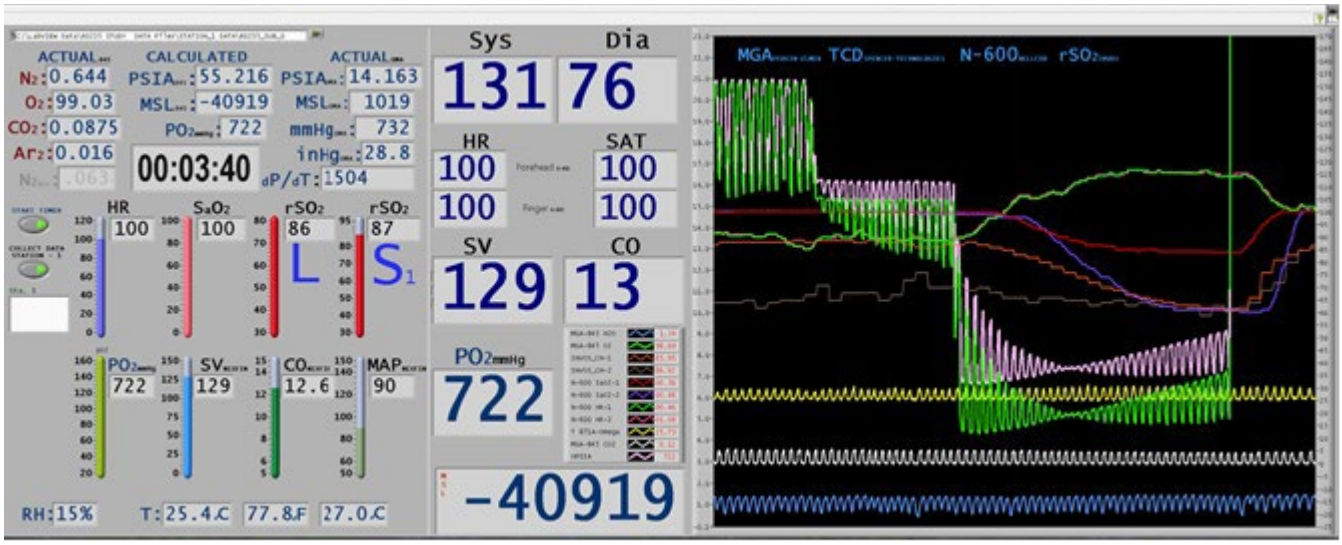

Figure 9 shows an example of the APRL's use of LabView to monitor physiological parameters during research. Readings for Nitrogen (N_2), Oxygen (O_2), Carbon Dioxide (CO_2), and Argon (Ar) are taken using an MGA-845. Readings from clinical equipment are taken and incorporated into the display as heart rate (HR), arterial blood oxygen saturation (SaO_2), cerebral oxygen saturation (rSO_2), cardiac stroke volume (SV), cardiac output (CO), and mean arterial blood pressure (MAP). Partial pressure of oxygen denoted here as PO_2 is derived through an algorithm generated from signals of the MGA combined with the actual pounds per square inch absolute (PSIA) readings. Values recorded during the experiment are shown relative to time by the graph on the right. The legend, just to the left of the lower portion of the graph, denotes many of the signals being monitored throughout the roughly six minutes visible on the graph. The graph allows physiologists to make out the BxB traces, the nPSIA representing the partial pressure of oxygen (pO_2), and the terracing in the graph representing the altitude profile used in the experimental protocol, i.e. in the figure, starting at the left, the experimental subjects were at ground-level for approximately two minutes. This is followed by an increase in altitude to 8K MSL for approximately two minutes. The almost vertical depression mid-graph is the simulated rapid decompression, and the up-slanted segment is the representation of the FAA-mandated three minutes that a pilot has to dive the plane into an environment that is capable of sustaining life.

In order to configure LabVIEW for proper display and recording of the testing environment, each signal needed for monitoring, recording and analysis for the test, from each piece of monitoring equipment is wired into a bus interface, which is connected to a dedicated personal computer (PC). Each signal wired into the interface will then need to be properly conditioned in the LabVIEW interface, through filtering and scaling each incoming signal. Each incoming signal will then be digitized and passed into the attached PC where they get consolidated, along with other signals, and presented via graphical display and recorded in two dimensional arrays for later analysis. This same general LabVIEW setup process is used by the APRL to record data for many different studies, using many different types of monitoring equipment, and in many different environments, i.e. the hypobaric-chamber. The signals from the MGA-1100, along with any other monitoring devices deemed necessary for a particular study are wired into the LabVIEW interface and then configured for proper display and recording of data.

