●招請講演

HYPERBARIC BRADYCARDIA

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Under a variety of hyperbaric conditions, the heart rate in humans is lower, both at rest and during exercise, than the sea-level value. In most dives, the so-called hyperbaric bradycardia (HB) persists throughout the pressure phases of a dive. Some researchers have reported transient bradycardia lasting several days initially then drifting toward the predive value. This review focuses on factors contributing to and possible mechanisms responsible for the HB. Existing data reveal two major mechanisms: O_2-dependent and O_2-independent mechanisms. Hyperoxia accounts for the majority of HB, without it HB still can be demonstrated but to a much lesser degree. Hyperoxia produces bradycardia through general peripheral vasoconstriction and the baroreceptor reflex, which is mediated by vagus nerves. Furthermore, hyperoxia lowers sympathetic activity by suppressing chemoreceptor drives. Hyperbaric factors such as high ambient pressure, elevated gas density, and increased inert gas pressure may act alone or together to bring about HB. Results from human experiments showed each of these factors causes a small but demonstrable effect contributing to HB. However, results from animal studies under normoxic conditions have eliminated the involvement of these factors. This review considers other possibilities such as the effects of autonomic nervous function, respiratory pattern and circulatory deconditioning. In hyperbaria, circulatory deconditioning occurs which elevates the resting heart rate. This may explain the diminishing HB in the later stage of a saturation dive. It is concluded that hyperoxia is the major factor responsible for initiating and maintaining hyperbaric bradycardia, whereas non-oxygen dependent hyperbaric factors play a minor role. The existence of HB suggests the use of the heart rate response may underestimate workload intensity under hyperbaric conditions.

In a hyperbaric environment, pressure is obviously high. In addition, inspired P_{O_2} and gas density are also elevated. Respiratory work rises and exercise capacity falls (Ohta et al.,1981). Therefore, planned work in a hyperbaric environment is modest in most cases. There are no cardiovascular problems of great concern, except for an acute circulatory deconditioning on compression which remains demonstrable postdive (Arita et al., 1987; Lin, 1987; Lin et al., 1991 ; Lin et al., 1995; Lin, 1999). The state of deconditioning caused no major problems when appropriate precautions were taken. In a deconditioned state, the cardiovascular system showed, compared to the control, an elevated resting heart rate, decreased stroke volume, reduced plasma and blood volume, and left ventricular diastolic volume, orthostatic intolerance, and a reduced exercise capacity (Sandler, 1986). All of these findings have been shown to occur during extended pressure exposures, except for the heart rate, which was lower in a hyperbaric environment both in humans (Lin , 1996; Lin & Shida, 1988; Lin et al., 1999) and in animals (Shida & Lin,1981), as well as in isolated preparations (Ornhagen, 1979; Doubt & Evans,1983). However, an elevated resting heart rate, compared to predive, appeared postdive indicating a state of deconditioning. In 1936, Shilling and associates termed this phenomenon the hyperbaric bradycardia (HB) and it has been reported repeatedly ever since. This brief review documents the existence of HB and follows this with a summary of factors contributing to and mechanisms responsible for HB.

THE PHENOMENON

Bradycardia occurs during pressure exposure was noted early in the history of diving (Heller *et al*,1897). Some investigators have reported a transient bradycardia lasting for a few days initially, then drifting toward the predive value (Matsuda *et al.*, 1975; Wilson *et al.*,1977). The Hyperbaric

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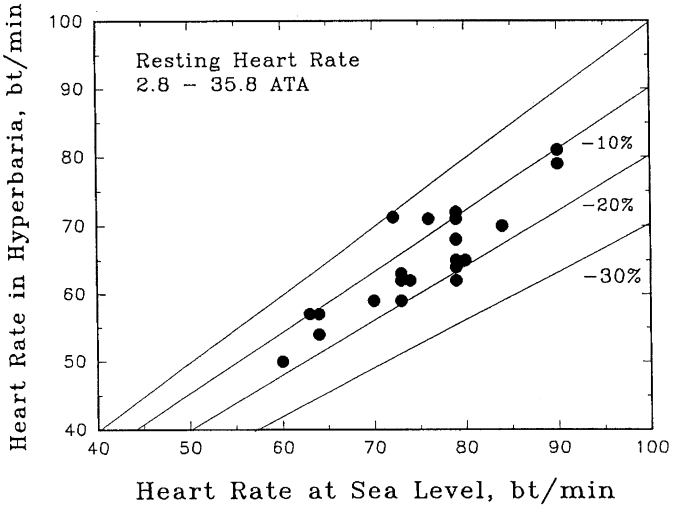

