J Appl Physiol 107: 336–345, 2009.
First published April 30, 2009; doi:10.1152/japplphysiol.91012.2008.

HIGHLIGHTED TOPIC | *The Physiology and Pathophysiology of the Hyperbaric and Diving Environments*

Arterial and pulmonary arterial hemodynamics and oxygen delivery/extraction in normal humans exposed to hyperbaric air and oxygen

Lindell K. Weaver,[1,2,3] Steve Howe,[2] Gregory L. Snow,[4] and Kayla Deru[2]

[1]*Pulmonary/Critical Care Medicine and* [2]*Hyperbaric Medicine, LDS Hospital, Salt Lake City;* [3]*Department of Medicine, University of Utah School of Medicine, Salt Lake City; and* [4]*Statistical Data Center, LDS Hospital, Salt Lake City, Utah*

Submitted 2 August 2008; accepted in final form 23 April 2009

Weaver LK, Howe S, Snow GL, Deru K. Arterial and pulmonary arterial hemodynamics and oxygen delivery/extraction in normal humans exposed to hyperbaric air and oxygen. *J Appl Physiol* 107: 336–345, 2009. First published April 30, 2009; doi:10.1152/japplphysiol.91012.2008.— Divers and hyperbaric chamber attendants breathe hyperbaric air routinely. Hyperbaric oxygen (HBO_2) is used therapeutically frequently. Although much is understood about the hemodynamic physiology and gas exchange effects during hyperbaric air and HBO_2 exposure, arterial and pulmonary arterial (PA) catheter data, including blood gas values during hyperbaric air and HBO_2 exposure of normal humans, have not been reported. We exposed 10 healthy volunteers instrumented with arterial and PA catheters to air at 0.85, 3.0, 2.5, 2.0, 1.3 (decompression stop), 1.12 (decompression stop), and 0.85 atm abs (our altitude) and then at identical pressures breathing O_2 followed by atmospheric pressure air while we measured arterial and PA pressures (PAP), cardiac output ($\dot{Q}$), and blood gas measurements from both arterial and PA catheters. Although hemodynamic changes occurred during exposure to both hyperbaric air and HBO_2, we observed a greater magnitude of change under HBO_2 conditions: heart rate changes ranged from −9 to −19% (air to O_2), respiratory rate from −12 to −17%, $\dot{Q}$ from −7 to −18%, PAP from −18 to −19%, pulmonary vascular resistance from −38 to −48%, and right-to-left shunt fraction from −87 to −107%. Mixed venous CO_2 fell 8% from baseline during HBO_2 despite mixed venous O_2 tensions of several hundred Torr. The stroke volume, O_2 delivery, and O_2 consumption did not change across exposures. The arterial and mixed venous partial pressures of O_2 and contents were elevated, as predicted. O_2 extraction increased 37% during HBO_2.

hyperbaric oxygen; pulmonary arterial catheter; cardiac output; oxygen extraction

THOUSANDS OF PATIENTS have been treated with hyperbaric oxygen (HBO_2); however, the precise arterial and pulmonary arterial (PA) hemodynamic and gas exchange responses that occur during HBO_2 are not clearly known. Determining precise hemodynamic and gas exchange information requires the subject or patient to be instrumented with arterial and PA (Swan-Ganz) catheters, permitting measurement of intravascular pressures and blood gases, and PA catheter data collected in normal humans exposed to HBO_2 has been reported only once (24).

It has long been established that heart rate (HR) falls during HBO_2 (3). Forty years ago, investigators reported that this reduction in HR was associated with decreased cardiac output ($\dot{Q}$) (48), an observation supported by subsequent research (Table 1) (21, 24, 27, 29, 48). Generally accepted hemodynamic effects of HBO_2 now "include mild bradycardia, leading to a proportional decline in $\dot{Q}$ and a small increase in systemic vascular resistance" (28).

As $\dot{Q}$ falls, O_2 consumption ($\dot{V}O_2$) may remain constant if O_2 extraction increases proportionally. No report of $\dot{V}O_2$ or O_2 extraction under hyperbaric conditions has been published.

HBO_2 can precipitate acute pulmonary edema in patients with reduced left ventricular function (43), possibly due to high O_2 concentrations reducing myocardial relaxation factor (nitric oxide), thereby making the heart stiffer (23), or by an increase in afterload from increased systemic vascular resistance (48). The systematic recording of intracardiac filling pressures of humans during HBO_2 exposure is limited to measurements at 3.0 atmospheres absolute (atm abs; 304 kPa) (24).

A wider alveolar-to-arterial P_{O_2} difference ($A\text{-}aD_{O_2}$) than predicted has been observed in normal humans exposed to HBO_2 (45). These data suggest an unexplained increase in right-to-left intrapulmonary shunt fraction ($\dot{Q}_s/\dot{Q}_t$), or venous admixture, due to HBO_2, but $\dot{Q}_s/\dot{Q}_t$ measurements during HBO_2 have not been published.

A description of the technique of using a PA catheter in patients treated in the monoplace hyperbaric chamber is available (41), and hemodynamic data obtained during HBO_2 therapy in critically ill patients have been presented (40), but these data from critically ill patients may not extrapolate to hemodynamic effects due to HBO_2 in normal humans.

The purpose of the present study was to measure the hemodynamic and blood gas responses of normal humans instrumented with arterial and PA catheters under hyperbaric air and HBO_2 conditions.

METHODS

The Institutional Review Board at the LDS Hospital approved the study protocol. After signing informed consent and completing a prehyperbaric exposure history and physical examination, 10 normal, healthy subjects (5 males and 5 females) between the ages of 18 and 41 yr were selected for participation in this study. None of the subjects had evidence of cardiac or pulmonary disease. None of the subjects smoked or were taking medications, including birth control pills. At least 24 h before undergoing catheter cannulation, each subject was compressed in a monoplace hyperbaric chamber (model 2500B; Sechrist Industries, Anaheim, CA) to 3.0 atm abs to be confident the

Address for reprint requests and other correspondence: L. K. Weaver, Hyperbaric Medicine, LDS Hospital, Eighth Ave. and C St., Salt Lake City, UT 84143 (e-mail: lindell.weaver@imail.org).

Table 1. *Previous cardiac output studies in humans exposed to hyperbaric oxygen*

						%Change From Breathing Air at 1 atm abs			
Study	Year	Technique	No. of Subjects	P_{Ch}, atm abs	FI_{O_2}	HR, beats/min	MBP, Torr	$\dot{Q}$, l/min	SVR, dyn·s·cm^{-5}
Whalen et al. (48)	1965	Indicator dilution	10	1	1.00	−5	1	−5	5
			10	3.04	0.21	−9	−1	−7	3
			10	3.04	1.00	−16*	3	−13*	16*
Kenmure et al. (21)	1972	Indicator dilution	20	1	1.00	−6*	2	−8*	12*
			20	2.0	1.00	−7*	3	−10*	15*
Pisarello et al. (29)	1987	Impedance	7	1.5	1.00	−5	−7	−16	6
			7	2.0	1.00	−15	14	−13	31
			8	2.5	1.00	−21*	−7	−15	9
			12	3.0	1.00	−10	−1	−8	8
Pelaia et al. (27)	1992	Impedance	10	2.2	1.00	−14	−3	−17	
McMahon et al. (24)	2002	Thermal dilution	12	3	1.00		10	−10	21

Values are percent changes from breathing air at 1 atm abs. P_{CH}, chamber pressure; FI_{O_2}, fraction of inspired O_2; HR, heart rate; MBP, mean systemic blood pressure; $\dot{Q}$, cardiac output; SVR, systemic vascular resistance. *$P < 0.05$, significant difference from breathing air at 1 atm abs.

subject could equalize middle ear pressure and could tolerate the confines of the chamber.

The subjects were encouraged to eat breakfast on the day of the experiment. No further nutrition was allowed during the data collection period. Water intake was permitted and was quantified.

The subject was placed supine and had five-lead electrocardiography (ECG) monitoring (GE Healthcare, Little Chalfont, UK). One percent lidocaine without epinephrine (1 ml) was injected as a local anesthetic in the dermis and subcutaneous space of the right subclavian cannulation site. A PA catheter (8 Fr, continuous cardiac output and mixed venous Oximetrix with extra infusion port; Baxter Healthcare, Irvine, CA) was placed through a 9-Fr Introducer sheath (Arrow International, Reading, PA) inserted in the right subclavian vein following standard aseptic techniques. The PA catheter distal port was connected to a pressure transducer (Transpac II disposable transducer; Abbott Laboratories, North Chicago, IL) permitting measurement and monitor display of the distal port pressure waveforms. Appropriate PA catheter position was confirmed by demonstrating a PA occlusion pressure waveform (wedge pressure) with a concomitant >10% rise in mixed venous pulmonary arterial O_2 saturation ($S\bar{v}_{O_2}$) (i.e., capillary gas) (14). Anterior-to-posterior chest radiographs performed on all subjects demonstrated acceptable PA catheter positions and no evidence of pneumothorax or hemorrhage. During chamber pressurization, pressure transducers were located inside the chamber.

Thermal dilution $\dot{Q}$ was measured by using a closed-loop injectable delivery system, using iced saline as injectate, with in-line temperature sensor (Baxter Healthcare). Continuous $\dot{Q}$ was measured using a continuous cardiac output catheter system (Baxter Healthcare).

A radial arterial catheter (A-Line RA-04020; Arrow International) was placed aseptically following standard hospital procedures. In seven subjects, an intra-arterial continuous O_2 sensor (Continucath 1000; Biomedical Sensors, Malvern, PA) was inserted through the arterial cannulas to permit continuous measurement of arterial O_2 tension (Pa_{O_2}).

