

Effects of hyperbaric oxygen on ventricular performance, pulmonary blood volume, and systemic and pulmonary vascular resistance

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Abel FL, McNamee JE, Cone DL, Clarke D, Tao J. Effects of hyperbaric oxygen on ventricular performance, pulmonary blood volume, and systemic and pulmonary vascular resistance. *Undersea Hyper Med* 2000; 27(2):67-73.—The cardiovascular effects of hyperbaric (3 atm abs) air, 100% oxygen, and hyperbaric oxygen (HBO₂) at 3 atm abs were investigated in 13 pentobarbital-anesthetized dogs. We measured heart rate, arterial pressure, pulmonary artery pressure, right atrial pressure, left and right ventricular pressure, and cardiac output. From these we determined end diastolic pressure, \pm maximal dp/dt, maximal (dp/p), end systolic elastance, cardiac work, and systemic (SVR) and pulmonary vascular resistance (PVR). Pulmonary blood volume was obtained from the mean transit time of ascorbic acid. The significant results with HBO₂ were a decrease in heart rate, cardiac output, and cardiac work. All left ventricular performance indices decreased, without a change in preload or afterload. In contrast, only right ventricular -dp/dt decreased. SVR increased but PVR did not change; 100% O₂ produced similar but less pronounced responses. Hyperbaric air had only mild effects. Pulmonary blood volume and lung wet/dry ratio did not change. Our data suggest that HBO₂ may act by a differential effect on the autonomic innervation of the right and left ventricles. The resultant ventricular imbalance may be of clinical importance in the mechanism of pulmonary edema in patients in congestive heart failure undergoing hyperbaric therapy,

maximal dp/dt, end systolic elastance, pulmonary edema, cardiac work, cardiac output, ventricular balance

Oxygen at both atmospheric and hyperbaric pressure is used as a therapeutic tool in the treatment of patients with problems in appropriate oxygenation of their blood or with difficulty in providing adequate blood flow to a given tissue. Patients are placed in hyperbaric chambers where oxygen can be delivered at 2–3 atmospheres of pressure, thereby substantially increasing physically dissolved O₂ in the plasma as well as completely saturating hemoglobin. Despite the long history of the use of high concentrations of O₂ in patients under a wide variety of conditions, and increasing use of hyperbaric oxygen (HBO₂) therapy; the effects of O₂ on the cardiovascular system have not been well documented. A major indicator for such use might be coronary vascular disease and congestive heart failure; the latter is, however, often regarded as a contraindication to HBO₂ because of the associated development of pulmonary edema.

In several clinical facilities operated or managed by us (D.C.), the incidence of pulmonary edema is about 1/1,000 and exacerbations of symptoms in congestive heart failure patients is considered a potential hazard. In

early experiments in animal models, Bean and coworkers (1,2) demonstrated that HBO₂ resulted in pulmonary edema and that hypophysectomy or adrenalectomy had a preventive effect, implicating epinephrine as a mechanism. It is also possible that with a reported increase in systemic vascular resistance (3), a higher afterload might be placed on the left heart, thereby causing patients with depressed left ventricular function to suffer a further decrease in an already compromised myocardial reserve.

One of the earlier studies of the effects of HBO₂ on cardiac function was by Hahnloser et al. (3), who demonstrated that cardiac output was reduced from 20 to 25% in both anesthetized and conscious dogs subjected to 4 atm abs for 90–120 min. There was also a consistent rise in total peripheral resistance in these animals, more marked under anesthesia, and evidence of cardiac rhythm disturbances after 4 h. This degree of hyperbaric oxygenation, however, is seldom used clinically, and animals subjected to myocardial infarction produced by embolism with microspheres demonstrated a significantly better survival when treated with 95–100% O₂ at 3 atm abs for

2 h (4). Similarly, animals subjected to hemorrhagic shock showed an increased survival rate (5). Awake patient volunteers, breathing 100% O₂ at 2 atm abs for approximately 45 min, showed significant increases in peripheral vascular resistance along with decreases in cardiac index, cardiac work, and heart rate (6).

