CARDIAC PRESSURE CHANGES WITH VENOUS GAS EMBOLISM AND DECOMPRESSION

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The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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Venous air embolism is reported with decompression to a decreased ambient pressure. With severe decompressions or in cases where an intracardiac septal defect (patent foramen ovale) exists, the venous bubbles can become arterialized and cause neurological decompression illness. Incidence rates of patent foramen ovale in the general population range from 25-34% and yet aviators, astronauts and undersea divers who have decompression-induced venous bubbles do not demonstrate neurological symptoms at these high rates. This apparent disparity may be attributable to the normal pressure gradient across the atria of the heart that must be reversed for there to be flow patency. We evaluated the effects of 1) venous air embolism (0.025, 0.05 and 0.15 ml*kg -1*min-1 for 180 min, 2) hyperbaric decompression, and 3) hypobaric decompression on the pressure gradient across the left and right atria. Left ventricular end-diastolic pressure was used as a measure of left atrial pressure. In a total of 92 experimental evaluations, there were no reported reversals in the mean pressure gradient across the atria, and a total of 3 transient reversals in the peak gradient pressures. This disparity may be due to insufficent amounts of venous gas to cause a pressure and hence flow reversal across the atria.

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INTRODUCTION

Venous air embolism (VAE) is commonly reported when decompression occurs to lowered ambient pressures as experienced by divers, astronauts and aviators. These circulating bubbles ultimately become trapped within the lungs where they are excreted via the airways or dissolved in the blood. Although venous bubbles may be associated with lung injury (14,20,24,45), even at moderate doses (11) these events are less severe than those reported with systemic arterial air embolism (28). Arterialization of the VAE can occur via; a) the lung microcirculation (9,10,12,61), b) large anatomical shunts within the lung parenchyma (38,44), or c) intracardiac septal defects (2,3,41,42,62,66).

An atrial septal defect (ASD), often manifest as a patent foramen ovale (PFO) located between the atria of the heart, may provide an anatomical route for the venous gas bubbles to access the systemic arterial circulation; i.e., paradoxical air embolism (PAE). These arterial bubbles can result in cerebral or myocardial embolization and infarction thereby causing a more significant injury or even death.

It is generally accepted that VAE commonly occur with even moderate decompressions either from elevated hydrostatic pressures or increasing altitude. With the reported incidence of ASD's ranging from 25-34% in the adult population (26,37), a disparity exists between these values and the actual cases of serious decompression illness (DCI) in aviators and astronauts that experience VAE. This disparity may be explained in part by the fact that the normal pressure gradient between the right and left atria must be reversed for VAE to cross into the left heart via an ASD. In those subjects exhibiting an ASD and that experience VAE after decompression, but no symptoms of any neurological involvement, it is likely that the extent of bubbling was perhaps inadequate to cause a reversal in atrial pressure gradients and to effect the abnormal transport of bubbles across the anatomical shunt. The mechanism by which VAE can cause a reversal in the normal pressure gradient between the atria involves the obstruction of pulmonary vessels or a corresponding vasoconstriction resulting from reflex or mediator activation. These actions cause an increase in vascular resistance, thereby increasing right atrial pressure and decreasing cardiac output which in return may cause the left atrial pressure to fall below that of the right atrium.

Recent studies have suggested a greater likelihood of serious hyperbaric DCI in individuals with an ASD (41,42,66), although this finding was not supported with altitude decompression (16). These observations do however, raise the question of the validity of screening divers, aviators and astronauts for the presence of ASD's to determine their acceptability/fitness for diving or flight duty.

The aim of the present study was to determine the effects of VAE as well as decompression to altitude or from hyperbaric pressures on the intracardiac pressures of anesthetized dogs and to determine at what point the left to right atrial pressure gradients are likely to reverse. Arterialization of the VAE was not studied.

METHODS AND MATERIALS

Venous Air Infusions

Surgery: Twenty-two mongrel dogs (22±6 kg) of both sexes were fasted for twenty four hours, anesthetized with pentobarbital sodium (25 mg/kg, IV) and maintained with 10 mg/hr. The dogs were intubated and mechanically ventilated with air using a volume regulated ventilator (Harvard) at a tidal volume (15 ml/kg) and frequency (10-14 breaths/min) adequate to maintain baseline arterial carbon dioxide ($paCO_2$) tensions at between 30-45 mmHg. The dogs were maintained in a supine position, temperature controlled with a water-heated blanket and hydrated with Ringer's lactate. Polyvinyl catheters were placed into the abdominal aorta via the left femoral artery for measurement of mean arterial blood pressure (MAP), in the right atrium (RAP), and the pulmonary artery via the right jugular vein (PAP), the right ventricle (RVP; mean, systolic and diastolic), the left ventricle via the right carotid artery for left ventricular end-diastolic pressure (LVEDP), as an indirect measure of left atrial pressure, and the inferior vena cava via the left femoral vein for venous access. Airway pressure was measured from a connector at the proximal end of the endotracheal tube. The right ventricular catheter was a double lumen with the proximal opening located at a point just above the right atrium, as verified by the pressure tracing, for the venous air infusions. The catheters, excepting the airway, were fluid filled with degassed heparinized saline and connected to calibrated pressure transducers (Isotec), zero referenced at the right atrial level. Cardiac output (CO) was measured using thermodilution (Arrow) via the multi-lumen pulmonary artery catheter. Arterial blood gases were measured (Instrumentation Laboratories) at baseline and hourly thereafter. End-tidal carbon dioxide ($ET-CO_2$) and arterial oxygen saturation (O_2-Sat) were continuously measured (Nellcor).

Air infusion: Following stabilization (30-45 min) and collection of baseline data, air was infused into the right atrium for 180 min using a volume controlled reciprocating servo pump (Harvard). The dogs in the air infusion studies were subdivided into three experimental groups (n = 6 each), depending upon the air infusion dose and one control group (n = 4). The three air doses were 0.025, 0.05 and 0.15 $ml*kg^{-1}*min^{-1}$. Hemodynamic measurements were collected throughout the air infusion and for a 60 min post infusion period. CO and blood gases were measured every 60 min. Each dog received the VAE infusion for 180 min only once. The internal diameter of the air infusion catheter was 500 microns, which approximated the initial size of the venous bubbles, although fracture into smaller progeny microbubbles in the sizes reported with decompression (27) likely occurred in the turbulent regions of the right ventricular outflow tract. The hearts were inspected post mortem for the presence of an ASD.