After placement of the invasive catheters, the subject rested supine within the monoplace hyperbaric chamber. Detailed methods describing how the catheters were passed out of the chamber, including how the transducers were connected, were presented in a prior report (41). After passing the appropriate leads, tubes, and wires through special pass-throughs in the monoplace chamber hatch (39, 41), the continuous $\dot{Q}$ system was activated and the $S\bar{v}_{O_2}$ and Continucath were calibrated, following the manufacturer's recommendations. The arterial catheter was continually flushed with saline containing heparin (10 U/ml saline) at 3 ml/h by the continuous flush device (Abbott Laboratories). A special bracket was constructed to hold the right atrial (RA) and PA pressure transducers in a fixed position relative to the subject. All transducers were zeroed to the RA reference level for each subject.

After all equipment was set up and functioning properly with the subject inside the chamber and the chamber hatch slightly open, the lights in the room were dimmed. The subjects were kept in a dim room in a resting state with as little external activity and conversation as possible to minimize external stimuli. The respiratory quotient (RQ) was measured by collecting exhaled gas from each subject after he/she quietly rested inside the chamber for at least 10 min (38).

Pressure measurements from the arterial catheter and RA and PA ports of the PA catheter were recorded with a strip chart (model 2200S; Gould, Cleveland, OH). Adequate frequency response was confirmed with both the arterial and PA catheters before data collection for all subjects (15).

All thermal dilution saline injection $\dot{Q}$ measurements (10 ml injected with in-line temperature measurements) were performed by one individual with extensive bedside critical care nursing experience using iced normal saline for bolus $\dot{Q}$ measurements injected through the injection port of the PA catheter, located outside the chamber (41). To verify reproducible $\dot{Q}$ measurements, we plotted the injection pressure vs. time of injection. A pressure transducer was connected with a four-foot luer-lock neonatal high-pressure monitoring line (Argon Medical Devices, Athens, TX) to a four-way stopcock (Baxter Healthcare), in-line with the $\dot{Q}$ syringe. A computer displayed a plot in real time of injection pressure vs. time. Successive $\dot{Q}$ measurements overlaid the previous displays on the computer screen. Five $\dot{Q}$ injections were performed at each sampling time. The three that had virtually identical pressure vs. time curves were selected for averaging as the thermal dilution $\dot{Q}$ value. The Baxter monitor displayed a conventional change in temperature vs. time with each of the injections of iced saline, and for selection, these individual $\dot{Q}$ measures also fell within ±10% of one another.

Collected baseline data included body surface area (BSA), subject core temperature as measured by PA catheter (T), HR, respiratory rate (RR), systemic blood pressure (BP), mean systemic blood pressure (MBP), PA pressure (PAP), mean PA pressure (MPAP), RA pressure (RAP), PA wedge pressure (balloon occlusion pressure; PAWP), RQ, arterial blood gas data including arterial pH (pHa), arterial partial pressure of CO_2 (Pa_{CO_2}), Pa_{O_2}, arterial O_2 saturation (Sa_{O_2}), arterial hemoglobin (Hba), mixed venous pH ($pH\bar{v}$), mixed venous partial pressure of CO_2 ($P\bar{v}_{CO_2}$), mixed venous partial pressure of O_2 ($P\bar{v}_{O_2}$), $S\bar{v}_{O_2}$, mixed venous hemoglobin ($Hb\bar{v}$), $\dot{Q}$ by thermal dilution, and

cardiac index (CI). Calculated baseline data include stroke volume (SV), right-to-left shunt fraction ($\dot{Q}_s/\dot{Q}_t$) (47), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) (25), O_2 content by arterial (Ca_{O_2}) and mixed venous ($C\bar{v}_{O_2}$) measurement, O_2 extraction ($Ca_{O_2} - C\bar{v}_{O_2}$), O_2 delivery ($\dot{Q}_{O_2}$), and $\dot{V}O_2$.

The subjects were compressed on air in the monoplace hyperbaric chamber to 3.0 atm abs (304 kPa), 2.5 atm abs (253 kPa), 2.0 atm abs (203 kPa), 1.3 atm abs (132 kPa), 1.12 atm abs (113 kPa), and then back to 0.85 atm abs (86 kPa) (barometric pressure at our altitude of 1,500 m above sea level) (Fig. 1). Upon completion of the first compression sequence with air and data gathering, the subject breathed 100% O_2 via a 100% O_2 reservoir bag through a one-way flow-directed valve (model 2600; Hans Rudolph, Kansas City, MO) fitted with a SCUBA mouthpiece while wearing a nose clip (chamber hatch slightly open). After the chamber hatch was closed, each subject continued to breathe 100% O_2 by demand regulator (model L451; Life Support Products, St. Louis, MO) supplied with 100% O_2 inside the chamber until we verified that the chamber gas concentration was $\geq$98% O_2. The chamber gas concentration was measured by placing a gas sampling line just above the subject's face, passing chamber gas out through a pass-through in the chamber hatch while measuring O_2 concentration with an O_2 analyzer, calibrated according to the manufacturer's recommendations. Once the chamber O_2 concentration measured $\geq$98%, the subject discontinued use of the demand regulator and breathed chamber O_2. The compression and data collection sequence was repeated in the same fashion on 100% O_2 (Fig. 1).

This compression sequence maximized the hemodynamic and blood gas data obtained while minimizing risk of decompression sickness to the subjects. The air compression was required to separate effects due to hyperbaric pressure from those due to 100% O_2. The decompression stops and times (1.3 and 1.12 atm abs, respectively) for the air compression were derived from the *US Navy Dive Manual* (9) using cross-corrections for altitude "diving" (1,500 m above sea level) (4).

Hemodynamic data were obtained at all pressure levels except 1.3 atm abs pressure, after 10 min at each pressure exposure and 30 min postcompression for both the air and O_2 exposures (Fig. 1). Arterial and PA mixed venous blood were simultaneously sampled at each data point. The blood gases were measured with an ABL 330 (Radiometer, Copenhagen, Denmark) located at the chamber side using methodology and instrumentation previously demonstrated to be valid (45, 46). The O_2 values were adjusted for blood using methods previously described (45, 46). Hemoglobin, carboxyhemoglobin, methemoglobin, and oxyhemoglobin were measured with an OSM3 (Radiometer). Data collected included T, HR, RR, BP, MBP, PAP, MPAP, RAP, PAWP, pHa, Pa_{CO_2}, Pa_{O_2}, Sa_{O_2}, Hba, $pH\bar{v}$, $P\bar{v}_{CO_2}$, $P\bar{v}_{O_2}$, $S\bar{v}_{O_2}$, $Hb\bar{v}$, and $\dot{Q}$ by bolus injection thermal dilution, CI, and $\dot{Q}$ and Pa_{O_2} by continuous measurement. SV, $\dot{Q}_s/\dot{Q}_t$, SVR, PVR, Ca_{O_2}, $C\bar{v}_{O_2}$, $Ca_{O_2} - C\bar{v}_{O_2}$, $\dot{Q}_{O_2}$, and $\dot{V}O_2$ were calculated for each data collection point.

Data for each hemodynamic parameter were tallied on a universal flow sheet and subsequently entered into a computerized database, with double checking for accuracy. The chamber T, HR, BP, RAP, and PAP values were continuously measured and stored every 5 min automatically by the HELP system at LDS Hospital (16, 17).

There was an obligate blood loss of ~150–200 ml per subject throughout the entire investigation. The subjects received ~800–1,200 ml of intravenous normal saline due to the number of bolus injection $\dot{Q}$ measurements (5 injections of 10 ml each at each data-gathering condition) during the experiment. The subjects were weighed before and after the experiment. Urine output was quantified.

After compression with O_2, data were recorded 30 min after atmospheric pressure was reached with the subject breathing 100% O_2 and, finally, after 30 min with the subject breathing air. At this point in time, the experiment was concluded. The PA catheter and the arterial catheters were withdrawn, and firm pressure was held for 10 min with suitable dressings applied. The subjects were encouraged to eat as needed and not to ascend in altitude for at least 24 h. The subjects also were encouraged to notify us if they had complaints referable to the study, especially if they had manifestations of decompression sickness. The subjects were evaluated the following day to ensure adequate hemostasis at the catheter sites and to discuss any worries or concerns.

The data collected by the continuous cardiac output catheter system and intra-arterial continuous O_2 sensor are not presented in this report. Transcutaneous O_2 and CO_2 data collected at this time, compared with Pa_{O_2} and Pa_{CO_2}, are available elsewhere (42).

For the $\dot{Q}_s/\dot{Q}_t$ or venous admixture calculations (47) and for all arterial content of O_2 calculations, we averaged all Hba values. Similarly, for the contents of O_2 in PA blood, all $Hb\bar{v}$ values were averaged. This averaging was done to minimize possible confounding errors from minor differences in hemoglobin concentrations from across conditions. We did not average hemoglobin when reporting contents of arterial or pulmonary arterial O_2 elsewhere.