Fig. 1 Heart rates of resting human subjects at sea level and at depths
Bradycardias of 0, 10, 20 and 30% are indicated (Lin, 1996).

bradycardia occurs at resting conditions, as well as during exercise.

1. At Rest

Fig.1 summarizes the resting heart rate at sea level and at depth ranging from 2.8 to 35.8 ATA (see Lin, 1996 for the source of data). The graph shows the heart rate at depth as a function of heart rate at the sea level. The reduction averaged 15% (mean = 14.8, SD = 4.05, N = 22), ranging from 7 to 22%. There was no clear pattern showing a pressure-dependent depression of heart rate. For example, the 7% reduction was associated with 11 ATA (Matsuda *et al.*,1978) and the 22% reduction with 12.8 ATA (Raymond *et al*, 1968), where differences in pressure was negligible. Not included in Fig.1 was a study by Buhlmann *et al.* (1970). They clearly demonstrated the existence of HB in a relatively short saturation dive to 31 ATA and a brief excursion to 36 ATA. The ambient condition consisted of 0.37-0.62 atm of Po_2. The heart rate decreased by 20-33% from the predive level.

2. During Exercise

Fig.2 summarizes 10 studies plotting the heart rate relative to the sea-level value as a function of oxygen consumption (see Lin, 1996 for the source of data). The depths ranged from 4.5 ATA (35 msw) to 31 ATA (300 msw). Open circles represent the sea level data, and the closed circles for data at depths between 4.5 and 19.7 ATA.In order to compare data from various publications, the resting heart rate at sea level was set to be 100% for each study. The relative responses are plotted against the level of exercise (indicated by the oxygen consumption rate). The data clearly shows that HB occurs at the resting condition and at elevated oxygen consumption. It is also clear that the exercise tachycardia for a given level of oxygen consumption was attenuated in hyperbaric environments. Again, there were no clear patterns of depth-dependent heart rate reduction, except at 31 ATA conditions (open triangles) where the strongest bradycardia was observed (Schaefer *et al.*, 1970). From these results, it is important to recognize the imprudence of using the heart rate-exercise relationship obtained at the sea-level condition in hyperbaria.

CONTRIBUTORY FACTORS

As demonstrated above, bradycardia occurs both at rest and during exercise in hyperbaria. A hyper-

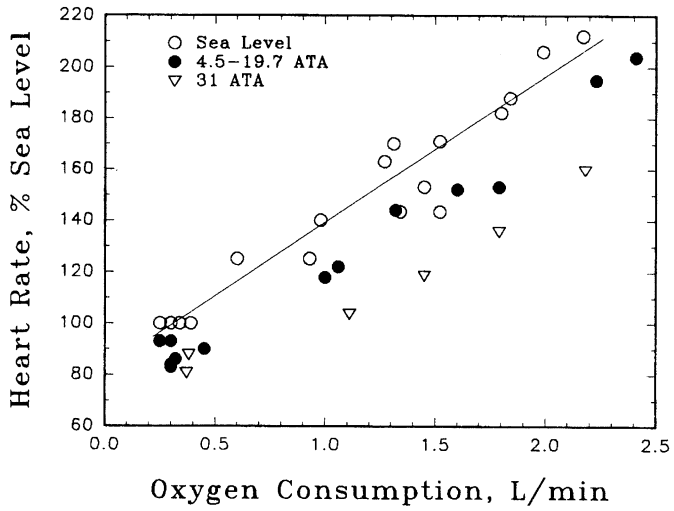

Fig. 2 Heart rate during exercise at sea level and at depths
The heart rate in hyperbaria was expressed as percent of resting heart rate at seal level (modified from Lin and Shida, 1988).

baric environment consists of an increased ambient pressure, gas density, inert gas pressure, and the partial pressure of oxygen. It is possible that high pressure *per se*, elevated gas density, and inert gases under pressure may produce, at least in part, the HB. Hyperoxia, commonly 0.4-0.5 atm, is present during compression, saturation and decompression phases. For this reason, the following factors may contribute to the occurrence of HB but they cannot, in most studies, be separated cleanly from the effect of hyperoxia.