Hyperbaric Decompression

Six dogs were prepared as previously described with the addition of placement of an ultrasonic Doppler probe used to detect VAE that formed as a result of the decompression. A pulsed Doppler probe (20 mHz, Hartley), mounted in a 7-9 mm acrylic cuff was surgically placed around the inferior vena cava via laparotomy, approximately 1-2 cm above the renal veins. The probe

signal was range gated to maximize the reflected audible signal representing bubble recordings. A small number of test bubbles, created by agitating 3-5 ml whole blood with < 0.25 cc air, were infused into the IV line to verify probe placement and probe excitation voltage. Decompression bubble signals were semi-quantitatively evaluated according to Grades 1-4 using a modified Spencer code (55) which consisted of periodic audio sampling at resting conditions and following deep knee bends with the bubble score recorded as the peak value obtained in the two conditions. In some cases, the signals were recorded on cassette (Maranz) for playback analysis or digitized directly for computer-assisted evaluation (13). The instrumented animals were placed in the experimental compression chamber, ventilation was switched to a pneumatic-driven time cycled ventilator (Bird) and compressed to 1.84 bar (60 feet of sea water, fsw) at 0.37 bar/min (12 fsw/min) for 120 min, then decompressed to sea level at 0.92 bar/min (30 fsw/min). The animals were then immediately removed from the chamber and monitored post dive for 90 min.

Altitude Studies

Six dogs were prepared as previously described, including the vena caval Doppler probe. LVEDP was measured with a non fluid-filled transducer-tipped catheter (Millar). Tetanic muscle stimulation was used while at altitude to release venous bubbles trapped within the capillary beds of the left hind limb for the Doppler detection. To effect muscle stimulation, two needle electrodes were inserted into the right biceps femoris muscle and the cables were connected to a nerve stimulator (Sun-Med) located outside of the chamber. The dogs were placed into the altitude chamber and all pressure and Doppler monitors were connected to through-pass devices for continuous recordings. Following baseline data collection the dogs were decompressed to 40,000 ft (4,000 ft/min) for 180 min. The animals were ventilated with room air to 20,000 ft and then switched to 100% oxygen thereafter. No oxygen prebreathing was administered. The animals were then recompressed to sea level at 10,000 ft./min. Monitoring was continued throughout the altitude simulation and until no further VAE could be detected by the Doppler, usually not exceeding 45 min. The breathing gas was switched back to air at 20,000 ft during descent.

Statistics

Data are expressed as mean $\pm$ SEM. Data were analyzed using analysis of variance (ANOVA) with individual comparisons made using Bonferroni corrected Student's t test. $p < 0.05$ was considered statistically significant.

RESULTS

Venous Air Infusions

Hemodynamic data are summarized in Tables 1-3. Figure 1 shows the time course of changes for PAP and RAP in both the VAE and altitude simulated studies. MAP decreased with each of the doses; reaching significance at particular intervals with each air dose. PAP increased significantly with each air dose, beginning within the first 5 min of the infusion and remaining elevated for the 180 min period (Figure 1). Peak increases were dose dependent; the maximum value reaching 104% above baseline (0.15 $ml*kg^{-1}*min^{-1}$). RAP values were unchanged at the 0.025 dose, decreased (nonsignificant) with the 0.05 dose and elevated with the 0.15 $ml*kg^{-1}*min^{-1}$ dose (nonsignificant). LVEDP values were not significantly different with any of the air infusion doses. RVP mean, diastolic and systolic values were unchanged with the lower two doses, while mean and systolic values increased significantly with the 0.15 $ml*kg^{-1}*min^{-1}$ dose. RVP diastolic values slightly increased (nonsignificant) with the higher two doses (Figure 2). The LVEDP-RAP mean gradient remained positive (non-reversed at each dose) (Figure 4). Reversals were observed however, intermittently with inspiration and within an individual cardiac cycle. Examining peak gradient pressure changes (maximum RAP and minimum LVEDP, i.e. LVEDP-RAPp) throughout individual respirations and cardiac cycles did demonstrate two incidents of reversal; (one dog at hour three in the 0.05 $ml*kg^{-1}*min^{-1}$ group; one dog at hour two in the 0.15 $ml*kg^{-1}*min^{-1}$ group. Three additional dogs had pressure gradients of 0 to 0.2 mmHg during the experimental phases. HR decreased with all three doses, reaching significance at hour three of the 0.15 $ml*kg^{-1}*min^{-1}$ dose. CO was decreased (significant) at the 0.025 and 0.05 $ml*kg^{-1}*min^{-1}$ doses (Figure 3). O_2-Sat and ET-CO_2 were decreased with each air infusion. PVR was increased at each dose (Figure 3), while TPR was elevated (nonsignificant) at the lower doses and slightly decreased (nonsignificant) at the 0.15 $ml*kg^{-1}*min^{-1}$ dose. Arterial pO_2 was decreased (significant) with the 0.05 and 0.15 $ml*kg^{-1}*min^{-1}$ dose and $paCO_2$ was elevated with each dose, 0.025 and 0.15 $ml*kg^{-1}*min^{-1}$ groups achieving significance.

Hyperbaric Decompressions

The hemodynamic changes associated with decompression from 1.84 bar are given in Table 4. MAP values were not significantly changed. PAP values increased to a peak 30 min post decompression (nonsignificant), and returned to baseline values over the next 60 min; RAP values were unchanged (Figure 1). LVEDP decreased within the first 10 min post decompression (nonsignificant) and remained slightly decreased. RVP pressures were slightly decreased (nonsignificant) for mean and systolic values, while diastolic values were slightly elevated (Figure 2). HR was decreased (nonsignificant) by 26% within the first 30 min post decompression, returning to within 13% of baseline over the 90 min recovery period. CO steadily decreased, reaching significance 90 min post dive (Figure 3). PVR increases reached peak values at 30 min post dive (155%) but were elevated throughout the 90 min (Figure 3). TPR increased progressively over the 90 min post dive period. The LVEDP-RAP mean gradient decreased post decompression while never achieving a reversal in the direction of the gradient (Figure 4). Arterial PAO_2 was elevated post decompression and

PCO_2 was unchanged. ET-CO_2 was decreased (significant) at 90 min, and O_2-Sat was unchanged. Doppler-detected venous bubbles were first recorded 12.3±4 min (10-18 min, range) post decompression and persisted for up to 120 min. Spontaneous bubbles were detected at a peak Grade of 2 in two dogs and Grade 3 and 4 in one dog each. Grade 4 bubbles were detected in three dogs with deep knee bends. No symptoms of arterial DCI were recorded.