Statistical methods. Data were analyzed using mixed-effects regression models where each subject was allowed to have a different random intercept, but the overall pattern was consistent between subjects. Each response was modeled separately using a guided stepwise procedure starting with the model that the response is predicted by gas and pressure (with a possibility of different slopes on pressure for air and O_2). Additional models were fit to see whether simpler models fit or if a more complex model was needed to best fit

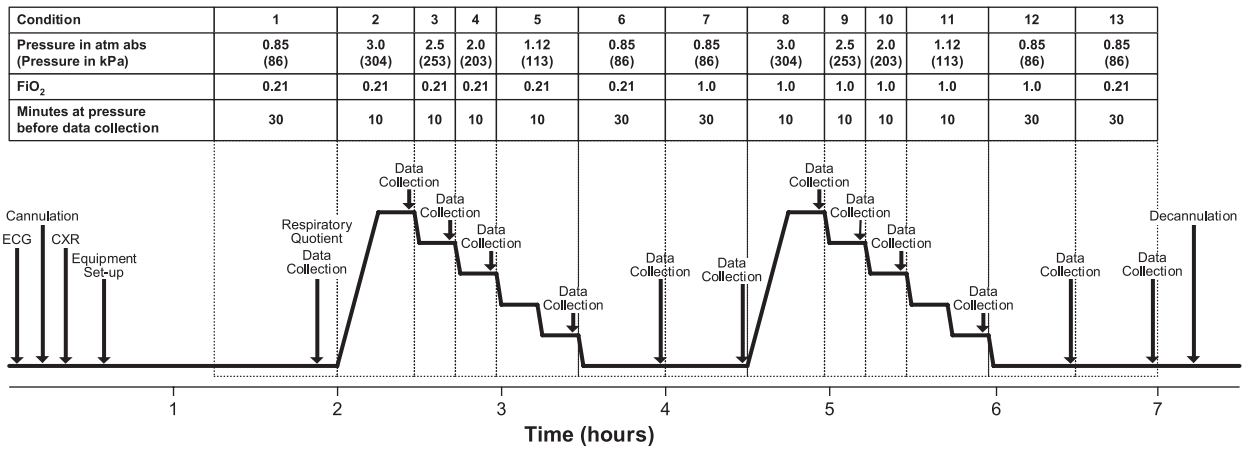


Fig. 1. Timeline for placing arterial and pulmonary arterial (PA) catheters, when and under what conditions data were collected, while the subject was exposed to hyperbaric pressure in a monoplace hyperbaric chamber. FI_{O_2}, fraction of inspired O_2; CXR, chest radiographs.

the data (curved relation with pressure, individual time points needing an offset from the base model). All tests were done using $\alpha = 0.05$ (2-sided). Descriptive data are expressed as means (SD).

RESULTS

Baseline characteristics of individual research subjects are shown in Supplemental Table 1. (Supplemental data for this article is available online at the *Journal of Applied Physiology* website.) One-half of the subjects were male. The subjects had no identified comorbid conditions or influences. All subjects completed the study protocol.

The baseline condition RQ was 0.87 (0.14). Average Hba across all experimental conditions was 14.2 (1.4) mg/dl. The average total blood loss was 185.3 (21.0) ml. The baseline Hba was 14.6 (1.4), and the final Hba was 14.2 (1.5). The baseline weight was 70.4 (13.2) kg, and the final weight was 69.8 (14.0) kg. The normal saline administered was 1,038 (352) ml. The liquid oral intake was 97 (77) ml. The urine output was 630 (299) ml. No complications were noted. The inside chamber temperature increased 3°C with chamber compression and then sloped downward to baseline as the chamber was decompressed (for chamber and subject temperature under experimental conditions, see Supplemental Fig. 1).

Results from this study are depicted in Figs. 2–9. Supplemental Table 2 reports mean change from baseline for each data point, with a 95% confidence interval and 25th and 75th percentiles.

Heart rate, respiratory rate, and blood pressure. Results are depicted in Fig. 2. Mean HR decreased 3.19 beats/min for each 1 atm abs pressure increase during exposure to air ($P < 0.001$). Mean HR was 1.95 beats/min lower while subjects breathed O_2 than during exposure to air ($P < 0.001$). Mean RR decreased 0.42 breaths/min for each 1 atm abs pressure increase while subjects were exposed to air ($P = 0.045$). Mean RR was 0.4 breaths/min lower on O_2 than on air ($P = 0.03$). Average systolic BP was ~3 Torr higher with O_2 than air breathing ($P = 0.009$). Diastolic BP was not significantly different while subjects were breathing air compared with that while breathing O_2 ($P = 0.105$). MBP for subjects breathing air was 88 Torr. MBP for subjects breathing O_2 was marginally higher, 89 Torr.

Right atrial, pulmonary arterial, and balloon occlusion pressures. Results are depicted in Fig. 3. RAP did not change across test conditions with the exception of data from two subjects with elevated RAP for test *condition 11* (100% O_2 at 1.12 atm abs).

Average systolic PAP was related to hyperbaric pressure, both on air and on O_2 ($P < 0.001$). Systolic PAP dropped 1.52 Torr for each 1 atm abs pressure increase ($P < 0.001$). With the first O_2 breathing interval at 0.85 atm abs (*condition 7*) and at the conclusion of the experiment (*condition 13*, breathing air at 0.85 atm abs), systolic PAP was 1.52 Torr lower for *condition 7* and 2.15 Torr higher for *condition 13* than predicted based on pressure measurements alone. Average diastolic PAP was 0.54 Torr lower per 1 atm abs pressure increase while subjects were exposed to air ($P = 0.005$). Average MPAP decreased 0.85 Torr per 1 atm abs increase in pressure ($P < 0.001$) and was 0.9 Torr lower during O_2 exposure ($P = 0.002$). Average PAWP increased 0.67 Torr while subjects were breathing HBO_2 ($P = 0.005$).

Cardiac output. The thermal dilution $\dot{Q}$ decreased from baseline 0.19 l/min per 1 atm abs increase in pressure ($P = 0.002$). $\dot{Q}$ was 0.46 l/min lower while subjects were breathing O_2 than while breathing air ($P = 0.001$). The CI dropped 0.11 $l \cdot min^{-1} \cdot m^{-2}$ for each 1 atm abs increase in pressure ($P = 0.001$). The CI was 0.25 $l \cdot min^{-1} \cdot m^{-2}$ lower while subjects were breathing O_2 than while breathing air ($P = 0.002$) (Figs. 4 and 5).

Arterial blood gases. Results are depicted in Fig. 6. pHa dropped during hyperbaric air and was higher than baseline during HBO_2 exposure. Pa_{CO_2} was lower during HBO_2 expo-

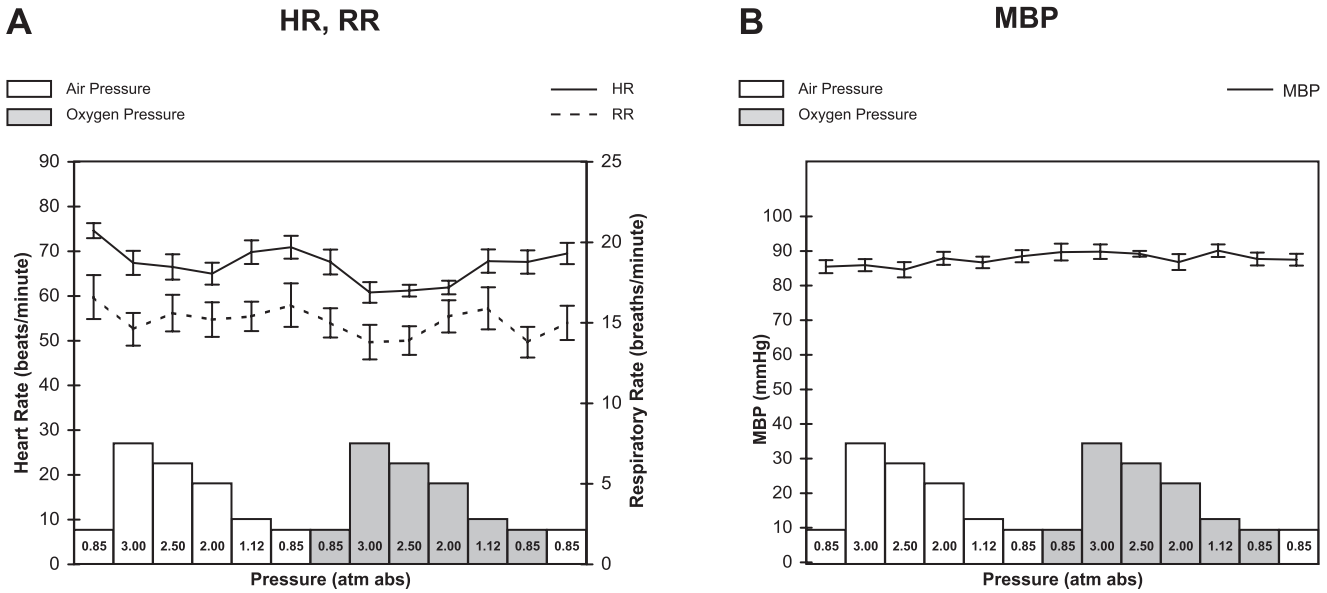


Fig. 2. Heart rates (HR; *A*), respiratory rates (RR; *A*), and mean arterial blood pressures (MBP; *B*) of subjects exposed to hyperbaric air and hyperbaric oxygen (HBO_2). Values are means ± SE. HR dropped with both hyperbaric air and HBO_2 exposures compared with baseline, with a larger reduction during HBO_2 exposure. RR trended downward from baseline with hyperbaric air exposure and was lower than baseline during HBO_2 exposure at 3.0 and 2.5 atm abs. Systolic BP was higher with O_2 than air breathing. Diastolic BP and MBP did not change across the hyperbaric air and HBO_2 conditions. Systolic and diastolic systemic BP values are shown in Supplemental Fig. 2.