2.2 PSIA, the MGA-1100 and Altitude

Altitude-physiologists commonly use PSIA (pounds per square inch absolute) units when referring to altitude above any specific mean-sea-level (MSL). Instruments measuring PSIA are mechanical in nature with calculations calibrated via National Institute of Standards and Technology (NIST) traceable standards. Algorithms are coded in National Instruments (NI) LabVIEW graphical programing language to ensure the signal measurements received are scaled and interpreted correctly for display and recording in the graphical and digital interfaces for ease of monitoring and analysis.

United States Standard Atmosphere, 1976 (USSA1976) constants are used in equations to scale the measurements generated in part by the mass spectrometer during research studies at the APRL. This atmospheric model provides calculations based upon changes in pressure, temperature, density, and viscosity of the Earth's atmosphere over a range of altitudes.

Our air, or atmosphere, is treated as a homogeneous mixture of several constituent gases. There are several trace gas species, or gases other than nitrogen and oxygen, that make up less than one percent of the total volume of air. The four major gases constituting Earth's atmosphere are nitrogen and oxygen, with the primary trace gases carbon-dioxide and argon. A typical example of a breakdown of the relative concentrations of these gases found in our atmosphere would be N_2@78.08%, O_2@20.95%, CO_2@0.004% and Ar@0.934%, with the remaining monoatomic gas species and molecules, which typically include helium (He), neon (Ne), krypton (Kr), xenon (Xe), methane (CH_4), and hydrogen gas (H_2), constituting less than one percent of the overall atmosphere.

Having the ability to compare the calculated altitude from measurements taken during testing against the barometric readings of each altitude studied is vital for the researchers to use to validate the actual testing conditions. This validated information is key to the proper interpretation of testing results, and the accuracy of the resultant conclusions and recommendations. Even though the hypobaric chamber utilized by APRL personnel is controlled via a NIST traceable instrument, it uses valves to increase and decrease vessel pressures according to a predefined profile specific to the experiment, there is still an element of uncertainty as to the exact instantaneous pressure that it has achieved at any given point in time. This uncertainty, combined with the fact that the breathing of human test subjects in the hypobaric chamber can change the gas mixture present inside the chamber, increases the need for independent measurements during testing. LabVIEW allows a programmer to apply the value of known percentages of gas, (i.e. O_2@ 20.95% for Earth's atmospheric oxygen concentration up to ~ 65K ft. MSL) to derive correctly scaled values from measurements such as the end-tidal partial pressure of oxygen during BxB experiments or the oxygen concentrations present within the hypobaric chamber itself. These independent measurements, used to verify the gas composition and effective barometric pressure inside the chamber continuously during the test, are crucial to proper interpretation of the physiological data recorded during the test.

2.3 Physiological Implications of Oxygen Saturation

There is still some level of disagreement in the scientific community as to the exact physiological progression that leads to loss of self-awareness and degraded capability to make decisions, which can lead to compromised performance on even basic tasks, as is experienced by aviators becoming hypoxic. Even

though the exact details and specific mechanisms may still be open to some level of debate, there is general agreement that part of the progression toward this debilitating condition is the loss of oxygen in blood traveling throughout the body. It follows, then, that measuring arterial blood gas saturations of oxygen (SaO_2) is the most frequently used indicator referenced by physiologists to indicate the level of an individual's awareness or consciousness. This value can be misleading in rare circumstances, but for the majority of instances it remains a reliable single source. Many evidence-based researchers do not rely exclusively on SaO_2 concentrations to argue the level of an individual's consciousness, but arterial blood-gas oxygen concentrations are always included when stating the level of consciousness of an individual.

The rationale for associating an individual's SaO_2 values with consciousness is that SaO_2 typically tracks very closely with hemoglobin (Hbg) levels, which indicates the oxygen carrying capacity of blood. Since Hbg distributes oxygen from the lungs throughout the body and into the tissues, and an adequate amount of oxygen must be provided to the brain tissues for optimal decision-making capability, Hbg O_2 saturation is used as an indication of how efficiently a human is operating. Although these assumptions may generally be true, it is not always the case. In some cases, subjects with a low number of oxygen-carrying blood cells or Hbg, may reflect high oxygen concentrations of SaO_2 but will not be able to provide a sufficient amount of oxygen to the tissues and sustain correct brain function. This condition would result in poor reasoning and impaired decision-making capacity in a test subject, while their SaO_2 appears normal.