Altitude Simulations

The hemodynamic changes resulting from decompression to simulated altitude are summarized in Table 5. MAP increased at 20,000 ft, probably due in part to the systemic vasoconstriction associated with the switch to 100% oxygen ventilation, and returned to lower than baseline values upon return to sea level pressures. PAP increased progressively (significant) to 20,000 ft, decreased momentarily with the switch to oxygen ventilation then continued to rise to a peak value (106%) 180 min into the simulated flight, presumably due to the persistent embolization of pulmonary vessels by VAE (Figure 1). RAP decreased upon transit to altitude, then increased after 60 min at 40,000 ft. RAP values taken at 120 and 180 min were decreased, although clotting of the venous pressure lines occurred in several incidence and were not corrected until descent (Figure 1). RVP values increased upon ascent and remained elevated throughout the flight (Figure 2). LVEDP increased over the duration of the flight and during the period of maximal venous bubbling (non-significant) then returned towards baseline upon return to sea level (Figure 2). HR was decreased. The LVEDP-RAP peak gradient increased throughout the flight, returning towards baseline with recovery (Figure 4). The mean LVEDP-RAP was never reversed, although one dog had a transient reversal upon arrival at a simulated altitude of 40,000 ft. CO was slightly decreased post flight while PVR was increased (significant) as was TPR (non-significant) (Figure 3). Arterial pO_2 and pCO_2 values were increased post flight. Venous gas bubbles were recorded at Grades 2-4 during the flights. No animals from any of the experimental or control groups had an ASD detected at autopsy. No arterial symptoms of DCI or air embolism were detected in any of the animals.

DISCUSSION

The results of this study demonstrated that the normal mean pressure gradient between the atria of the heart (LAP > RAP, using LVEDPm and p as a measure of LAP) was not reversed with venous air infusions of 0.025, 0.05 and 0.15 $ml*kg^{-1}*min^{-1}$, or with hypo- or hyperbaric decompressions in anesthetized dogs with intact atrial septa. Examining peak gradient changes throughout individual respiratory and cardiac cycles revealed three incidence (3%) with momentary reversals occurring during the experimental air infusions or decompressions, out of a total of 92 recorded measurements.

This relatively low rate for the atrial pressure gradient to reverse with VAE or decompression is consistent with reported findings that patients with a PFO who have VAE do not appear to be symptomatic of arterial embolism at rates predictable from the incidence rates of PFO's in the general population (16). The incidence of PFO's in individuals with no history of cardiac disease has been demonstrated at autopsy to be 27-35% (26,60). Using preoperative precordial echo ultrasound, the detection rate has been reported from 10% to 30% (25,37). Failure to demonstrate a PFO with echocardiography can still occur as a result of improper contrast technique, poor image resolution or inability to produce flow through the defect because of inadequate atrial pressure changes. An inadequate degree of sensitivity and specificity of precordial echocardiography can, for example, result in failure to correctly identify surgical patients at risk of PAE (34,46), examples of which are reported where actual PAE did subsequently occur (3,17). False negative results of preoperative screening for ASDs using precordial echocardiography are not uncommon (33), although superior sensitivity is reported with contrast imaging using transesophageal echo machines (46). Reported use of echocardiography for detection of flow across a PFO suggests that incidence rates range from 5-10% (3,25,29,32,33,37) for resting conditions and from 10-24% for provoked maneuvers (25,33). A review of these incidence rates and of the rates of false-negative transesophageal echocardiography saline-contrast studies is presented by Rafferty (51). From these data, Rafferty concluded that positive tests for a PFO are definitive in nature, however a negative study does not necessarily preclude the possibility of flow patency, especially without proof that any provoked maneuver indeed caused a reversal in the atrial pressure gradient (32).

VAE circulate into the pulmonary microcirculation resulting in both mechanical obstruction and reflex vasoconstriction (30). The subsequent pulmonary hypertension and increase in vascular resistance can cause an increase in RAP relative to LAP that would result in a shunting of blood flow through an ASD. However, even in the presence of VAE, the interatrial pressures, and hence flow, may not always be reversed. Quite often PFOs are located just below the limbus of the fossa ovalis which in some cases may be shielded from superior vena cava blood flow (2). Further, it has been demonstrated that interatrial shunting via ASD's consists predominantly of inferior vena caval blood flow (53,58). Consequently, it may be conjectured that even though significant VAE may occur as a result of decompression, trans-atrial movement of the bubbles as predicted by a reversal in the LAP-RAP gradient may not always occur. The duration of embolization or the speed at which the VAE enter the lung microcirculation may represent other factors influencing flow

reversal through a PFO. In fact, Mehta, et al., (40) reported that rapid bolus injections of 0.5 - 1.5 $ml*kg^{-1}*min^{-1}$ of air into the right atria of dogs with intact atrial septa did not cause a pressure reversal, but that 2.0 $ml*kg^{-1}$ did. This dose was 13.3 times the dose in the present study and far exceeded that normally seen with decompression (49). Vik, et al., (62) reported PAE in anesthetized pigs receiving venous air infusions as small as 0.05 $ml*kg^{-1}*min^{-1}$, and who had PFOs detected by transesophageal echocardiography. Furthermore, in their study the size of the PFOs (4.5 $\pm$ 3.1 mm dia) were not related to the occurrence of PAE and although RAP was elevated (non-significantly) they did not report left heart values. Interestingly, there appear to be significant differences in the tolerance of VAE by swine and dogs; earlier studies by Vik, et al., (61) showed much greater increases in PAP and decreases in MAP than reported for the same air doses in the present study using dogs. Further, the PAP and atrial pressure gradient data with 0.05 $ml*kg^{-1}*min^{-1}$ VAE and altitude decompression reported in the present study approximated each other.

It is important to consider both mean atrial pressures and transient pressure changes that occur throughout a cardiac or respiratory cycle (3) when evaluating PAE via an ASD. This is most evident when examining for the presence of an ASD using contrast echocardiography during the release phase of a valsalva maneuver or following a cough (19,37). With these maneuvers, it is often possible to detect an ASD in subjects that otherwise have normal intra-cardiac pressure gradients across the atria (57). The initial strain phase of a Valsalva causes intrathoracic pressure to increase thereby decreasing venous return and thus RAP. Upon release, the venous return abruptly increases as well as RAP. In subjects with pressure gradients of different magnitudes, varying degrees of intrathoracic pressure release may not be adequate to cause a flow reversal (29). Three percent of the total number of VAE or decompression tests in the present study showed transient reversals in the atrial pressure gradient. These values may change however, with individuals undergoing physical activity.

MAP decreased with each VAE dose, and although statistically significant for the 0.025 and 0.15 $ml*kg^{-1}*min^{-1}$ doses, these values never exceeded 17% of baseline. ECG changes reported with VAE, such as S-T segment depression or T-wave inversion have been associated with reductions in cardiac output and myocardial contractility (9). MAP was not significantly affected by the altitude or hyperbaric decompressions, although the decrease in HR likely contributed to the decrease in CO. PAP was increased in a dose response fashion for the three VAE doses and closely approximated the hypobaric decompression values. These responses have been previously reported over a wider range of air doses (8,10) and are attributable to increased mechanical obstruction, shunt, reflex vasoconstriction and release of vasoactive mediators. These combined effects on the pulmonary microcirculation account for the significant elevations in PVR and to some degree the increase in peripheral vascular tone. RVP values (mean, systolic and diastolic) increased with VAE due to the increased PVR. This finding was previously reported by Powell, et al., (49) who correlated RVP values with decompression-induced venous gas loads to the pulmonary circulation based on an algorithm that was determined from calibrated venous gas infusions.