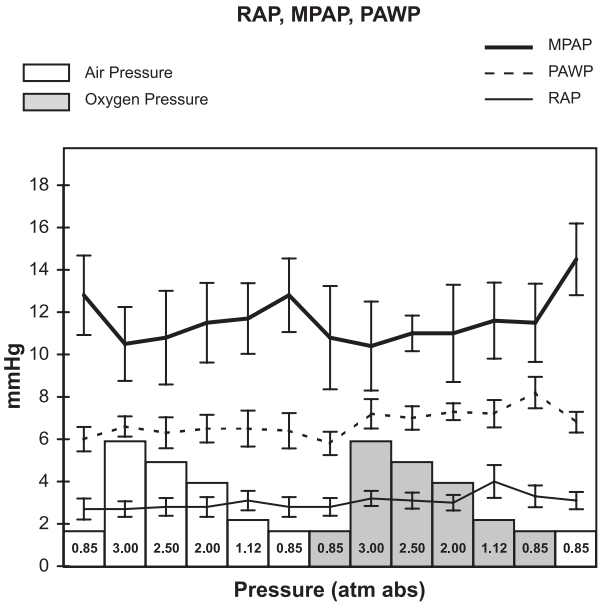


Fig. 3. Right atrial pressures (RAP), mean pulmonary arterial pressures (MPAP), and PA catheter balloon occlusion pressures, or PA wedge pressures (PAWP), of subjects exposed to hyperbaric air and HBO_2. Values are means ± SE. The RAP elevation under *condition 11* (100% O_2 at 1.12 atm abs) is explained by 2 subjects. The systolic PAP and MPAP values were lower than baseline during hyperbaric air and HBO_2 exposures. The PAWP value increased compared with baseline during HBO_2 exposure. Systolic and diastolic PA pressures are shown in Supplemental Fig. 3.

sure compared with the initial baseline or hyperbaric air exposures. From the mixed-effects model, Pa_{CO_2} sloped upward as HBO_2 pressure decreased ($P < 0.001$) (Fig. 5). The nadir for Pa_{CO_2} occurred at 100% O_2 at 3 atm abs and increased as HBO_2 pressure decreased. The Pa_{O_2} measurements were in the range predicted based on the subjects' inhaled partial O_2 pressures.

Pulmonary arterial (mixed venous) blood gases. Results are depicted in Fig. 7. pH$\bar{v}$ was essentially constant across test conditions. $P\bar{v}_{CO_2}$ was lower during HBO_2 exposure at 3.0 and 2.0 atm abs ($P = 0.02$). $P\bar{v}_{O_2}$ and $S\bar{v}_{O_2}$ were elevated during hyperbaric air and O_2 exposures.

Calculations from arterial and pulmonary arterial measurements. Ca_{O_2} and $C\bar{v}_{O_2}$ increased as the partial pressures of inhaled O_2 increased, during both hyperbaric air and HBO_2 exposures (Fig. 8). From the mixed-effects model, $Ca_{O_2} - C\bar{v}_{O_2}$ decreased 0.18 Torr with each 1 atm abs increase in air pressure ($P = 0.006$). $Ca_{O_2} - C\bar{v}_{O_2}$ increased 0.61 Torr for each 1 atm abs pressure increase with O_2 breathing ($P < 0.001$). $Ca_{O_2} - C\bar{v}_{O_2}$ was higher during HBO_2 breathing at 3.0, 2.5, and 2.0 atm abs (Fig. 8). The $\dot{Q}_{O_2}$ delivery ($\dot{Q} \times Pa_{O_2}$) and $\dot{V}O_2$ [$\dot{Q} \times (Ca_{O_2} - C\bar{v}_{O_2})$] were relatively constant across test conditions (Fig. 8).

There was no significant change in SV across conditions (Fig. 9). From the mixed-effects model, SVR increased 58.7 dyn·s·cm^{-5} with each 1 atm abs increase in air pressure ($P = 0.003$). SVR was higher during HBO_2 breathing at 2.5 and 2.0 atm abs compared with baseline (Fig. 9). From the mixed-effects model, PVR decreased 15 dyn·s·cm^{-5} with each 1 atm abs increase in pressure ($P < 0.001$) and was 39.4 dyn·s·cm^{-5} lower with HBO_2 than air exposure ($P < 0.001$). $\dot{Q}_s/\dot{Q}_t$ was 15% during all air breathing periods at 0.85 atm abs. During both hyperbaric air and HBO_2 breathing, $\dot{Q}_s/\dot{Q}_t$ decreased. This change was greater during HBO_2 than hyperbaric air breathing (Fig. 9).

DISCUSSION

This is the only study that reports arterial and PA hemodynamic measurements with blood gases of healthy volunteers exposed to both hyperbaric air and HBO_2. Limited observations in prior human studies measuring $\dot{Q}$ suggest that HR and $\dot{Q}$ decrease ~20% during HBO_2 exposure (21, 24, 27, 29, 48). In our subjects, we noted a decrease in HR with exposure to hyperbaric air and HBO_2. The $\dot{Q}$ value also dropped with HBO_2 exposure, but the magnitude of change was <20% and could have been influenced by noise in thermal dilution measurements (34), despite making these measurements carefully. Although not using HBO_2 in their experimental protocol, some studies noted a decrease in $\dot{Q}$ on exposure to hyperoxia (1, 30). However, other studies found that $\dot{Q}$ did not change with exposure to hyperoxia (2, 23). Only a few studies have measured cardiac output during HBO_2 exposure (Table 1). In a prior report (24), investigators used flow-directed PA catheters in 11–12 healthy volunteers exposed to air at 0.56 atm abs, then air at 1 atm abs, and then 100% O_2 at 3 atm abs and found that exposure to HBO_2 resulted in decreases in $\dot{Q}$, PAP, and PVR. The fall in HR and $\dot{Q}$ during HBO_2 exposure may be due to increased vagal stimulation, since atropine administration reverses the fall in HR and $\dot{Q}$ with 100% O_2 at 1 atm abs (14). However, in an animal study, dogs pretreated with propranolol, phentolamine, and atropine demonstrated decreased $\dot{Q}$ during HBO_2 exposure (35), presumably due to physiological autoregulation of the myocardium (35) and vasculature (5) due to increased Pa_{O_2}.

Hyperoxic breathing at 1 atm abs may increase left ventricular end-diastolic pressure (LVEDP) (23). Explanations for this finding are reductions in nitric oxide myocardial relaxant factor attributable to increased Pa_{O_2} (28, 33). LVEDP was not measured in this study, but PAWP approximates LVEDP closely in normal individuals (11, 19). The PAWP values in this study were slightly lower than baseline with inhalation of

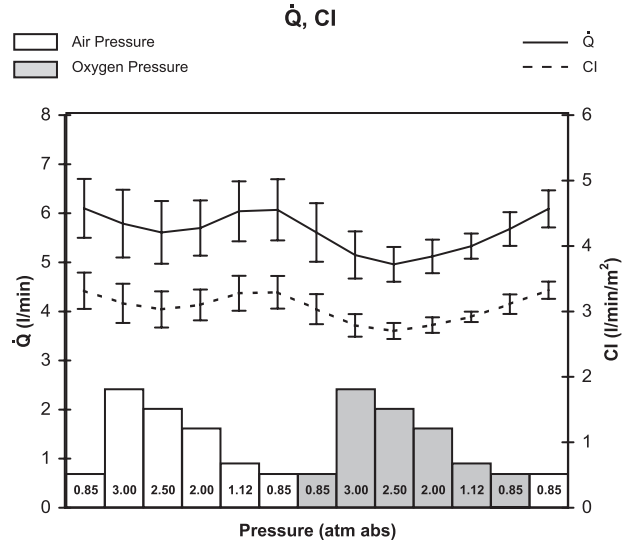
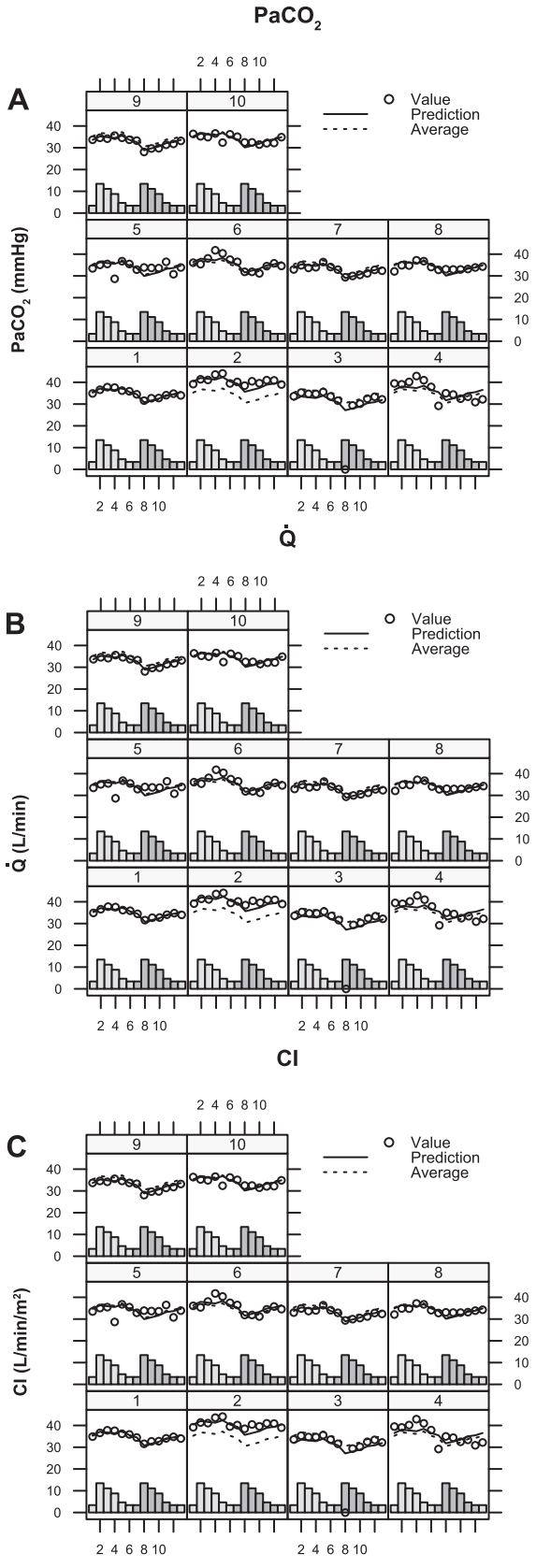


Fig. 4. Cardiac outputs ($\dot{Q}$) and cardiac indexes (CI) of subjects exposed to hyperbaric air and HBO_2. Values are means ± SE. The $\dot{Q}$ and CI values were lower than baseline during HBO_2 exposure.