Altitude Physiology Research Laboratory personnel use an MGA-1100 to measure and report the air readily available to subjects, the composition of the inhaled gases as they are entering the subject's trachea, as well as the gas compositions of their expired air. This allows a level of flexibility in the design of the experiments and provides a level of integrity to the collected data, which allows other measurements in the experiment to be temporally synchronized to changes in measured gas compositions, which allows more accurate interpretations by APRL scientists. This cross-validation, which is built into the APRL's standard experimental design through the use of the MGA-1100, various signal interfaces, various sensors, and LabVIEW, provides a basic layer of integrity to any experiments conducted in the APRL. This approach allows the researchers to fully focus on the question at hand. Often, the basic question is if a newly proposed design for in-flight supplemental oxygen delivery is predicted to provide the same or a better level of protection to humans involved in aerospace travel.

2.4 Other Gas Concentrations

As mentioned above, the MGA is capable of separation and quantification of several gas-species or molecular compounds including nitrogen, oxygen carbon dioxide, water, argon, helium, hydrogen, and sulphur hexafluoride along with several anesthetic gaseous compounds including nitrous oxide and halogenated ethers.

2.5 BxB Ventilation

Ventilatory flow, defined as ambient temperature, pressure and water saturation (ATPS), and respiratory rate, is measured with a heated, low dead-space pneumotach and acquired at a sampling rate of 1KHz on

a personal computer for subsequent analysis. Tidal volume is calculated on a breath-to-breath basis after digital integration of the flow signal at actual barometric pressure using LabChart Pro software V.7 (AD Instruments, Colorado Springs, CO).

2.6 Resting Oxygen Consumption (VO_2)

Resting oxygen consumption (VO_2) is measured immediately prior to normobaric hypoxia exposure. Breath-by-breath respiratory gas exchange may be measured via VMax 229 Encore Respiratory Diagnostics System (Care Fusion, Inc., Yorba Linda, CA), using a flow-through mask. This system analyzes expired gas for oxygen concentration using a paramagnetic oxygen analyzer and for carbon dioxide concentration by using a nondispersive infrared analyzer. Gas analyzers are calibrated before each measurement using three known standard gas concentrations (16% O_2, 4% CO_2; 26% O_2, 0% CO_2; room air 20.94% O_2, and 0.05% CO_2).

Calibration is complete when gas analyzers measured oxygen and carbon dioxide concentration within ±5% of expected values. Measurements are considered complete once a 5-min steady-state period is achieved. VO_2 values are recorded every minute, and then averaged over the entire epoch. The duration of the measurement is variable depending on how long it takes the subject to reach stable values (5 consecutive VO_2 values differing by 2% or less). The VMax 229 is connected to an IBM-compatible personal computer for management and storage of data by using the CardioSoft/VMax Vision software for Windows (version 6.51, Care Fusion, Inc., Yorba Linda, CA). In practice, subjects are tested in the same sitting position as a subsequent hypoxia exposure.

2.7 Oxygen Flux Rates

Breath-by-breath oxygen consumption and loss (± VO_2) are measured during the entire profile. Inhaled and end-tidal O_2, CO_2, and N_2 percentages, inhalation volume (V_{in}) converted to standard temperature pressure dry (STPD) volumes, and respiratory rate are recorded. V_{in} was adjusted for both anatomic and spirometry apparatus dead space. Anatomic dead space was estimated in each subject as a function of height using the relation $V_d = [7.585*(height^{2.363})]*10^{-4}$, established by Hart et al. (1963; r= 0.917)). VO_2 was then computed using the Haldane transformation (Haldane, 1912 & 1922) of the Fick principle through the following equation:

$$VO_2 = (V_{in} * \%O_{2in} - \left[\left(\frac{\%N_{2in}}{\%N_{2exp}} * V_{in}\right) * \%O_{2exp}\right] * bpm$$

2.8 Data Acquisition and Recording Scheme

Analog signals from monitoring equipment except ventilatory and ECG sensors are digitized at 20 samples/second and recorded with a custom-built LabView data acquisition instrument (National Instruments Corp., Austin, TX). Ventilatory signals (flow, volume, and rate) and ECG are digitized at 1 KHz and recorded using a modular Bio Amp (Powerlab Model ML880, AD Instruments, Bella Vista,

Australia). Data files are synchronized *post hoc* by introducing a generated square wave with a function generator (Hewlett Packard model 3310B; Palo Alto, CA) into both data acquisition systems during experiments.