1. Decompression.

In an 80-m heliox dive over 8 days, Gao and associates (1991) recorded ECG continuously and obtained 24-hr averages of heart rate in 4 young subjects. Po_2 was maintained at 0.4 atm during the saturation phase. They showed the heart rate decreased from 72±2.7 bpm predive to 66±4.0, 62±6.2, and 60±7.9 bpm, respectively, on the 1st, 2nd, and 3rd day at 80 msw. The heart rate fell further during decompression, when Po_2 was raised from 0.4 ATA to 0.5 ATA, the heart rate fell further to 57±6.5 at 50 m and 30 m, and rose slightly to 60±7.7 bpm just before completing the decompression. Upon lowering the Po_2 value to sea level (0.2 atm), the heart rate returned to the predive range (**Fig. 3**).

Gardette *et al* (1984) showed that bradycardia can occur in a shallow dive (2.5 ATA air, Po_2 = 0.5 atm). The heart rate fell, on the average, from 82 to 74 bpm during saturation at 2.5 ATA and fell further to 67 bpm during decompression. The heart rate fell below 50 bpm on occasion, according to the authors.

These results show that bradycardia occurs not only during the compression and saturation phases but also during decompression. Hyperoxia lowers the heart rate despite the falling ambient pressure.

2. Hydrogen Environment.

Hyperbaric bradycardia occurs in nitrogen, helium, and hydrogen environments as well. In the COMEX's *Hydra 10* dive in 1992, the compression to 700 msw was accomplished initially by using a helium-oxygen mixture while maintaining Po_2 at 0.4-0.5 atm throughout. Hydrogen was introduced and maintained at 20 atm after the He-O_2 pressure exceeded 21 ATA, at which time the concentration of O_2 (%) was too low to support combustion. Then

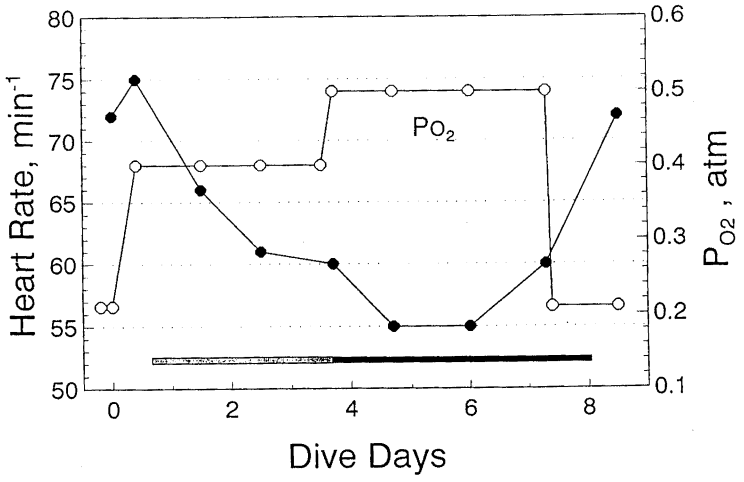

Fig. 3 The effect of inspired Po_2 on the heart rate during a heliox saturation dive at 80-meters sea water depth

The heart rates are averaged over a 24- hours period (modified from Gao *et al.*, 1991).

they injected helium to reach a total of 71 ATA. Po_2 was maintained at 0.4-0.5 atm throughout the 42-day experiment (Lafay *et al.*, 1995). With this mixture, the highest gas density was 10.99 g/L or about 9.3 times the air density at sea level, which was only slightly higher than that of the heliox mixture at 300m depth. The bradycardia was impressive, between 40 to 50% below the predive level. The bradycardia showed no signs of diminishing throughout the 15-days saturation period in all 3 subjects, and in 2 out of the 3 subjects during the decompression period as well. In the 3rd subject, bradycardia occurred only during compression and saturation, but returned to the predive level during decompression. This study demonstrates the occurrence of HB in a hydrogen environment just as in a nitrogen or helium environment and with the HB continuing into the decompression phase where hyperoxia was present.