Arterial oxygen tensions and saturation values decreased with each VAE dose (significant at the larger doses) due largely because of the development of physiological shunt by obstruction of pulmonary vessels by the gas bubbles. Further explanations reported earlier include: 1) changes associated with lung injury that cause diffusion impairment such as edema or atelectasis, 2) changes in the ventilation-perfusion ratio, or 3) opening of pulmonary shunts (36,44,54,56). Obstruction of pulmonary vessels reduces the CO_2 tensions in the exhaled gases ($ET-CO_2$), thereby increasing the values in the arterial blood ($paCO_2$). The increased paO_2 post decompression may be due to the increased oxygen tension at depth (hyperbaric) and reduced extraction post decompression.

Certain conclusions drawn from the present study are dependent to some degree on the degree of confidence that can be placed in the approximation of LAP by LVEDP. Braunwald, et al., (6) reported that in normal individuals LVEDP exceeds LAP mean by an average of only 0.2 mmHg. They further suggested that although atrial systole increased the ventricular filling rate, it did not cause LVEDP to further increase above LAP mean. In another study, Braunwald, et al., (5) reported little difference between LAP mean, LAP z-wave (atrial pressure at onset of left ventricular contraction) and LVEDP. Additionally, the LAP a-wave peak (atrial contraction) was the same as the left ventricular a-wave which represents the transmission of the atrial contractile wave into the left ventricle (6,39). The tallest wave in the LAP pulse is the V-wave which is the pressure at the time that the mitral valve opens. Although the apparent differences in LVEDP (obtained in a closed chested animal) and LAP (principally V waves, obtained by thoracotomy) pose some interpretative limitations on the determination of the atrial gradients, the relative advantage of using a closed-chested versus open-chested preparation presents a compelling argument for its use.

When a reversal of the atrial pressure gradient occurs, either transiently or with mean values during VAE and a PFO exist, the subject is at risk for PAE with subsequent cerebral complications if the bubbles circulate into the brain. This risk factor has been previously recognized in hyperbaric decompression sickness (41). In a later retrospective study of 90 divers, Moon, et al., (42) found a statistically significant relationship between PFO and serious DCI. For the individuals with a resting PFO (i.e., valsalva maneuver or cough was not required to provoke venous contrast transmission through the septal defect) they reported a five-fold increase in risk for serious DCI. Valsalva-induced shunts were not significantly correlated with an increased risk of DCI. Further, no data was reported on the incidence of neurologic DCI and with precordial bubble Grade and PFO. Wilmshurst, et al., (66) studied 61 divers with DCI and 63 controls without DCI and reported that the incidence of PFO did not impact onset of neurologic DCI more than 30 min after surfacing but did so for those with early symptoms. Interestingly, they reported that the group of symptom-free divers had a higher incidence of PFOs than reported in the echocardiographic studies of healthy individuals. Further, they also found that many divers with neurologic DCI and PFOs had undergone other dives with more provocative pressure-time profiles yet without complication. This finding, plus the fact that many symptomless divers had shunts, adds further evidence to the argument put forth in the present study that the amount of gas phase present in the venous circulation is likely to be

an important factor influencing a reversal of the atrial pressure gradient. Some of the variability may therefore be due to the degree of venous bubble formation which is not always predictable, even at identical exposures and with the same subjects.

The extent of venous bubble formation with decompression is difficult to predict, even with the same individual at identical exposures. The physiological impact of the bubbles, apart from mechanical obstruction of the pulmonary microcirculation, involves other criteria such as gas composition (50,56) as well as the release of numerous vasoactive mediators that are likely to relate to the total bubble count or gas/blood interface upon which the biochemical reaction is initiated.

Decompression-induced VAE react with the blood to induce cellular surface changes resulting in the formation of a platelet and lipoidal material "layer" about the blood/bubble interface (48,65). This material includes an electron-dense layer of protein, including fibrinogen, that leads to further obstruction to blood flow and hence elevation in right heart pressures. Other blood/bubble biochemical changes include 1) agglutination of red blood cells; 2) microthrombus formation; 3) platelet aggregation; 4) neutrophil aggregation and activation; 5) alignment and denaturation of plasma proteins; 6) attraction of oriented phospholipids and 7) alterations in blood viscosity, each of which may be involved with the release of vasoactive mediators as well as capillary permeability changes (7,35,43,45). Platelet aggregation (21,47,48,59) can result in release of ADP, serotonin and catecholamines (47) as well as further potentiate microvascular obstruction. Once activated, neutrophils become larger and less deformable (52,67), which reduce their flow through the lungs in acute injury (18). Emigration of neutrophils to the gas bubbles with subsequent sequestration in the pulmonary capillaries is likely triggered by a number of chemotactic factors (31) of which complement activation, reportedly increased with decompression (64) is likely to play a role. Wang, et al. (63) reported that VAE in isolated rat lungs did not increase the leukocyte count in the perfusate but did elevate those leukocytes that were activated. Several investigatcrs have also reported a significant elevation in thromboxane B_2 with VAE (4,22). Thromboxane B_2 is a metabolite of the cyclooxygenase pathway and is an active pulmonary vasoconstrictor. Wang also reported increases in endothelin with VAE, which is a recently described endothelium derived peptide with profound vasoconstrictor effects (15). Although the specific role of each of these vasoactive mediators in the pathogenesis of DCI and the subsequent hemodynamic changes in vascular resistance that may alter the LAP-RAP gradient are not resolved, it is likely that further studies in this area will elucidate a combination of cause and effect relationships.

It has been established that systemic VAE pose a significant risk to personnel undergoing decompression and further postulated that a PFO may increase that risk factor. Reversal of the normal atrial pressure gradient can occur, at least transiently, with release of a valsalva maneuver, cessation of positive pressure breathing, cessation of the L-1 or M-1 anti-G straining maneuver, Muller maneuver, negative pressure breathing or even a cough (1,2,23). Further, pulmonary hypertension resulting from hypoxic pulmonary vasoconstriction as a consequence of altitude exposure (23) or following

mediator release caused by VAE may also elevate RAP and contribute to an atrial pressure gradient reversal.

Altitude decompression resulting in the formation of VAE and DCI has occurred for many years and is likely to continue as aircraft altitude capability increases. Continued exposure of individuals with a PFO to these environments requires a better understanding of their hemodynamic consequences. This report addresses some of these issues.