2.9 Electroencephalogram (EEG) BIS

Four-channel EEG is monitored via Bispectral Index (BIS), manufactured by Aspect Medical Systems, Inc., at One Upland Road Norwood, MA 02062 United States. It is thought that the BIS monitor could be used to detect the onset of hypoxia. However, even if it appears to be an accurate detector of hypoxic onset, the proof of this would be difficult, since the details of the algorithm used to create the BIS index have not been disclosed by its developer. The reliability of BIS results has been questioned, in part, because its calculation cannot be proven to rely on any underlying physiological model of how the brain functions, nor how awareness is generated. The APRL is developing credibility with the results of this instrument by correlating its results with the results of other, more globally accepted physiological data used to detect hypoxic onset. Ideally, this would provide a reliable addition of noninvasive data to substantiate both onset and, to some degree, depth of hypoxia being exhibited by subjects.

2.10 Hemoglobin Oxygen Saturation (SaO_2) and Heart Rate (HR) via Pulse Oximetry

Percent hemoglobin saturation is expressed as the ratio of oxyhemoglobin to reduced hemoglobin in arterial blood. It is measured at the APRL with a pulse oximeter sensor clamped to the index finger of a subject's non-dominant hand and with a forehead sensor placed above the right supraorbital ridge. SaO_2 and HR are fed into the dedicated monitoring device provided, which computes the scaled values from the sensor data it receives (Nellcor Model N600-X &_or N200, Covidien Corp, St. Louis, MO) and displays it as percent saturation and beats per minute (bpm), respectively, on its graphical display.

2.11 Finger Plethysmographic - Hemodynamic Variables

Beat-to-beat monitoring of arterial blood pressure and its first derivative is employed using finger photoplesthysmography (NexFin, Edwards Life Sciences Corporation/BMeye of Irvine, CA). In practice, a finger cuff is attached to the middle phalanx of the right third finger to measure finger arterial blood pressure. Stroke volume is determined by a three-element model of arterial input impedance (Nichols & O'Rourke, 1990). Cardiac output is calculated as the product of stroke volume and heart rate.

2.12 Intracranial blood flow

During experiments at the APRL, continuous mean, systolic, and diastolic blood flow velocity in the right and left middle cerebral arteries (MCAs) are measured in all subjects. Backscattered Doppler signals, available as analog voltages, are continuously and simultaneously monitored by means of an ST3 pulsed digital transcranial Doppler (TCD) system (Model # PMD 150 by Spencer Technologies of Seattle, WA).

Ipsilateral MCA velocity measurements are made using 2- MHZ probes via the posterior temporal windows immediately above the zygomatic arch. Middle cerebral arteries are identified bilaterally within depths of isonation between 35 to 56 mm.

2.13 Electrocardiograph (ECG)

Electrocardiograph is obtained with a modular Bio Amp Powerlab Model ML880 by AD Instruments, of Bella Vista, Australia. ECG is digitized at 1 KHz and recorded by the Bio Amp.

2.14 Serum S100b Measurements

To confirm that the hypoxia exposures are not resulting in clinically significant brain anoxia, S100b biomarker levels are measured. Whole blood samples are collected from an indwelling catheter placed in the left antecubital vein in Serum Separator Tubes (BD Vacutainer® SST™ 367986; BD, Franklin Lakes, NJ, USA), typically at four times, designated "Baseline," "T2," "T3," and "T4." The first sample is collected immediately before altitude exposure. Remaining samples are collected immediately after exposure, 15 minutes after exposure, and 2 hours after exposure. S100b concentrations are determined from 50uL/well in triplicate on a custom Milliplex® Map magnetic bead sandwich ELISA kit (Cat. # HNDG4MAG-36K, Millipore Corporation, Billerica MA) measured on a BioPlex 100 by BioRad Laboratories in Hercules CA, according to the manufacturer's recommended protocol and instrument settings.

2.15 The Normobaric Breathing Apparatus

Normobaric exposures are accomplished using a reduced oxygen breathing device (ROBD) by Environics, Inc. of Tolland, CT. The ROBD uses thermal mass flow controllers to mix breathing air and nitrogen to produce the sea level equivalent atmospheric oxygen contents for altitudes up to 35,000 ft. The device is calibrated on a primary flow standard traceable to the NIST. The ROBD outlet hose is connected to the inlet port on a two-way non-rebreathing valve made by Hans Rudolph, Inc. of Shawnee, KS, having three ports. The inhalation and exhalation ports each have a unidirectional diaphragm that directs flow to and from the mouth. This valve is connected in series with a heated (37°C), low dead space pneumotachometer that has a linear voltage output from 0 to 800 L/minute. The valve is a model 3813A series by Hans Rudolf, with dead space of 87.8 ml and flow resistance from 0.3 to 8.2 cmH2O/80-800L/ min). The pneumotachometer is connected to a differential pressure research pneumotach system (model RS100HR; Hans Rudolf, Shawnee, KS). A spirometry microbial/moisture filter mouthpiece by Care Fusion, Inc. of Yorba Linda, CA, with dead space of 50 ml, is attached to the pneumotachometer. Total dead space in the apparatus was 223.1 ml. A sampling line was connected to a mass spectrometer (model MGA-110; Perkin-Elmer, Waltham, MA) from a port close to the non-rebreathing valve, monitoring the composition of inhaled and exhaled gasses.