Quantitative reports of ventricular performance are few; however, Savitt et al. (7) measured the effects of HBO₂ on left ventricular contractility, coronary blood flow, and myocardial O₂ consumption in conscious animals during autonomic blockade. They concluded that while total coronary blood flow, cardiac output, and myocardial O₂ consumption were all decreased by 100% O₂ at 3 atm abs, no alteration in myocardial contractility occurred; the myocardium had adjusted its coronary flow and output to accommodate the higher levels of available arterial O₂ tension. Ishikawa et al. (8) reported an 11% increase in myocardial contractile force when arterial blood was oxygenated to a PO₂ of 460 mmHg; they interpreted this as due to a direct beneficial effect of O₂ on the myocardium. Opposite results were, however, obtained by Kioschos et al. (9); left ventricular function was measured in anesthetized animals, following surgical AV block, at 3.6 atm abs of O₂ applied for 15 min. They concluded that stroke volume, stroke work, and maximal dp/dt decreased, and isometric contraction time increased, even under conditions of constant heart rate and without a change in filling pressure or afterload. Therefore, a decrease in myocardial contractility occurred.

The mechanism for these effects of HBO₂ on the heart and circulatory system remains obscure. We hypothesized that the problem of pulmonary edema in patients in heart failure might be related to a differential effect of HBO₂ on ventricular balance, perhaps related to alterations in autonomic tone as postulated by earlier workers (2). Differential effects on right vs. left ventricular contractility could result in a shift of blood volume into the pulmonary circuit. These experiments were undertaken to determine if HBO₂ decreased left ventricular function more than right ventricular function. Control experiments were performed to separate the effects of high O₂ concentrations alone from the effects of HBO₂ on the function of the two ventricles.

METHODS

All animal studies were done under a protocol approved by the Institutional Animal Care Committee. Satisfactory data were obtained in 13 mongrel dogs of both sexes. The animals were anesthetized with sodium pentobarbital, 30 mg · kg⁻¹, and the trachea cannulated. In the initial

experiments, a catheter was placed in the left ventricle via the left carotid artery, in the right atrium via the right jugular vein, and in the central aorta via the left femoral artery. Cardiac output was measured in three animals using the thermodilution technique with a Swan-Gans catheter in the pulmonary artery. To obtain additional information on ventricular function in the remaining 10 animals, cardiac output was directly measured using a midline thoracotomy approach and a positive pressure ventilator. An electromagnetic flowmeter probe was placed around the root of the aorta and connected to a Carolina Medical Electronics flowmeter (King, NC). The flowmeter probe was later calibrated using dialysis tubing and whole blood of appropriate hematocrit from the experimental animal. This approach also allowed a high frequency Millar pressure tip transducer catheter (Millar Instruments, Houston, TX) to be directly inserted into the left and right ventricles. The carotid arteries on both sides were left intact for possible chemoreceptor responses. In seven animals, a catheter was also placed in the pulmonary artery to evaluate pulmonary vascular resistance.

After the surgical procedures, the animal was placed in a hyperbaric chamber designed for animal research (Mechidyne Systems, Inc., Houston, TX, model 20000). The chamber could be pressurized with air or oxygen. HBO₂ consisted of 3 atm abs of 100% O₂. The chamber was pressurized and depressurized over a 3- to 5-min period; the animals were maintained at the experimental state for 30–60 min.

We also measured pulmonary blood volume using ascorbic acid injected into the main pulmonary artery and sensed by a positively polarized polarographic electrode placed in the left atrium; details of this technique have been previously described (10). The resultant indicator dilution curves were corrected for re-circulation, assuming an exponential downslope; mean transit time was calculated from the integral of the concentration × time, divided by the integral of the concentration (11). Pulmonary blood volume was obtained from the product of mean transit time and the simultaneous flowmeter cardiac output.

The data were analyzed by an online digital computer sampling at 200 samples per second per channel. From the pressure transducers, the high frequency Millar transducer tracings, and the aortic flow waveforms, we calculated for individual cardiac cycles: maximal ± dp/dt and peak ventricular pressure (PVP) for both the right and left ventricles (LV), maximal LV dp/p, end diastolic pressure, mean right atrial pressure, stroke volume, stroke work, heart rate, cardiac output, cardiac

work, mean arterial pressure, mean systolic arterial pressure (MSAP) (chosen as an indicator of afterload), mean pulmonary artery pressure, pulmonary vascular resistance, and total or systemic vascular resistance (SVR). To further evaluate left and right ventricular function, we used a determination of P_{\max} , the maximum potential pressure that can be produced by an isovolumically contracting ventricle from a given end diastolic pressure as described by Sunagawa et al. (12) and altered by us (13) using the formula: $P_{\max} = \text{maximal } dp/dt \times \tau/\pi$, where τ is the length of ventricular systole from end diastolic pressure to the same pressure in early diastole, and π is a scaling factor. Using this value along with end systolic pressure obtained at the point of maximal negative dp/dt (14) and stroke volume, we were able to obtain a beat-to-beat estimate of the slope of the end systolic pressure-volume relationship, or "end systolic elastance" (EES) (15,16).