100% O_2 at 0.85 atm abs, and LVEDP should have been similarly reduced from baseline under these conditions. During HBO_2 exposure, the PAWP was higher than baseline or air breathing values, and therefore the LVEDP should have been higher. This finding supports other evidence that HBO_2 may increase left ventricular wall stiffness (23, 43). Hyperoxia may reduce myocardial relaxant factor and increase left ventricular myocardial stiffness, resulting in increases in LVEDP, which could contribute to acute lung edema in heart failure patients treated with HBO_2 (43). However, during HBO_2 exposure, RAP and PAP did not increase compared with baseline values: their values were lower than baseline. It is possible that only the left ventricle increases filling pressures during HBO_2 exposure. It also is possible that the hyperbaric air exposure before HBO_2 exposure modified the RAP and PAP responses to HBO_2 with the increased partial pressures of nitrogen modulating a subsequent HBO_2 effect. It also is possible that the duration of O_2 inhalation was insufficient to alter RAP or PAP. Differences in intracardiac pressure measurement results also may be accounted for by different dosing of O_2 inhalation [P_{O_2} ~0.7 atm abs (23) compared with 0.85 to 3.0 atm abs in this study].

The pHa increased and Pa_{CO_2} decreased during HBO_2 exposure, a confirmatory finding (22). A previous study reported hypocapnea during hyperbaric oxygen inhalation caused by a central accumulation of CO_2, contributing to hyperventilation (22).

Whalen et al. (48) demonstrated that in 10 healthy volunteers breathing 100% O_2 at 3.04 atm abs, Pa_{CO_2} did not change compared with baseline, whereas $P\bar{v}_{CO_2}$ increased 4 Torr from baseline. However, we observed that $P\bar{v}_{CO_2}$ was slightly lower during HBO_2 exposure. Explanations these conflicting data include the following. *1*) Whalen et al. did not measure true mixed venous blood, since the sampling catheter was located near the RA, not the PA. *2*) A reduction in $\dot{V}_{O_2}$ and CO_2 production during HBO_2 exposure could contribute to reduced $P\bar{v}_{CO_2}$. In our study, $\dot{V}_{O_2}$ did not change during the experiment, so this explanation is not supported by the data. *3*) If Pa_{CO_2} fell sufficiently during HBO_2 exposure, $P\bar{v}_{CO_2}$ might not elevate as expected, since the arterial capillary values were lower. *4*) There may be ventilatory effects such as hyperventilation (22) acting independently regarding the reduction seen in Pa_{CO_2}. *5*) It is possible the prior hyperbaric air exposure influenced the CO_2 measurements during subsequent HBO_2 exposure, although we do not have an explanation based on physiological principles. *6*) The time course from the baseline value to those obtained during HBO_2 exposure in our study was several hours, whereas was likely a shorter interval in research conducted by Whalen et al. *7*) Finally, it is possible a difference in measurement technique of CO_2 in 1965 compared with that used now has contributed to small differences in observed results.

As expected, Pa_{O_2}, $P\bar{v}_{O_2}$, Sa_{O_2}, and $S\bar{v}_{O_2}$ were elevated during exposure to hyperbaric air and HBO_2, within predicted

Fig. 5. Predictions from the mixed-effects model for arterial carbon dioxide tension (Pa_{CO_2}; *A*), $\dot{Q}$ (*B*), and CI (*C*). Plots at the *top* of each panel represent data for 1 subject with circles showing the actual data values, solid lines showing the predicted values from the model for that specific subject, and dotted lines showing the average predicted values (the prediction for a new subject). Bar graphs at the *bottom* of each panel show the air and oxygen pressure exposures for that subject (see Fig. 1).

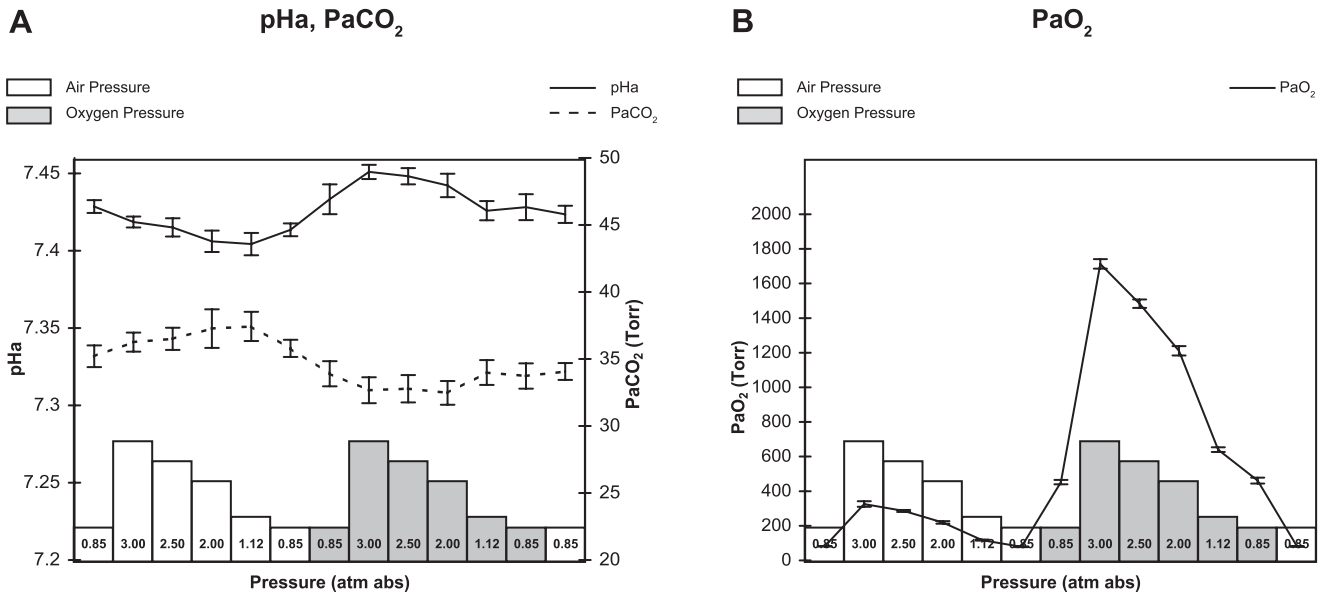


Fig. 6. Arterial pH (pHa; *A*), Pa_{CO_2} (*A*), and arterial oxygen tension (Pa_{O_2}; *B*) values of subjects exposed to hyperbaric air and HBO_2. Values are means ± SE. The pHa was lower than baseline during hyperbaric air exposure and greater than baseline during HBO_2 exposure. Pa_{CO_2} was lower than baseline during HBO_2 exposure. Pa_{O_2} increased as the alveolar partial pressure of O_2 increased during hyperbaric air and HBO_2 exposures.

ranges (6, 8, 24, 41, 45). The SV was constant across the experimental conditions. This finding is expected, since the reduction in $\dot{Q}$ seems to be proportional to the reduction in HR.

Although $\dot{Q}_{O_2}$ and $\dot{V}O_2$, as determined using Pa_{O_2}, $P\bar{v}_{O_2}$, and $\dot{Q}$ by thermal dilution, did not change across conditions, $Ca_{O_2} - C\bar{v}_{O_2}$ increased during HBO_2 exposure. If $\dot{V}O_2$ remains constant (as expected in a normal volunteer while at rest) and if $\dot{Q}$ falls, $Ca_{O_2} - C\bar{v}_{O_2}$ must increase because $\dot{V}O_2$ is proportional to $\dot{Q} \times (Ca_{O_2} - C\bar{v}_{O_2})$.

As expected, SVR increased during HBO_2 exposure. Since SVR is calculated as (MPAP − RAP)/$\dot{Q}$, if the pressures in the numerator remain constant and $\dot{Q}$ falls, then SVR must increase. Since vascular tone was not actually measured in our study, we cannot determine whether the actual caliber of arterial blood vessels was reduced during HBO_2 exposure.

PVR fell while subjects breathed increased partial pressures of O_2, during both hyperbaric air and HBO_2 exposures. It is well accepted that increased partial pressures of O_2 reduce pulmonary pressures in patients with chronic pulmonary disease or in patients with hypoxic vasoconstriction, but normobaric hyperoxia has no significant effect on PAP (10). However, in our study, hyperbaric oxygen pressures were used. Our findings are in agreement with the limited data presented by McMahon et al. (24).