As an orientation, all subjects breathe ground-level ambient air through the circuit for two minutes prior to an altitude exposure. The apparatus has negligible physiological effects as evidenced by the lack of changes in oxygen saturation or end-tidal CO_2 concentrations.

2.16 The Flow Volume Simulator (FVS) Apparatus

Hans Rudolph, Inc. (HRI) Series 1120 Flow / Volume Simulator (FVS) is a servo motor driven piston pump that can be used for testing spirometry and respiratory values. It is designed to be used in product development and manufacturing test applications. It is used in the APRL to mimic human breathing in normobaric or hypobaric testing. The FVS operates in three modes. The exhale waveform mode is used to test spirometry devices using the American Thoracic Society, (ATS) waveforms, peak flow waveforms or custom waveforms. The steady flow mode can be used to generate steady state flows over a wide range of flow rates. This mode can be used to test and calibrate flow meters and other devices. The breathing waveform mode can be used to produce a continuous inhale / exhale flow waveform that closely simulates breathing. All of the modes provide graphical representation for flow and pressure signals via proprietary software. Data collection during testing can be saved to a file for additional analysis. Built-in pressure sensors measure the barometric pressure and cylinder pressure during experiments. Pressure data is used internally to correct the calculated flow for gas compression. Another differential pressure sensor is provided for connection to pressure taps on or near a device under test. This pressure reading can be used to determine the flow resistance of the device being tested.

An optional HRI pneumotach can be attached to the outlet of the FVS. A pressure sensor is provided to measure the differential pressure at the pneumotach so that a measured flow signal can also be graphed and recorded. Two graphs are used to display on a PC, the flow and pressure data that is collected. The flow graph can display the calculated flow based on the piston position, measured flow from the optional-pneumotach, and the target flow from the desired waveform. The pressure graph can display the cylinder pressure and auxiliary pressure signals. Both graphs can be dynamically scaled and panned to allow a user to zoom in and view specific parts of the waveforms or see the complete waveform. Printouts of the graphs can be made, if needed. The optional pneumotach is used at the APRL to generate analog signals, which are conditioned and digitally recorded to a PC using a custom-built National Instruments data acquisitioning system.

Altitude Physiology Research Laboratory personnel designed and developed an experiment using the FVS to emulate a pilot breathing on a mask/delivery system while in a simulated situation: an aircraft with CO_2 generated by degrading dry ice during transport of medical specimens. The model demonstrated that under current cabin ventilation standards, the dry ice sublimed into a lethal level of carbon dioxide within the confinement of the cabin. Adding to that scenario is the temperature outside, if it is cold, air entering into the aircraft cabin would be limited; and thus the situation could end in tragedy. If pilots are lax about being safely protected, they could become insidiously affected and ultimately lose consciousness. The FVS provided a means to accurately collect data valuable to the flying industry for any situation using dry ice for refrigeration in small confined areas without actually exposing a human-subject to the noxious environment.

2.16.1 FVS SPIROMETRY TESTING

In the exhale waveform mode, the FVS will generate ATS waveforms for testing spirometry products. Custom waveforms can be created using supplied utilities. The waveforms can be scaled up or down to adjust the waveform for different flows and volumes. Different starting positions for the piston allow the user to change the internal volume.

2.16.2 FVS PEAK FLOW METER TESTING

The waveforms defined by EN 13826 for testing peak flow meters can be produced. The simulator has been tested by Physikalisch-Technische Bundesanstalt (PTB) in Berlin and certified for use in testing peak flow meters. PTB is the German national metrology institute providing scientific and technical services.

2.16.3 FVS STEADY FLOW

The steady flow mode can be used to check the calibration of a flow meter or provide a constant flow for spirometer calibration. The volume delivered can be adjusted up to 8.5 liters. The desired flow rate can be set from 0.1 to 16 liters per second. The user can select either inhale or exhale as the flow direction. The pressure and flow data collected during the test is displayed on the graphs after the test.