The data were statistically evaluated using analysis of variance with replications, and a post-hoc Scheffe test. A paired t test was used on individual variables in a single group. Significance was accepted as a $P \leq 0.05$.

RESULTS

The animals were evaluated under three different conditions: Group 1 breathing air at atmospheric pressure compared with air at 3 atm abs for 30 min, 4 animals; group 2 breathing air at atmospheric pressure compared with breathing 100% O_2 at atmospheric pressure for 30 min, 12 animals; group 3 breathing air at atmospheric pressure vs. 100% O_2 at 3 atm abs (HBO_2) for 30–60 min, 13 animals. (Some of the same animals were used in different groups, e.g., air at 3 atm abs and O_2 at 3 atm abs. A minimum of 30 min was allowed for stabilization between any two procedures.)

The data are presented in Tables 1 and 2. For the four animals subjected to air at 3 atm abs, there was a small decrease only in the variable cardiac work (Tables 1 and 2), not in the other variables. The results for heart rate, MSAP, cardiac output, and SVR are also shown for the 100% O_2 and HBO_2 groups in Fig. 1. For the animals breathing 100% O_2 , there was a decrease in heart rate, MSAP, and cardiac output. For the animals subjected to HBO_2 , no significant change in heart rate or MSAP occurred, but a decrease in cardiac output and an increase in SVR was observed.

Ventricular performance: The following indices of performance were obtained for the left ventricle: PVP, cardiac work, \pm maximal dp/dt ($\pm dp/dt$), maximal dp/p (dp/p), and the derived variables P_{\max} and EES. For the

right ventricle, from high frequency pressure tracings, similar variables were obtained: PVP, $\pm dp/dt$, P_{\max} , and EES. Figures 2 and 3 and Tables 1 and 2 show the results for the left ventricle: PVP, $\pm dp/dt$, dp/p , and P_{\max} decreased with 100% O_2 and HBO_2 , cardiac work decreased in all three groups (without a change in end diastolic pressure), but EES only decreased significantly with HBO_2 . For the right ventricle, there was a decrease in pulmonary artery pressure, PVP, and maximal negative dp/dt under HBO_2 ; no other variable was significantly affected by either 100% O_2 or hyperbaric oxygenation. Figure 4 compares four of these variables for the right and left ventricles; left ventricular $\pm dp/dt$ and P_{\max} decreased in comparison with that of the right ventricle. An example from one animal of this difference in response of P_{\max} in the right and left ventricles is shown in Fig. 5.

Pulmonary blood volumes: Despite these changes in ventricular function, we could not demonstrate a significant increase in pulmonary blood volume in the time periods used in these experiments. The percentage changes vs. controls were 105.1 ± 6.1 (mean \pm SE) for 100% O_2 and 104.6 ± 6.3 for HBO_2 . Absolute volumes for 100% O_2 in six animals were $13.4 \pm 2.6 \text{ ml} \cdot \text{kg}^{-1}$. Overall lung wet:dry weight ratio was 4.69 ± 0.06 , with a slight increase only in the left upper lobe relative to the other lobes, probably related to the surgical procedure in which this lobe was wrapped in gauze and retracted. Pulmonary vascular resistance did not change significantly (although there was a tendency to decrease, the results were too variable to be significant). Although pulmonary artery pressure decreased, so did cardiac output without a change in left atrial pressure (estimated from left ventricular EDP).