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Table 1

VENOUS AIR INFUSION

AIR DOSE: 0.025 $ml*kg^{-1}*min^{-1}$ (N = 6)

	Baseline	60 min	120 min	180 min
MAP	165±7	157±6	155±5	148*±6
PAP	13.1±1.2	16.3*±1.7	16.5*±1.3	17.3*±1.5
RAPm	-0.4±0.9	0.1±1.2	-0.4±0.7	-0.6±0.4
RAPp	1.3±1.0	2.7±1.4	2.0±0.8	1.5±0.6
LVEDPm	4.7±1.2	4.6±0.7	4.4±0.6	5.1±1.0
LVEDPp	5.0±1.4	5.6±1.1	5.8±1.1	5.7±1.0
RVPm	8.0±0.5	10.0±1.9	8.4±1.1	8.9±1.3
RVPs	20.3±1.7	22.2±2.9	20.8±1.8	21.5±1.6
RVPd	1.6±0.5	2.3±1.1	1.8±0.5	2.2±0.7
LVEDP-RAPm	5.1±0.9	4.6±1.1	4.8±0.4	5.7±0.7
LVEDP-RAPp+	3.7±0.8	2.8±1.2	3.8±1.2	4.2±0.7
HR (beats/min)	166±6	165±5	148±4	145±5
CO (liters/min)	3.22±0.2	3.01±0.3	2.48*±0.2	2.26±0.2
PVR (dyn*s*cm-5)	217±43	310±21	395*±30	441*±38
TPR (dyn*s*cm-5)	4150±276	4334±365	5192±525	5487±609
	BLOOD GASES			
paO_2 (mmHg)	102±3	96.8±4	94.9±6	98.5±4
$paCO_2$ (mmHg)	29.8±0.4	32.9*±0.6	34.2*±1.2	34.5±1.4
pH	7.43±0.01	7.38*±0.01	7.37*±0.01	7.36*±0.01
ET-CO_2 (mmHg)	33±1.4	31±2.6	28±2.3	28±2.1
O_2-Sat (%)	98±0.6	97±0.9	96±1.1	96±1.0

NOTES:
1. Pressure units are mmHg
2. * is $p < 0.05$ vs. Baseline
3. + LVEDP and RAP values taken at peak inspiration
4. m = mean, s = systolic, d = diastolic, p = peak

Table 2

VENOUS AIR INFUSION

AIR DOSE: 0.05 $ml*kg^{-1}*min^{-1}$

	Baseline	60 min	120 min	180 min
MAP	160±5	142±9	150±6	154±4
PAP	15.7±1.8	19.2*±1.6	19.2*±1.5	19.2*±1.5
RAPm	1.1±0.5	0±0.2	0±0.3	0.3±0.4
RAPp	4.1±0.9	3.0±0.5	3.1±0.5	3.4±0.8
LVEDPm	6.2±1.1	4.5±0.7	4.2±0.3	6.5±1.0
LVEDPp	7.6±1.3	6.2±1.1	6.0±0.4	7.2±1.4
RVPm	12.5±1.5	14.0±1.8	12.3±1.5	11.8±1.0
RVPs	25.1±1.6	26.5±0.8	26.7±2.2	25.5±2.3
RVPd	0.3±1.1	2.0±0.6	1.4±0.8	2.0±1.4
LVEDP-RAPm	5.1±0.9	4.7±0.6	4.2±0.4	6.3±1.1
LVEDP-RAPp+	3.5±0.9	3.1±1.2	2.9±0.7	3.8±1.6
HR (beats/min)	160±17	168±9	159±9	155±7
CO (liters/min)	4.21±0.5	3.55±0.4	3.13*±0.4	2.69*±0.3
PVR (dyn*s*cm-5)	193±28	363±82	437*±103	426*±98
TPR (dyn*s*cm-5)	3267±409	3338±283	4048±405	4956±767
	BLOOD GASES			
paO_2 (mmHg)	115±4	96.4*±4	101±7	98.4±8
$paCO_2$ (mmHg)	35.6±1.5	40.1±1.4	41.9±1.9	41.3±1.1
pH	7.36±0.01	7.32*±0.01	7.33±0.01	7.33±0.01
ET-CO_2 (mmHg)	34±1.0	33±0.5	31±1.0	31±1.6
O_2-Sat (%)	96±0.4	94±0.4	94±0.7	94±1.2

NOTES:
1. Pressure units are mmHg
2. * is $p < 0.05$ vs. Baseline
3. + LVEDP and RAP values taken at peak inspiration
4. m = mean, s = systolic, d = diastolic, p = peak

Table 3

VENOUS AIR INFUSION

AIR DOSE: 0.15 $ml*kg^{-1}*min^{-1}$

	Baseline	60 min	120 min	180 min
MAP	155±8	129±14	134±11	139*±9
PAP	13.4±0.9	26.3*±0.9	27.0*±1.3	27.4*±0.9
RAPm	-1.0±0.6	-0.2±0.6	0.0±0.8	0.0±0.6
RAPp	2.1±0.7	3.3±0.5	3.8±0.8	2.9±0.9
LVEDPm	5.7±0.7	5.3±0.9	5.6±1.1	6.1±0.9
LVEDPp	7.2±0.7	6.7±1.1	6.5±1.3	7.7±1.0
RVPm	8.5±1.2	14.9*±0.4	19.6*±4.4	17.0*±1.7
RVPs	16.7±1.3	31.8*±2.9	32.1*±2.3	34.9*±1.5
RVPd	3.1±0.8	4.8±1.4	3.6±0.6	4.6±2.2
LVEDP-RAPm	6.4±0.6	5.5±1.1	5.8±1.0	6.2±0.9
LVEDP-RAPp+	5.1±0.2	3.3±0.9	2.7±1.1	4.8±1.1
HR (beats/min)	161±9	148±9	151±12	135±10
CO (liters/min)	2.81±0.1	2.87±0.2	2.88±0.1	2.87±0.1
PVR (dyn*s*cm-5)	233±30	601*±52	593*±40	594*±27
TPR (dyn*s*cm-5)	4468±231	3636±386	3761±394	3921±326
		BLOOD GASES		
paO_2 (mmHg)	116±2	70.2*±6	76.6*±6	83.1*±7
$paCO_2$ (mmHg)	37.9±3.1	47.6*±1.9	47.6*±1.8	47.5*±2.3
pH	7.34±0.03	7.25±0.01	7.26±0.01	6.42*±0.84
ET-CO_2 (mmHg)	35±0.5	28*±1.2	27*±1.3	27*±1.3
O_2-Sat (%)	96±0.5	90*±1.4	90*±2.1	91±2.6

NOTES:
1. Pressure units are mmHg
2. * is $p < 0.05$ vs. Baseline
3. + LVEDP and RAP values taken at peak inspiration
4. m = mean, s = systolic, d = diastolic, p = peak