2.16.4 FVS BREATHING WAVEFORM

A breathing waveform can be created from the FVS, using the supplied utilities and then used to create a simulated breathing flow pattern. The amplitude and breath rate are adjustable, so different breathing patterns can be simulated with the same waveform file. This approach is used at the APRL for testing O_2 delivery equipment.

Altitude Physiology Research Laboratory personnel are developing experimental methods to use the FVS for a situation where a passenger exposed to a rapid decompression attempts to don a mask, but takes one breath of the decompressed cabin air before successfully getting the mask on. We believe that at higher flight levels this could render the person unconscious before recovery from the protective O_2 concentrations being provided by the mask can occur. Altitude Physiology Research Laboratory personnel have also studied the performance of pulse oxygen systems with the FVS. Similar modeling will look at performance of masks that have various methods of delivering O_2. Utilizing the FVS facilitates modeling and simulation activity without endangering humans through unnecessary exposure to extreme hypobaric conditions. Research utilizing human subjects provides the most accurate results when collecting physiological data. Therefore, mathematical models should only be used when they have been thoroughly validated through the use of data collected from human subjects, where possible, with levels of manageable risk.

2.17 Medical Screening

For some tests using human subjects, the APRL scientists conduct medical screening prior to an experiment. When necessary, subjects undergo a complete pulmonary function test (PFT) using a VMax 229 Encore Respiratory Diagnostics System by Care Fusion, Inc. of Yorba Linda, CA, and a 12-lead electrocardiogram (EKG) by Page Writer Xli, a Hewlett Packard Company located in Palo Alto, CA.

Typically, pulmonary function testing is performed with the subjects in sitting posture using a mouthpiece (dead space = 50 ml) and a nose clip. The system calculates the diffusing capacity of the lungs for carbon monoxide (DLCO) using standard Jones-Meade criteria (Jones & Meade, 1961) and an anatomic dead space algorithm (Hart, Orzalesi & Cook, 1963). DLCO measurements are adjusted for the subject's own total hemoglobin value (Masimo Rainbow SET®, Masimo, Irvine, CA) and then converted to DLO_2 using the method of Comroe et al. (Comroe, Forster, Dubois, Briscoe & Carlsen, 1962).
The system is calibrated before each experiment by using a certified (± 3%) 3-liter syringe. Additionally, each subject is given a 6-min, sub-maximal Åstrand Bike Test (Åstrand & Ryhming, 1954) to provide an estimate of VO_{2max}. The test is conducted on a Velotron Dynafit Pro computer-controlled, precision electronic bicycle ergometer/trainer (Racermate, Inc, Seattle. WA). The energy output in watts of the rider is monitored with proprietary software from Racermate of Seattle, WA, which has a self-calibrating function. Heart rate is recorded continuously and is averaged during the last minute of the test. These tests, along with a medical history questionnaire, are used as a screening tool by the Medical Monitor, a physician, to rule out any evidence of disease that would constitute unacceptable risk.

2.18 Regional Oximetry; INVOS - Cerebral/Somatic Tissue Perfusion System

The INVOS™ system is used to provide information about the test subject's gas exchange during blood transport. INVOS is non-invasive and provides information about a test subject's microvasculature in order to give information about blood volume and transport. Through measuring blood oxygenation in the microvasculature, insights are provided on perfusion adequacy. Using additional sensors available for the INVOS, information about perfusion distribution across the brain and the body can be gathered for human test subjects.

INVOS™ technology measures both venous and arterial blood and can therefore provide venous-weighted percent saturation and other metrics such as oxygen supply versus demand and venous oxygen reserve. Venous oxygen reserve is the oxygen remaining after extraction by tissues and vital organs. Decreases in venous oxygen reserve can warn of developing pathology and deteriorating patient condition. INVOS provides continuous, real-time adequacy of perfusion data in up to four sites.

3.0 Notes and Tips from Past Tests

3.1 Experimental Procedure for the APRL's Rapid Decompression (RD) profile using the ROBD breathing Device

The percentage of oxygen the device delivers can be adjusted to account for the differential effects of water vapor pressure on inspired gas, using the technique of Conkin (2011). To simulate the inspired partial pressure of O_2 (PIO_2) seen at the barometric pressure corresponding to a rapid decompression (RD) of 35,000 ft, one can set the ROBD to deliver 4.05% O_2, which produces an inspired PIO_2 of 27.48 mm Hg.PO_2. The ROBD can hold this altitude for 10 sec, and then can be programmed to ramp down to the PIO_2 computed for 25,000 ft (58.8 mm Hg; 7.23% O_2) over 120 sec (Figure 1). For example, during a past experiment, when a subject reached 25,000 ft, the ROBD switched to 100% O_2 until baseline arterial oxygen saturation (SPO_2) was reestablished. P_b was monitored with a NIST-traceable precision absolute

manometer (model M2O2; Meriam Process Technologies; Cleveland, OH), and was used each time to calculate the desired percentage of O_2 the ROBD delivered.