DISCUSSION

As indicated by the parameters used to describe ventricular function obtained in this study, including end systolic elastance, performance of the left ventricle was moderately decreased during hyperbaric oxygenation. This decrease was accompanied by little or no changes in systemic variables, slight decreases in heart rate, and an increase in SVR, cardiac output, and cardiac work, without a change in either preload or afterload. The alterations obtained seem to be associated with a primary decrease in the contractile state of the left ventricle; the changes were, however, quite small and may be consistent with a decrease in cardiac work and requirements of the body for oxygen delivery (7). However, the right heart, although it may not have the same degree of sensitivity

Table 1: Effects of Air and Oxygen on Left Ventricular Function^a

	n	HR	MSAP	LV EDP, mmHg	LV PVP	LV (+)dp/dt	LV P _{max}	LV dp/P	LV (-)dp/dt	LV EES	RAP, mmHg
HBO ₂ at 3 atm abs	13	97.4±3.4	97.2±2.7	-1.4±1.1	93.3±2.6	85.5±4.2 ^{b,c}	85.8±4.4 ^{b,c}	85.5±4.0 ^c	89.5±3.7 ^c	83.5±7.0 ^c	-0.2±0.4
100% O ₂	12	96.2±2.0 ^b	91.0±4.6 ^c	0.5±0.6	95.0±2.0	89.2±3.8 ^{b,c}	87.7±3.7 ^{b,c}	89.7±3.7 ^c	93.5±3.1 ^c	92.4±7.7	-1.0±0.8
Air at 3 atm abs	4	99.3±3.0	100±3.1	0.6±0.6	103.8±3.8	96.7±2.7	97.6±3.7	96.5±2.6	104.4±9.2	100.3±6.9	-0.2±0.5

Key: HR = heart rate; MSAP = mean systolic arterial pressure; LV = left ventricle; EDP = end diastolic pressure; PVP = peak ventricular pressure; EES = end systolic elastance; RAP =

^aAll values as percent of control except EDP and RAP, which are absolute changes in millimeters of mercury, mean ± SE.

^bP ≤ 0.05 vs. right ventricle or pulmonary circulation. ^cP ≤ 0.05 vs. control

Table 2: Systemic, Pulmonary, and Right Ventricular Effects^a

	CO	CW	SVR	MPAP	RV PVP	RV (+)dp/dt	RV (-)dp/dt	RV P _{max}	PVR	RV EES
HBO ₂ @ 3 atm abs	90.3±4.6 ^b	88.2±5.8 ^a	119.5±5.6 ^{b,c}	73.5±12.1 ^b	84.2±5.4 ^b	99.9±0.2	78.7±6.9 ^b	98.9±3.0	74.8±15.9	91.3±14.8
n	13	13	13	5	6	7	5	7	5	5
100% O ₂	91.1±4.3 ^b	83.0±6.2 ^b	103.9±8.6	64.9±17.0 ^b	85.8±4.5 ^b	99.9±0.1	88.3±7.9	96.2±2.3	98.5±5.0	85.8±8.5
n	12	12	12	7	8	8	7	8	5	6
Air @ 3 atm abs	92.9±4.5	92.5±2.5 ^b	109.0±8.7							
n	4	4	4							

Key: CO = cardiac output; CW = cardiac work; SVR = total or systemic vascular resistance; MPAP = mean pulmonary arterial pressure; RV = right ventricle; PVP = peak ventricular pressure; PVR = pulmonary vascular resistance; EES = end systolic elastance.

^aAll values as percent of control, mean ± SE ^bP ≤ 0.05 vs. control; ^cP ≤ 0.05 vs. right ventricle or pulmonary circulation.

CARDIOVASCULAR EFFECTS OF HYPERBARIC OXYGEN

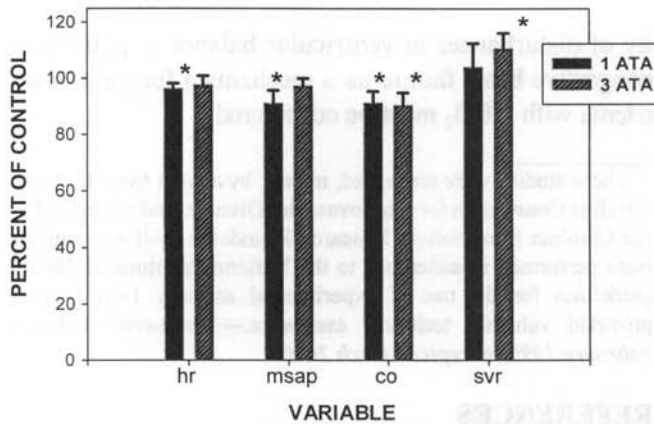


FIG. 1—Effects of 100% O₂ and 3 atm abs on heart rate, MSAP, cardiac output, and SVR. Mean \pm SE. Asterisk = $P \leq 0.05$ vs. air at atmospheric pressure.