Table 4

HYPERBARIC DECOMPRESSION

POST DIVE

	Baseline	10 Min	30 Min	60 Min	90 Min
MAP	128±15	133±7	126±7	127±9	126±9
PAP	8.3±1.8	7.1±0.6	9.4±1.9	7.6±0.8	7.8±1.4
RAPm	-2.4±0.9	-2.7±0.3	-2.4±0.3	-2.3±0.3	-2.4±0.3
RAPp	0.0±0.4	0.6±0.8	0.5±0.3	0.1±0.3	0±0.3
LVEDPm	3.1±0.3	2.0±0.2	2.4±0.2	2.7±0.3	2.4±0.4
LVEDPp	3.5±0.4	3.1±0.9	2.1±0.4	2.3±0.4	2.3±0.4
RVPm	6.2±1.7	7.5±2.0	6.7±1.3	5.3±1.0	5.4±0.7
RVPs	20.6±2.3	16.8±1.9	17.5±1.3	16.9±2.5	16.1±1.2
RVPd	-1.4±0.5	-0.9±0.4	-0.6±1.0	-0.5±0.9	-0.9±0.5
LVEDP-RAPm	5.4±0.8	4.6±0.5	4.8±0.5	5.0±0.5	4.9±0.5
LVEDP-RAPp	4.5±0.4	2.6±0.9	1.2*±0.5	2.3*±0.4	2.4*±0.4
HR (beats/min)	162±11	108±21	105±18	126±5	123±6
CO (liters/min)	1.65±0.7	1.21±0.3	1.01±0.1	1.06±0.2	0.87*±0.1
PVR (dyn*s*cm^{-5})	250±81	368±97	638*±228	408±105	514*±117
TPR (dyn*s*cm^{-5})	6392±859	10580±2058	10573±1188	10334±1438	12215*±1479
			BLOOD GASES		
paO_2 (mmHg)	103±7.3	123*±7.1	120*±6.1	124*±5.6	121*±7.0
$paCO_2$ (mmHg)	37.1±1.6	39.4±2.6	38.5±0.9	37.0±0.9	37.4±1.7
pH	7.34±0.02	7.33±0.02	7.33±0.01	7.35±0.01	7.34±0.01
ET-CO_2 (mmHg)	34±1	34±4	31±3	29±2	28*±2
O_2-Sat (%)	98±1	100±0	100±0.5	100±0.5	100±0

NOTES:
1. Pressure units are mmHg
2. * is $p < 0.05$ vs. Baseline
3. LVEDP and RAP values taken at peak inspiration
4. m = mean, s = systolic, d = diastolic, p = peak

Table 5

ALTITUDE DECOMPRESSION (N = 6)

40,000 FEET

	Baseline	0 Min	60 Min	120 Min	180 Min	Post Flt
MAP	138±4	144±5	133±3	134±4	136±5	128+5
PAP	9.6±1.1	14.9*±1.4	17.6*±2.6	19.6*±2.7	19.8*±3.0	11.5+1.9
RAPp	2.5±0.7	2.3±1.3	2.9±0.9	1.8#±1.3	1.0#±0.9	2.5+0.4
LVEDPm	3.1±0.5	5.5±0.1	4.5±0.5	5.0±0.2	4.3±0.3	4.1+0.2
LVEDPp	4.7±0.8	6.5±1.7	7.1±1.4	6.3±1.6	5.3±1.7	6.0+1.8
RVPm	6.7±1.7	8.2±2.8	9.2±2.5	10.2*±2.1	9.8*±2.0	5.9+1.8
RVPs	23.5±1.7	27.0±3.7	28.0±6.6	37.5*±2.2	29.8±3.9	21.3+1.9
RVPd	-0.1±0.9	-0.4±1.8	1.4±2.6	5.1*±0.9	4.4±1.4	-0.1+1.4
LVEDP-RAPm	3.5±1.2	6.0±1.2	4.3±1.7	3.9±1.7	3.7±1.4	4.2+1.6
LVEDP-RAPp	2.2±0.9	4.2±1.8	5.4±2.8	3.8±1.8	2.9±1.3	3.4+1.8
HR (beats/min)	175±10	172±13	154*±10	153*±8	149*±6	149*+7
CO (liters/min)	2.21±0.5	-	-	-	-	1.84*+0.5
PVR (dyn*s*cm^{-5})	333±62	-	-	-	-	505*+115
TPR (dyn*s*cm^{-5})	6145±1096	-	-	-	-	7088+1231
			BLOOD GASES			
paO_2 (mmHg)	100.5±5.3	-	-	-	-	153.4+47
$paCO_2$ (mmHg)	43.8±0.9	-	-	-	-	45.2+2.0
pH	7.30±0.02	-	-	-	-	7.3+0.02

NOTES:
1. Pressure units are mmHg
2. * is $p < 0.05$ vs. Baseline
3. LVEDP and RAP values taken at peak inspiration
4. m = mean, s = systolic, d = diastolic, p = peak
5. # = Values affected by clotting of lines