3.2 The Analysis

Analyses are performed using programs such as SPSS (Chicago, IL), SAS (Cary, NC), and others. Statistical significance is set at alpha ≤ 0.05.

3.3 Clinical Monitoring

For all the APRL's tests, where human subjects are used, to ensure subject safety, real-time clinical noninvasive monitoring of cardiovascular, pulmonary, and neurological indexes is carried out and monitored by a physician.

4.0 Overview of Laboratory Equipment Usage

4.1 Gas Composition

Physiological characteristic being monitored or recorded

Gas composition of inhaled and exhaled air by human subjects, along with gas compositions of the surrounding room air.

Lab equipment typically used for this purpose

Perkin-Elmer Medical Gas Analyzer MGA-1100 by PerkinElmer Life and Analytical Sciences, Inc. of Waltham, MA. The MGA-1100 can simultaneously monitor the gas compositions of a human subject's inhaled air, exhaled air, as well as the gas composition of the room air surrounding the test subject, in near real-time quantitative measurements.

4.2 Pulse Oximetry

Physiological characteristic being monitored or recorded

Measuring the pulse rate and oxygen saturation of human subjects is accomplished through use of one or more Pulse Oximeters during human performance testing, however, the results from this alone can be misleading and need to be considered with other measurements for proper interpretation.

Lab equipment typically used for this purpose

- *Nellcor OxiMax N-600x Pulse Oximeter by Medtronic/Covidien - Nellcor Puritan Bennet, LLC of Boulder, CO*
- *Pulse oximetry SaO_2, (Nellcor) finger and/or eyebrow/forehead*
- *Nellcor OxiMax N-200 Pulse Oximeter (older model) by Medtronic/Covidien - Nellcor Puritan Bennet, LLC of Boulder, CO*
- *Pulse oximetry SaO_2, (Nellcor) finger and/or eyebrow/forehead*

4.3 Total Hemoglobin

Physiological characteristic being monitored or recorded

Measuring the pulse rate, oxygen saturation, perfusion index, and total Hgb of human subjects provides additional information that can assist in the proper interpretation of the measurement of oxygen saturation in human test subjects.

Lab equipment typically used for this purpose

Pronto Pulse CO-Oximeter by Masimo of Irvine, CA. The Pronto Pulse CO-Oximeter measures red-blood cell count in addition to the pulse rate, oxygen saturation, and perfusion index, non-invasively, and with good tolerance to patient motion during measurement. This is important for our human subject testing since individuals with a low red-blood cell count can become hypoxic easier while still showing an arterial blood-oxygen saturation in the normal range.

4.4 Regional Oxygen Saturation

Physiological characteristic being monitored or recorded

Measuring site-specific, regional oxygen saturation, including the ability to measure the amount of blood in the brain, in real-time.

Lab equipment typically used for this purpose

INVOS™ 5100C Cerebral/Somatic Oximeter by Medtronic/Covidien - Nellcor Puritan Bennet, LLC of Boulder, CO. INVOS Provides continuous, real-time, site-specific, regional oxygen saturation (rSO_2) of blood in the brain.

4.5 Cardiac Output

Physiological characteristic being monitored or recorded

Cardiac output of human subjects during testing, non-invasively.

Lab equipment typically used for this purpose

Nexfin HD monitor by Edwards Life Sciences Corporation (BMeye) of Irvine, CA. The Nexfin HD monitor measures cardiac output (CO) continuously in a non-invasive manner by an inflatable finger cuff,

which is the only interface with the patient. The Nexfin HD measures continuous finger blood pressure (BP) using Volume Clamp Technology and transforms it into a brachial artery waveform. Applying a 3rd generation pulse contour method (which is based on a full 3-element Windkessel model), and following the input of patient's gender, age, height, and weight, continuous CO (CCO) is measured and displayed. The CCO is calculated without external calibration although it can be so calibrated. This technology is based on an extension and combination of elements of two previous generations of algorithms, the so-called corrected characteristic impedance or cZ method (Wesseling 1974) and the model flow method (Wesseling 1993). The Nexfin HD measures continuous blood pressure (systolic, diastolic, and mean), heart rate, continuous cardiac output (CCO), stroke volume (SV), systemic vascular resistance (SVR), and left ventricular contractility (dP/dT). It also collects CO, BP, HR, PdV1-V2, etc., through a finger BP/oximeter device with an external pump mounted near the same hand on the wrist.