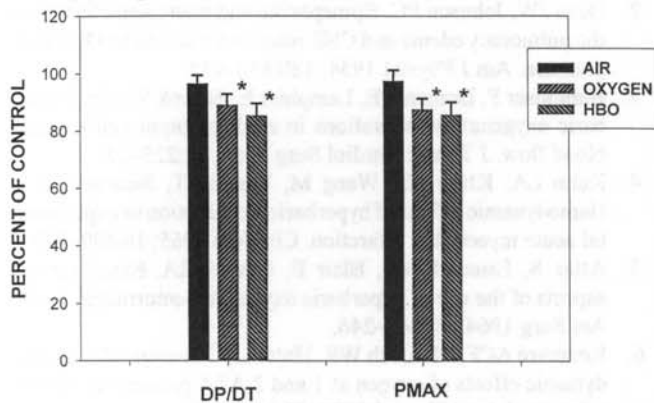


FIG. 2—Effects of HBO₂, hyperbaric air, and 100% O₂ on left ventricular maximal dp/dt (dp/dt) and P_{max} (defined in text). Mean \pm SE. Asterisk = $P \leq 0.05$ vs. air at atmospheric pressure.

for alterations in its contractile state, did not show any observable decrease in contractility except for a decrease in negative dp/dt, a relaxation parameter.

In our experience, congestive heart failure patients who receive HBO₂ may develop pulmonary edema during or after treatment. It is tempting to postulate that pulmonary edema may be related not to depression of left ventricular function, but rather to an alteration of the balance between the pumping ability of the right and left hearts. If the left heart decreased its contractility because of lesser need of the body for O₂ and perhaps less sympathetic tone, but the right heart maintained its contractile ability, blood would be shifted from the systemic to the pulmonary vasculature. A measurable increase in pulmonary blood volume could not, however, be demonstrated in the normal animal.

No animal was in congestive heart failure. Attempts to create an acute model of heart failure using aortic clamping, propranolol, and i.v. infusions were not successful in producing significant pulmonary edema, although we obtained an increase in lung weight during HBO₂ with

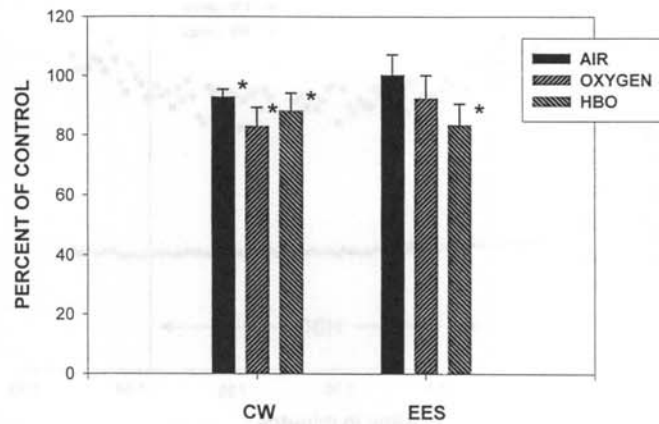


FIG. 3—Effects of HBO₂, hyperbaric air, and 100% O₂ on left ventricular cardiac work and EES. Asterisk = $P \leq 0.05$ vs. atmospheric air.

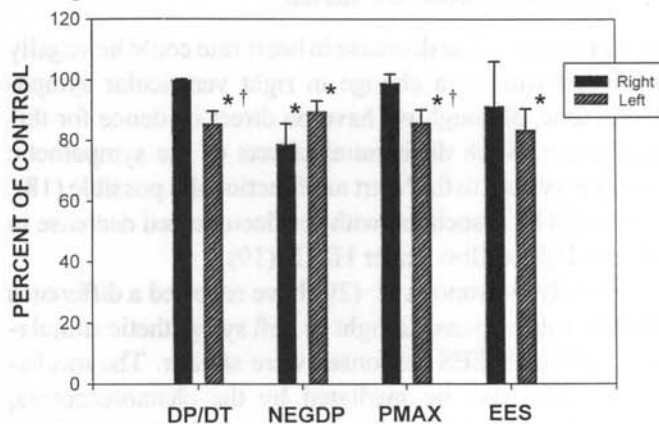


FIG. 4—Comparison of the effects of HBO₂ at 3 atm abs on the right and left ventricles. Maximal (+) dp/dt (dp/dt), maximal (-) dp/dt (NEGDP), P_{max}, and EES. Asterisk = $P \leq 0.05$ vs. air at atmospheric pressure. Dagger = $P \leq 0.05$ for left vs. right ventricle.