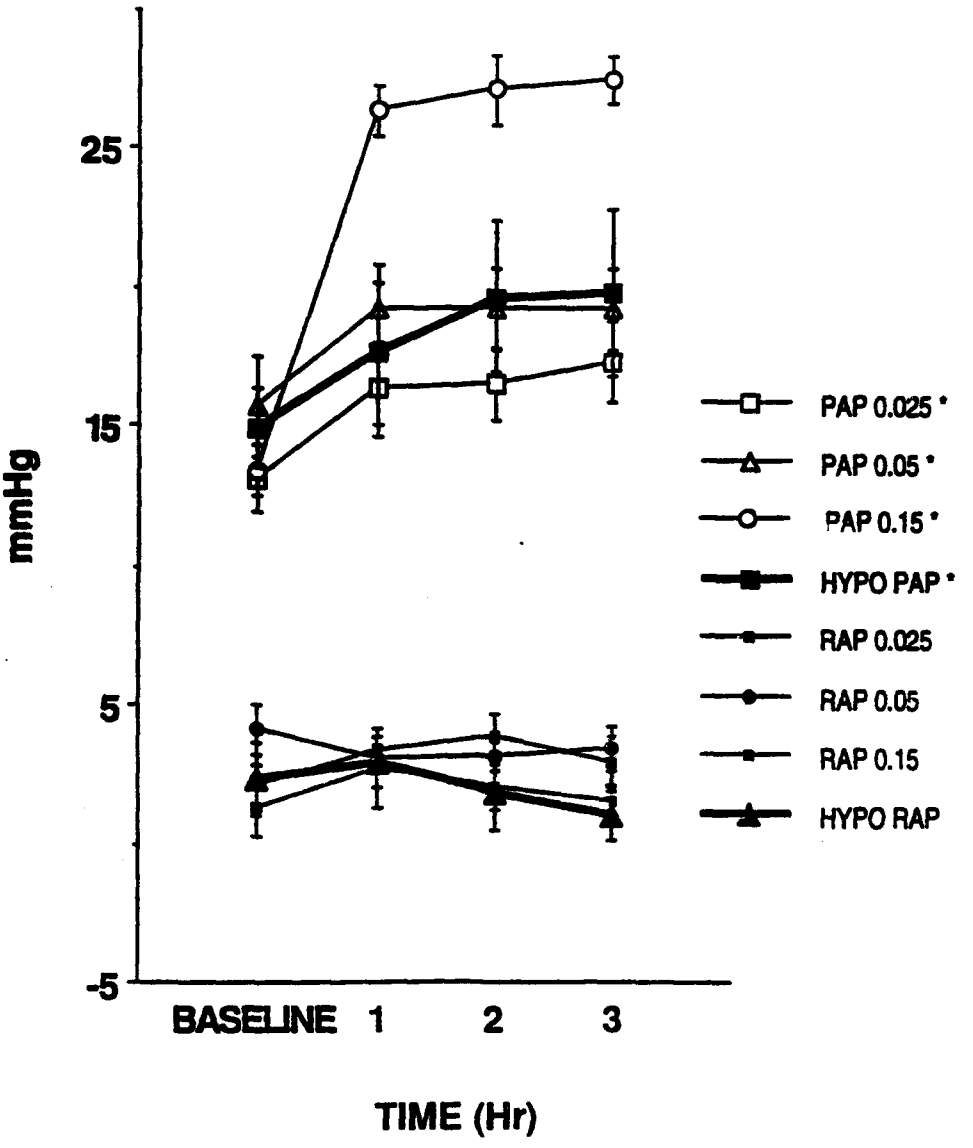

Figure 1: Pulmonary artery pressures (TOP) and LVEDP-RAP (BOTTOM) gradient over time in both venous air embolism and altitude stimulated studies
HYPO = hypobaric

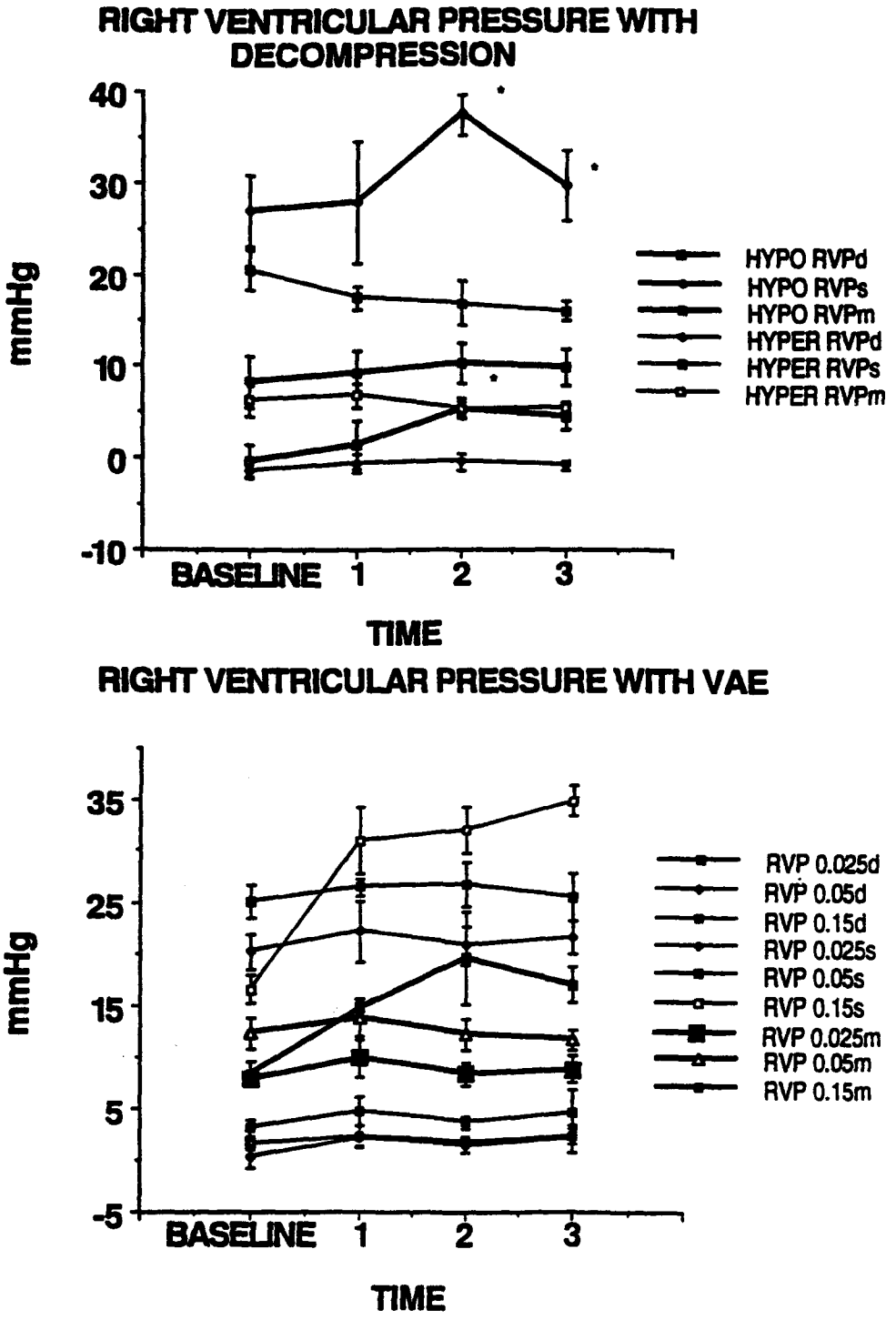

Figure 2: Right ventricular mean, diastolic, and systolic pressure values with decompression (TOP) and venous air embolism (BOTTOM)