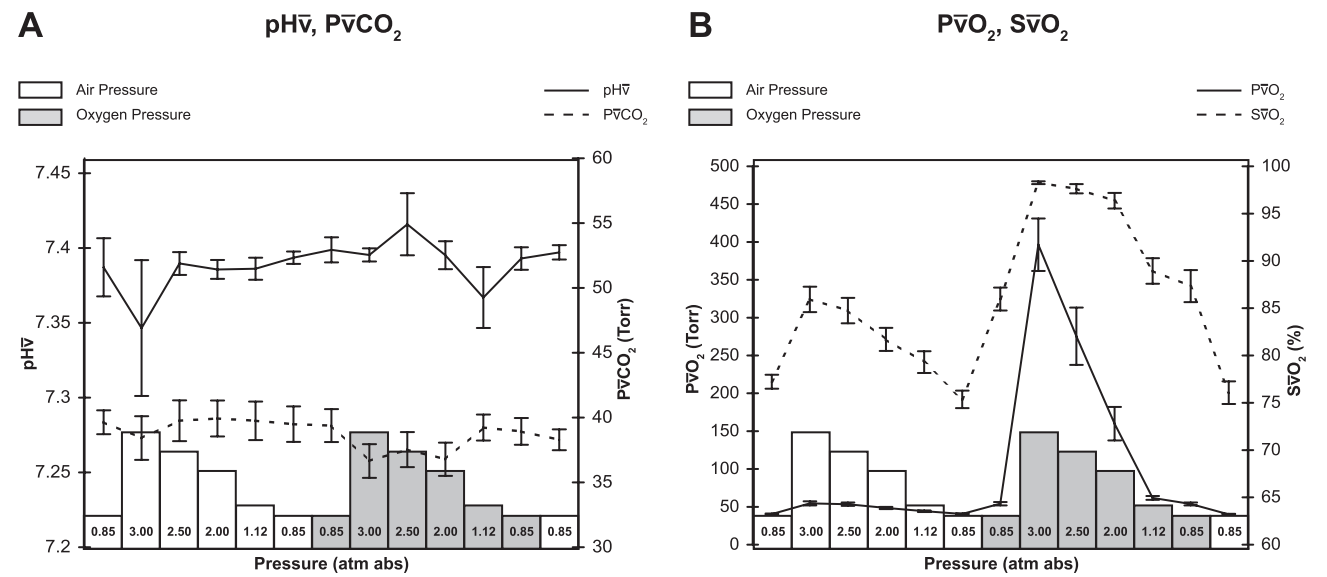


Fig. 7. Pulmonary arterial pH ($pH\bar{v}$; *A*), pulmonary arterial carbon dioxide tension ($P\bar{v}_{CO_2}$; *A*), pulmonary arterial oxygen tension ($P\bar{v}_{O_2}$; *B*), and pulmonary arterial oxyhemoglobin saturation ($S\bar{v}_{O_2}$; *B*) of subjects exposed to hyperbaric air and HBO_2. Values are means ± SE. The $pH\bar{v}$ did not change from baseline across conditions. $P\bar{v}_{CO_2}$ was lower than baseline during HBO_2 exposure at 3.0 and 2.0 atm abs. $P\bar{v}_{O_2}$ and $S\bar{v}_{O_2}$ increased as the alveolar partial pressure of O_2 increased during hyperbaric air and HBO_2 exposures.

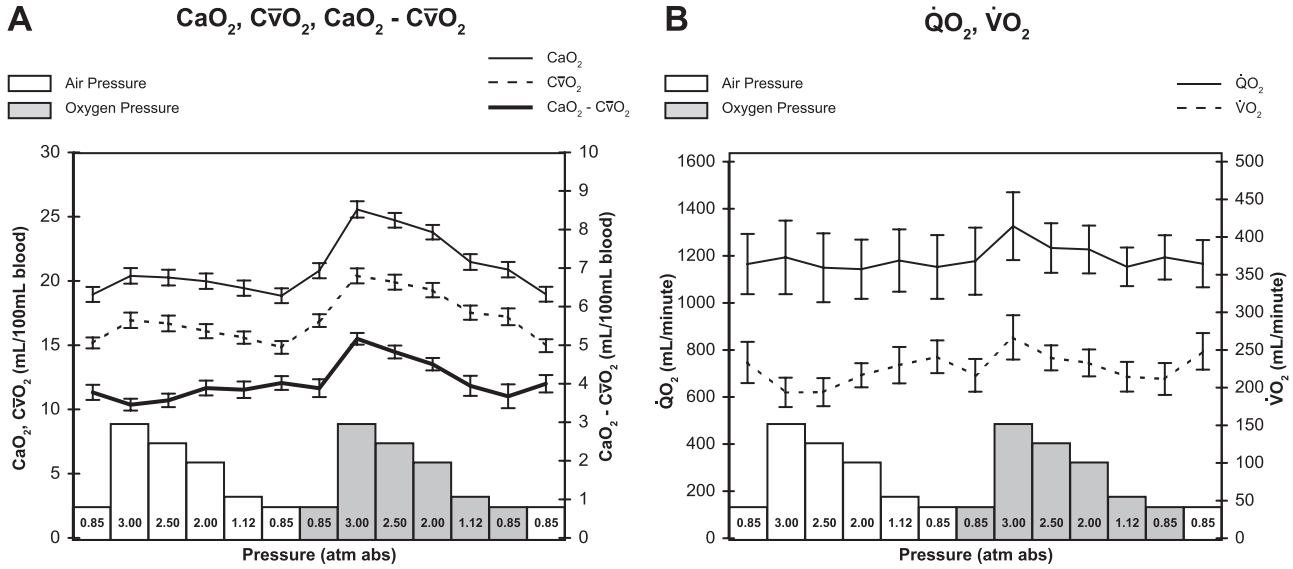


Fig. 8. Arterial (Ca_{O_2}; *A*) and pulmonary arterial oxygen contents ($C\bar{v}_{O_2}$; *A*), the arterial minus the mixed venous oxygen contents, or oxygen extraction ($Ca_{O_2} - C\bar{v}_{O_2}$; *A*), oxygen delivery ($\dot{Q}_{O_2}$; *B*), and oxygen consumption ($\dot{V}_{O_2}$; *B*) of subjects exposed to hyperbaric air and HBO_2. Values are means ± SE. With increased partial pressures of O_2, Ca_{O_2} and $C\bar{v}_{O_2}$ increased due to increased dissolved O_2 (*A*). $Ca_{O_2} - C\bar{v}_{O_2}$ increased during HBO_2 exposure. $\dot{Q}_{O_2}$ and $\dot{V}_{O_2}$ were relatively constant during hyperbaric air and HBO_2 exposures.

$\dot{Q}_s/\dot{Q}_t$ was higher than expected while subjects breathed air at 0.85 atm abs. One explanation for this elevation is the fact that this research took place at 1,500 m above sea level, where the resting baseline Pa_{O_2} was 75–80 Torr. In one study, intubated patients with pulmonary problems breathing supplemental oxygen also had increased $\dot{Q}_s/\dot{Q}_t$ (10), but we could find no other experiment in normal human subjects where $\dot{Q}_s/\dot{Q}_t$ was measured by incorporating data from PA catheters at increased altitude. Other investigators have demonstrated that ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatch does not increase while breathing at increased altitude at rest (13, 18, 37). If $\dot{V}_A/\dot{Q}$ does not change, it is reasonable to assume that $\dot{Q}_s/\dot{Q}_t$ will not change. An increased $\dot{Q}_t$ due to stress or exercise could increase $\dot{Q}_s/\dot{Q}_t$ while breathing air at our altitude, but all subjects were at rest and simultaneous measurements of $\dot{Q}_t$ were normal. Atelectasis could contribute to an increased $\dot{Q}_s/\dot{Q}_t$ value. All subjects in this study were normal, and a chest radiograph taken only a short period before measurement of the initial $\dot{Q}_s/\dot{Q}_t$ value was normal in all 10 subjects, without evidence of atelectasis. However, subjects were supine for up to 2 h before initial $\dot{Q}_s/\dot{Q}_t$ measurement, so it is possible undiscovered atelectasis played a role in increasing $\dot{Q}_s/\dot{Q}_t$ in these subjects.

During breathing of 100% O_2 at 1.12 atm abs, a pressure slightly greater than sea level, $\dot{Q}_s/\dot{Q}_t$ was 7%, a value that is within the expected range. With exposure to HBO_2, $\dot{Q}_s/\dot{Q}_t$ dropped to zero. It is reasonable to assume that this low $\dot{Q}_s/\dot{Q}_t$ value is attributable to high O_2 concentrations in mixed venous blood and in other circulations that contribute to venous admixture (e.g., Thebesian and bronchial circulation) such that venous admixture (physiological shunt) do not significantly contribute to increasing the shunt fraction.

In addition, intrapulmonary shunts may contribute to $\dot{Q}_s/\dot{Q}_t$ (20). With high alveolar oxygen tensions during hyperbaric oxygen exposure, these intrapulmonary shunts may participate in gas exchange because of high oxygen diffusion gradients. In patients with abnormal lung function, Pa_{O_2} was greater than predicted during HBO_2 compared with 1.0 atm abs measurements, suggesting their $\dot{Q}_s/\dot{Q}_t$ fell during HBO_2 exposure (44). Mathematical modeling demonstrates that $\dot{Q}_s/\dot{Q}_t$ falls as the ratio of Pa_{O_2} to FI_{O_2} (fraction of inspired O_2) increases (31), such as during hyperbaric air and HBO_2 breathing, which our data support. This is the first published report measuring $\dot{Q}_s/\dot{Q}_t$ of humans exposed to HBO_2, so these results cannot be compared with other work.