crystalloid infusion in one animal. An increase in capillary permeability would add to lung weight and lung water without an increase in intravascular volume, but the wet:dry weights did not show this. Similarly, a shift of blood from the systemic to the pulmonary circulation should have caused an increase in pulmonary blood volume. Unfortunately, our methods would probably not detect small changes. An increase in pulmonary blood volume may also be associated with an increase in sympathetic tone in patients in congestive heart failure. In one experiment we occluded the inferior vena cava to measure venous compliance using descending aortic flow as the inflow [see (17) for methods]. No changes in inferior vena caval compliance were obtained.

As a mechanism for the left vs. right ventricular alterations in ventricular function, we could postulate a differential effect of autonomic tone on the left vs. the right heart. A decrease in sympathetic tone to the left heart is indicated by the decrease in ventricular contractil-

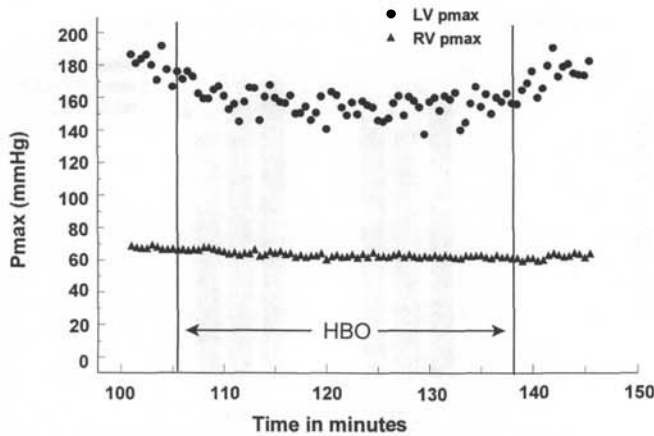


FIG. 5—An example of the effects of HBO₂ at 3 atm abs on P_{max} for the right (RV P_{max}) and the left ventricle (LV P_{max}). Data points from averaged cycles at about 30-s intervals.

ity parameters. The decrease in heart rate could be vagally mediated without a change in right ventricular sympathetic tone, although we have no direct evidence for this conjecture. Such differential effects of the sympathetic nervous system to the heart are functionally possible (18), and could be associated with the documented decrease in cerebral blood flow under HBO₂ (19).

Recently, Miyano et al. (20) have reported a difference in heart rate response to right vs. left sympathetic stimulation, although EES responses were similar. The mechanism might also be mediated by the chemoreceptors, although we know of no report of alterations in chemoreceptor activity in response to high oxygen concentrations. Therefore, all the cardiac effects we observed could be related to a decrease in sympathetic tone to the left ventricle. An increase in parasympathetic tone could produce the same effects, although these effects are usually too mild to be observed in an intact left ventricle (21). An accompanying increase was found in peripheral resistance, possibly as the result of washout of a vasodilator such as nitric oxide (22). The time periods, usually 30 min, but in a few cases up to a maximum of 1 h, subjected to 100% O₂ or HBO₂ at 3 atm abs, seem to be too short to be associated with pulmonary toxicity; the lack of associated changes in pulmonary blood volume and lung wet:dry weights tend to support this. Further studies are required to verify these results in a better congestive heart failure model.

In summary, these studies in intact, anesthetized animals confirm depression of left ventricular function under conditions of either 100% oxygenation or of hyperbaric oxygenation. Small associated systemic vascular changes were also observed. Significantly, the right ventricle did not participate in the depression of ventricular function seen in the left ventricle. The possibil-

ity of disturbances in ventricular balance in patients in congestive heart failure as a mechanism for pulmonary edema with HBO₂ must be considered.

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CARDIOVASCULAR EFFECTS OF HYPERBARIC OXYGEN

73

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