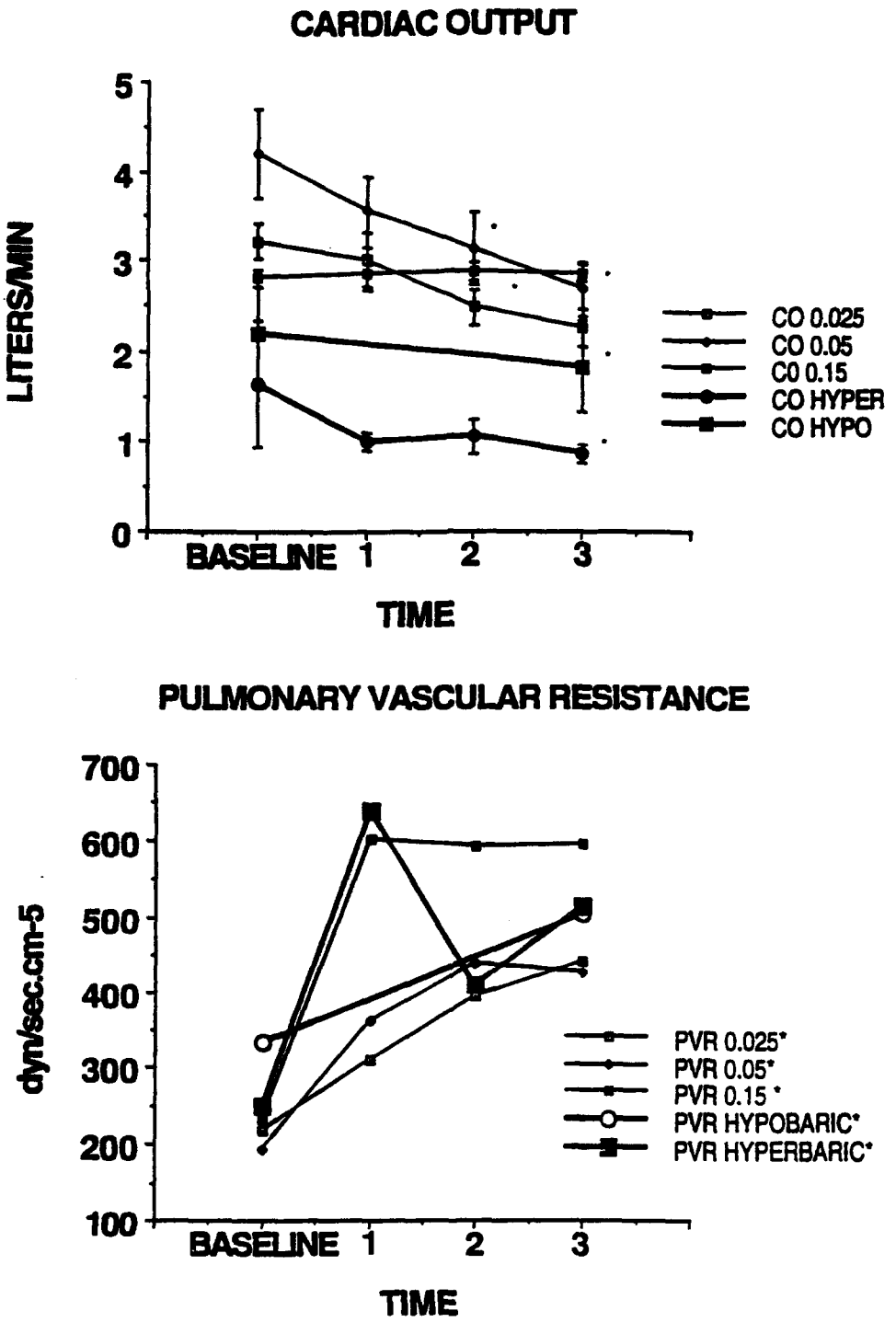

Figure 3: Cardiac output (TOP) and pulmonary vascular resistance (BOTTOM) with decompression and venous air embolism

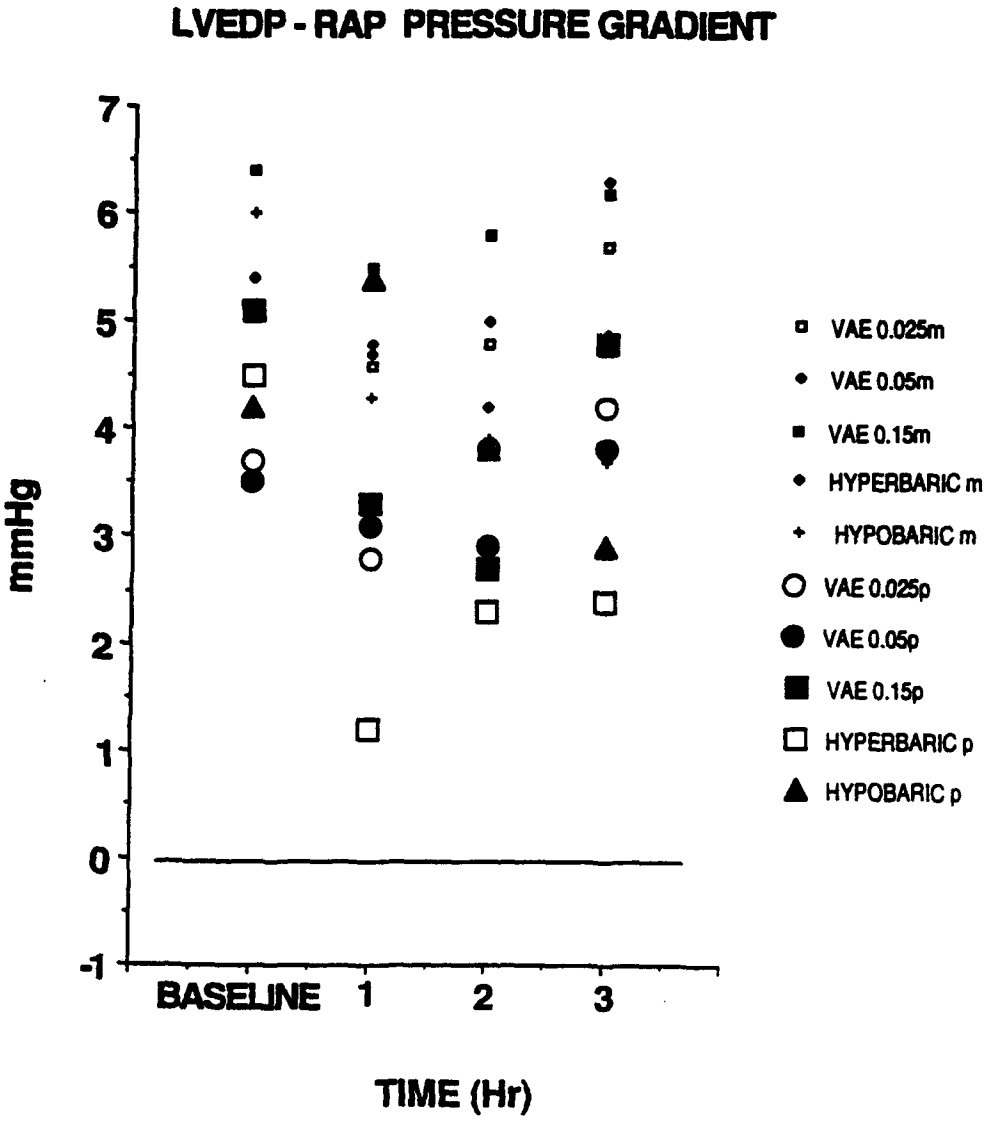

Figure 4: Peak LVEDP-RAP gradient pressure change

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