In prior research, we found subjects exposed to HBO_2 had a wider A-aD_{O_2} (45) compared with those in a prior study (7), similar to a finding in patients following open-heart surgery (32). These findings raise the question of whether the increased A-aD_{O_2} might be due to a worsening $\dot{Q}_s/\dot{Q}_t$ in association with HBO_2. On the contrary, in this present study, we found $\dot{Q}_s/\dot{Q}_t$ fell below baseline and did not increase.

Study limitations. Our study is limited due to the relatively small sample size of 10 subjects and individual variability. Other limitations include confounding covariables such as the stress of catheter insertion and variation in ambient chamber temperature. The contribution to hemodynamic variables of a change in chamber temperature up to 3°C is unknown but is probably of little significance.

Measurements of $\dot{V}_{O_2}$ in this study may be limited by measurement of $\dot{V}_{O_2}$ by PA catheter. Because of the technical challenges of measuring $\dot{V}_{O_2}$ when a subject breathes 100% O_2, compounded by the difficulty performing $\dot{V}_{O_2}$ measurements inside a monoplace hyperbaric chamber, we were not able to overcome this limitation.

The apparent reduction in calculated $\dot{Q}_s/\dot{Q}_t$ may not reflect an actual reduction in $\dot{Q}_s/\dot{Q}_t$ because of limitation in the calculations when applied to HBO_2 conditions. Inaccuracy can occur in this calculation when very high Pa_{O_2} and $P\bar{v}_{O_2}$ values are present, as well as by low effective solubility of oxygen during HBO_2 (36).

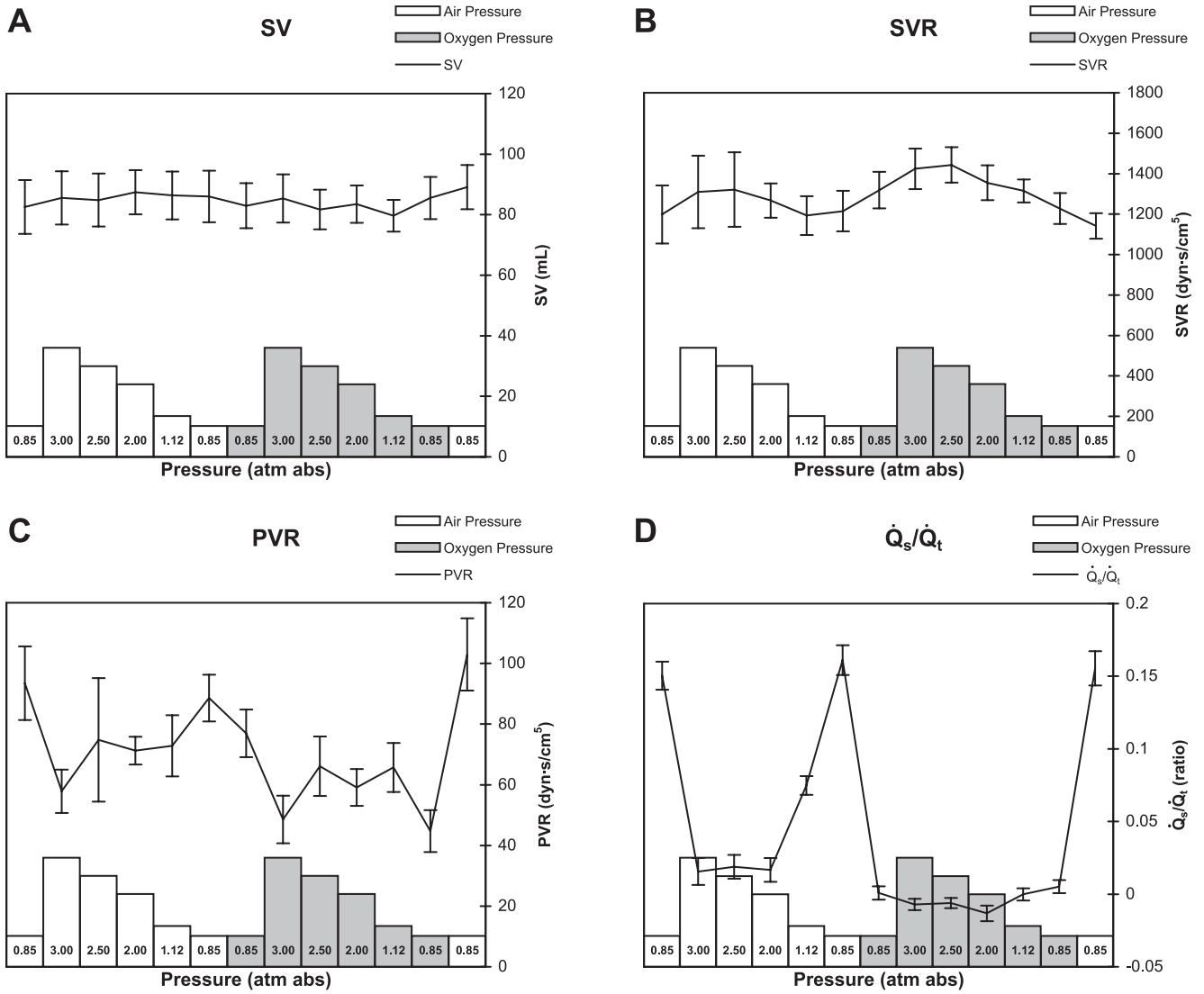


Fig. 9. Stroke volume (SV; *A*), systemic vascular resistance (SVR; *B*), pulmonary vascular resistance (PVR; *C*), and right-to-left shunt fraction ($\dot{Q}_s/lAp_t$; *D*) of subjects exposed to hyperbaric air and HBO_2. Values are means ± SE. SV (*A*) did not change across conditions. SVR was higher than baseline during HBO_2 exposure (*B*). PVR fell during hyperbaric air and HBO_2 exposures compared with baseline (*C*). $\dot{Q}_s/\dot{Q}_t$ was similar at ~0.15 with subjects breathing air at atmospheric pressure (0.85 atm abs at an altitude of 1,500 m above sea level). During hyperbaric air exposures, $\dot{Q}_s/\dot{Q}_t$ fell from baseline to ~0.02. During HBO_2 exposures, $\dot{Q}_s/\dot{Q}_t$ approximated zero and then returned to baseline with air breathing at atmospheric pressure (*D*).

It is possible the hyperbaric air exposure modified the subjects' hemodynamic response to 100% O_2 inhalation, including HBO_2. To maximize the information obtained from each subject, they were compressed with analogous hyperbaric profiles, differing only in the $F_{I_{O_2}}$. Subjects underwent the hyperbaric air profile before the HBO_2 profile to reduce the risk of decompression sickness. The study design could have been improved by randomly allocating subjects to receive either hyperbaric air or HBO_2 initially, but we did not have a sufficient number of subjects to gain useful information by randomization. Hyperbaric air compression could have been omitted but would have limited the conclusions that could be drawn regarding the effect of hyperbaric pressure vs. the effect of HBO_2.

Conclusion. This study examined the effect of hyperbaric air and HBO_2 on arterial and PA hemodynamics and blood gas measures. The data presented are in agreement with others that HR and $\dot{Q}$ fall with HBO_2 exposure. The Pa_{O_2}, $P\bar{v}_{O_2}$, $S\bar{v}_{O_2}$, and Pa_{CO_2} values were within expected ranges during hyperbaric air and HBO_2 exposures. PVR and $P\bar{v}_{CO_2}$ decreased during HBO_2 exposure. Finally, $\dot{Q}_s/\dot{Q}_t$ was higher than expected with subjects breathing air at atmospheric pressure and fell to zero during HBO_2 exposure.

ACKNOWLEDGMENTS

We are very grateful to the subjects who volunteered for this study. We thank Jeff Noyes, CV monitoring, for assistance with the arterial catheter placements. The support and critique of study design of Dr. Terry Clemmer, Director of Critical Care, LDS Hospital, is appreciated. We also thank Gary Willoughbee, Baxter Healthcare, for equipment and technical advice. We also appreciate the assistance of Dr. David Kristo, Valerie Larson-Lohr, Shauna Hein, and Diane Haberstock.

Present address of S. Howe: Medical Informatics, LDS Hospital, Salt Lake City, UT 84143.

GRANTS

This study was supported by Deseret Foundation Grant 268; LDS Hospital; Baxter Healthcare Corporation, Irvine, CA; Abbott Critical Care Systems, Chicago, IL; Biomedical Sensors, Malvern, PA; and Arrow International, Reading, PA.