4.6 Respiratory Gas Exchange Simulation

Physiological characteristic being monitored or recorded

Measuring the respiratory gas exchange or breath-by-breath (BxB) analysis prior to using human test subjects, in real-time.

Lab equipment typically used for this purpose

Breathing Machine by Hans Rudolph Inc. (HRI) of Shawnee, K . This device provides capability to model inhalation and exhalation, allowing control of the rate of inhalation under varying environmental barometric pressures and control tidal volume and exhale under varying conditions. This allows the APRL to model a Rapid Decompression (RD) with a known tidal volume and measure what happens to gas exchanges during a RD in real barometric conditions.

PowerLab Data Acquisition System by ADInstruments Inc. of Colorado Springs, CO. PowerLab is a flexible data acquisition hardware that accepts a variety of analog and digital signals, providing a way to sample and digitize signals, and to synchronize the data from multiple systems through common reference signals and triggers.

Breath-by-breath analysis is typically accomplished via simulation in the APRL through a combination of a PowerLab Data Acquisition System, Hans Rudolph pneumotach hardware and Breathing Machine to provide quantitative breath-by-breath measurements, and gas composition measurements from the MGA-1100.

4.7 Respiratory Gas Exchange

Physiological characteristic being monitored or recorded

Measuring the respiratory gas exchange or breath-by-breath (BxB) analysis using human test subjects, in real-time.

Lab equipment typically used for this purpose

Breath-by-breath analysis is typically accomplished in the APRL through a combination of a PowerLab Data Acquisition System, and using gas composition measurements from the MGA-1100, to gather information when using human subjects for testing.

4.8 Cerebral Blood Flow Velocities

Physiological characteristic being monitored or recorded

Measuring the cerebral blood flow velocities of human test subjects, in real-time.

Lab equipment typically used for this purpose

ST3 Transcranial Doppler (TCD) by Spencer Technologies of Redmond, WA. This is a bilateral, two-channel system for measuring cerebral blood flow velocities. It accepts a handheld diagnostic probe or two monitoring probes and includes Power M-mode with high definition oversampling (HDO) digital processing. With this device, arterial flow within the brain is measured using TCD microphones (on headframe) near each subject's temples, used with ultrasound gel. This allows the researcher to target any of three arteries that usually present bilaterally for measurement during human subject tests.

4.9 Conscious State

Physiological characteristic being monitored or recorded

Monitoring the conscious state to predict the decision-making capacity of human subjects during testing, in real-time.

Lab equipment typically used for this purpose

BIS Complete Monitoring System by Medtronic/Covidien - Nellcor Puritan Bennet, LLC of Boulder, CO. A user-configurable patient monitoring system designed to monitor the conscious state of the brain based on acquisition and processing of EEG signals. It processes raw EEG signals to produce a single number, called the Bispectral Index™, or BIS, which correlates with the patient's level of awareness. It uses a BIS EEG 4-channel, forehead sensor stick-on cluster.

4.10 Simulated Environments

Environmental conditions created for physiological research

To test and/or predict the impact of different environmental conditions on the cognitive and physical abilities and health of passengers and flight crew operating at high altitudes. Altitude Physiology Research Laboratory equipment is used to simulate the effect of travelling at high altitudes, via pressure modification or the mix of available breathing gases in a controlled environment.

Lab equipment typically used for this purpose

Hypobaric Research Chamber by Environmental Tectonics Corporation (ETC) of Southampton, PA. The APRL includes a hypobaric research chamber that simulates flying by creating a pressure differential inside the enclosed chamber to mimic travelling at different altitudes.

Normobaric Hypoxic Tents by Colorado Altitude Training (CAT) of Boulder, CO and Reduced Oxygen Breathing Devices (ROBD) by Environics Inc. of Tolland, CT. Normobaric tents and devices simulate different altitudes through modification of the relative mixture of breathing gases available to the subjects. It is used in the APRL for testing where experiencing pressure altitude is not necessary for the desired experiment, as a pre-cursor to later hypobaric research using pressure altitudes, or in cases where it would not be safe to subject the test participants to the effects of the hypobaric environment.