REFERENCES

1. **Andersen A, Hillestad L.** Hemodynamic responses to oxygen breathing and the effect of pharmacological blockade. *Acta Med Scand* 188: 419–424, 1970.
2. **Barratt-Boyes BG, Wood EH.** Cardiac output and related measurements and pressure values in the right heart and associated vessels, together with an analysis of the hemodynamic response to the inhalation of high oxygen mixtures in healthy subjects. *J Lab Clin Med* 51: 72–90, 1958.
3. **Behnke AR, Forbes HS, Motley EP.** Circulatory and visual effects of oxygen at 3 atmospheres pressure. *Am J Physiol* 114: 436–442, 1935.
4. **Bell RL, Borgwardt RE.** The theory of high-altitude corrections to the US Navy standard decompression tables The cross corrections. *Undersea Biomed Res* 3: 1–23, 1976.
5. **Bergo GW, Risberg J, Tyssebotn I.** Effect of 5 bar on cardiac output and organ blood flow in conscious rats. *Undersea Biomed Res* 15: 457–470, 1989.
6. **Boerema I, Meyne NG, Brummelkamp WH, Bouma S, Mensch MH, Kamermans F, Stern Hanf M, Van Aalderen W.** Life without blood; a study of the influence of high atmospheric pressure and hypothermia on dilution of blood. *J Cardiovasc Surg* 1: 133–146, 1960.
7. **Clark JM, Lambertsen CJ.** Alveolar-arterial oxygen differences in man at 0.2, 10, 20, and 35 ata inspired P_{O_2}. *J Appl Physiol* 30: 753–763, 1971.
8. **Committee on Hyperbaric Oxygenation.** *Fundamentals of Hyperbaric Medicine* (Publication 1298). Washington, DC: National Academy of Sciences, 1966.
9. **Department of the Navy.** *US Navy Diving Manual.* Washington, DC: Government Printing Office, 1985.
10. **Douglas ME, Downs JB, Dannemiller FJ, Hodges MR, Munson ES.** Change in pulmonary venous admixture with varying inspired oxygen. *Anesth Analg* 55: 688–695, 1976.
11. **Falicov RE, Resnekov L.** Relationship of the pulmonary artery end-diastolic pressure to the left ventricular end-diastolic and mean filling pressures in patients with and without left ventricular dysfunction. *Circulation* 42: 65–73, 1970.
12. **Fife CE, Camporesi EM.** Physiologic effects of hyperbaric hyperoxia. In: *Problems in Respiratory Care*, edited by Moon RE, Camporesi EM. Philadelphia, PA: Lippincott, 1991, vol. 4, no. 2.
13. **Gale GE, Torre-Bueno JR, Moon RE, Saltzman HA, Wagner PD.** Ventilation-perfusion inequality in normal humans during exercise at sea level and simulated altitude. *J Appl Physiol* 58: 978–988, 1985.
14. **Gardner RM.** Direct blood pressure measurement-dynamic response requirements. *Anesthesiology* 54: 227–236, 1981.
15. **Gardner RM.** Hemodynamic monitoring: from catheter to display. *Acute Care* 12: 3–33, 1986.
16. **Gardner RM, Maack BB, Evans RS, Huff SM.** Computerized medical care: the HELP system at LDS Hospital. *J AHIMA* 63: 68–78, 1992.
17. **Gardner RM, Pryor TA, Warner HR.** The HELP hospital information system: update 1998. *Int J Med Inform* 54: 169–182, 1999.
18. **Hammond MD, Gale GE, Kapitan KS, Ries A, Wagner PD.** Pulmonary gas exchange in humans during normobaric hypoxic exercise. *J Appl Physiol* 61: 1749–1757, 1986.
19. **Henry DA, LeBolt S.** Invasive hemodynamic monitoring: radiologist's perspective. *Radiographics* 6: 535–572, 1986.
20. **Imray CH, Pattinson KT, Myers S, Chan CW, Hoar H, Brearey S, Collins P, Wright AD; The Birmingham Medical Research Expeditionary Society.** Intrapulmonary and intracardiac shunting with exercise at altitude. *Wilderness Environ Med* 19: 199–204, 2008.
21. **Kenmure AC, Murdoch WR, Hutton I, Cameron AJ.** Hemodynamic effects of oxygen at 1 and 2 ata pressure in healthy subjects. *J Appl Physiol* 32: 223–226, 1972.
22. **Lambertsen CJ, Stroud MW, Gould RH, Kough JH, Ewing JH, Schmidt CF.** Oxygen toxicity; respiratory responses of normal men to inhalation of 6 and 100 per cent oxygen under 3.5 atmospheres pressure. *J Appl Physiol* 5: 487–494, 1953.
23. **Mak S, Azevedo ER, Liu PP, Newton GE.** Effect of hyperoxia on left ventricular function and filling pressures in patients with and without congestive heart failure. *Chest* 120: 467–473, 2001.
24. **McMahon TJ, Moon RE, Luschinger BP, Carraway MS, Stone AE, Stolp BW, Gow AJ, Pawloski JR, Watke P, Singel DJ, Piantadosi CA, Stamler JS.** Nitric oxide in the human respiratory cycle. *Nat Med* 8: 711–717, 2002.
25. **Milnor WR.** Principles of Hemodynamics. In: *Medical Physiology* (14th ed.), edited by Mountcastle VB. St. Louis, MO: Mosby, 1980.
26. **Paulus WJ, Vantrimpont PJ, Shah AM.** Acute effects of nitric oxide on left ventricular relaxation and diastolic dispensability in humans: assessment by bicoronary sodium nitroprusside infusion. *Circulation* 89: 2070–2078, 1994.
27. **Pelaia P, Rocco M, Conti G, De Blasi RA, Bufi M, Antonelli M, Bortone C.** Hemodynamic modifications during hyperbaric oxygen therapy. *J Hyperb Med* 7: 229–237, 1992.
28. **Piantadosi CA.** Pulmonary gas exchange, oxygen transport, and tissue oxygenation. In: *Physiology and Medicine of Hyperbaric Oxygen Therapy*, edited by Neuman TS, Thom SR. Philadelphia, PA: Saunders Elsevier, 2008.
29. **Pisarello JB, Clark JM, Lambertsen CJ, Gelfand R.** Human circulatory responses to prolonged hyperbaric hyperoxia in Predictive Studies V. In: *Underwater and Hyperbaric Physiology. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology*, edited by Bove AA, Bachrach AJ, Greenbaum LJ Jr. Bethesda, MD: Undersea and Hyperbaric Medical Society, 1987.
30. **Plewes JL, Farhi LE.** Peripheral circulatory responses to acute hyperoxia. *Undersea Biomed Res* 10: 123–129, 1983.
31. **Räsänen J, Downs JB, Malec DJ, Oates K.** Oxygen tensions and oxyhemoglobin saturations in the assessment of pulmonary gas exchange. *Crit Care Med* 15:1058–1061, 1987.
32. **Rodionov VV, Abbakumov VV, Efuni SN, Kharitonov SA, Nurpeisov AZ.** Effect of hyperbaric oxygenation on central hemodynamics and oxygenating function of the lungs in open-heart surgery. *Fiziol Zh* 37: 52–57, 1991.
33. **Rubanyi GM, Vanhoutte PM.** Superoxide anions and hyperoxia inactivate endothelium-derived relaxing factor. *Am J Physiol Heart Circ Physiol* 250: H822–H827, 1986.
34. **Runciman WB, Ilsley AH, Roberts JG.** An evaluation of thermodilution cardiac output measurement using the Swan-Ganz catheter. *Anaesth Intensive Care* 9: 208–220, 1981.
35. **Savitt MA, Rankin JS, Elberry JR, Owen CH, Camporesi EM.** Influence of hyperbaric oxygen on left ventricular contractility, total coronary blood flow, and myocardial oxygen consumption in the conscious dog. *Undersea Hyperb Med* 21: 169–183, 1994.
36. **Wagner PD.** Susceptibility of different gases to ventilation-perfusion inequality. *J Appl Physiol* 46: 372–386, 1979.
37. **Wagner PD, Smith CM, Davies NJ, McEvoy RD, Gale GE.** Estimation of ventilation-perfusion inequality by inert gas elimination without arterial sampling. *J Appl Physiol* 59: 376–383, 1985.
38. **Wanger J.** *Pulmonary Function Testing: A Practical Approach.* Baltimore, MD: Williams & Wilkins, 1992.
39. **Weaver LK.** Critical care of patients needing hyperbaric oxygen therapy. In: *Physiology and Medicine of Hyperbaric Oxygen Therapy*, edited by Neuman TS, Thom SR. Philadelphia, PA: Saunders Elsevier, 2008.
40. **Weaver LK.** Pulmonary artery catheter use in critically-ill patients treated in the monoplace hyperbaric chamber (Abstract). *Undersea Biomedical Res* 17, *Suppl*: 132, 1990.
41. **Weaver LK.** Technique of Swan-Ganz catheter monitoring in patients treated in the monoplace hyperbaric chamber. *J Hyperb Med* 7: 1–17, 1992.
42. **Weaver LK.** Transcutaneous oxygen and carbon dioxide tensions compared to arterial blood gases in normals. *Respir Care* 52: 1490–1496, 2007.
43. **Weaver LK, Churchill S.** Pulmonary edema associated with hyperbaric oxygen therapy. *Chest* 120: 1407–1409, 1988.
44. **Weaver LK, Howe S.** Arterial oxygen tension of patients with abnormal lungs treated with hyperbaric oxygen is greater than predicted. *Chest* 106: 1134–1139, 1994.
45. **Weaver LK, Howe S.** Normobaric measurement of arterial oxygen tension in subjects exposed to hyperbaric oxygen. *Chest* 102: 1175–1181, 1992.
46. **Weaver LK, Howe S, Berlin SL.** Normobaric measurement of O_2 tension of blood and saline tonometered under hyperbaric O_2 conditions. *J Hyperb Med* 5: 29–38, 1990.
47. **West JB.** *Respiratory Physiology* (4th ed.). Baltimore, MD: Williams & Williams, 1990.
48. **Whalen RE, Saltzman HA, Holloway DH Jr, McIntosh HD, Sieker HO, Brown IW Jr.** Cardiovascular and blood gas responses to hyperbaric oxygenation. *Am J Cardiol* 15: 638–646, 1965.