3. Pressure and Gas Density

The possibility that hydrostatic pressure *per se* causes HB was demonstrated in the following experiments. In human experiments, Dressendorfer *et al.* (1977) elevated chamber pressure to 18.6 ATA, but kept Po_2 at sea level conditions. The heart rate fell both at rest and during exercise. Next they raised Po_2 from 0.2 to 0.3 ATA without changing the ambient pressure. The heart rate fell further. Although changes were small, the HB was demonstrable (**Fig. 4**).

In a study conducted by Fagraeus and associates (1974), the O_2 concentration was first raised to 100% at sea level. The heart rate fell slightly as expected. It fell further when the ambient pressure was raised to 4.5 ATA, while Po_2 Was kept constant at equivalent to 100% O_2 at the sea level condition. While the change was small, the results showed that either the elevated pressure, increased gas density, or both contributed to (Fig.4).

Under normoxic conditions (Po_2 = 147-162 mmHg), when raising the pressure from 1 to 3.27 ATA then to 5.45 ATA, the mean heart rate fell from 84 to 76 to 75 bpm with each increase in pressure, both at rest and during exercise, despite a constant gas density, 1.11g/L and Po_2 (Flynn *et al.*, 1972). Again, under normoxic conditions, raising gas density from I .1 1 to 3.61 g/L (at 3.27 ATA) or from 1.11 to 6.02 g/L (at 5.45 ATA) changed the

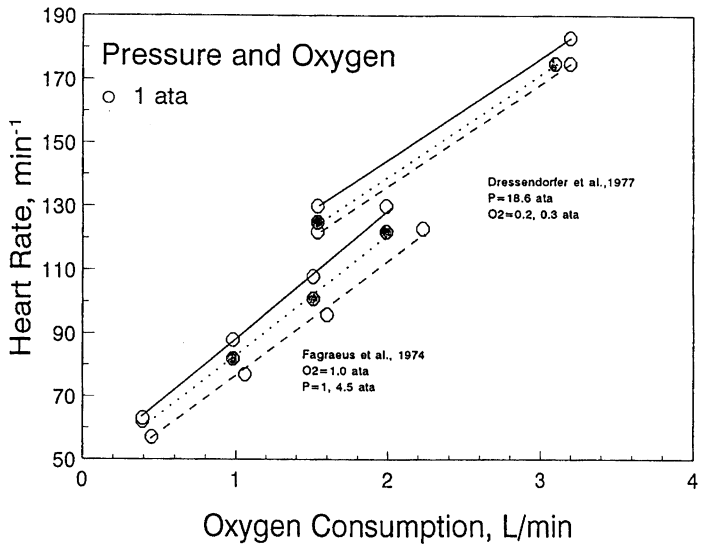

Fig. 4 Effect of hydrostatic pressure and inspired Po_2 On the heart rate during exercise
In humans, Dressendorfer *et al.* (1977) elevated the chamber pressure to 18.76 ATA keeping Po2 at 0.2 atm (dots) then raise the Po_2 to 0.3 atm (dashes). In the experiment of Fagraeus *et al.* (1974), they raised Po_2 to 1.0 atm at sea level (dots), then raised the pressure to 4.5 ATA keeping Po_2 constant at equivalent to 100% O_2 at the sea level (dashes).

heart rate insignificantly. The complicating factor here was the use of two inert gases, namely, helium and nitrogen, to maintain gas density at constant for different pressures. This experiment shows the hydrostatic pressure lowered the heart rate by 8%.

On the other hand in rat experiments, Shida and Lin (1981) varied ambient pressure 10 fold from 1-10 ATA, gas densities over 30 fold from 0.36 to 10.33 times the sea level air, and Po_2, from 142 to over 1,500 mmHg. Either nitrogen or helium was used to make up the gas mixture, except in 100% oxygen. They found that under normoxic conditions, the heart rates varied between 97% to 104% compared to their respective pre-exposure controls. These changes were not statistically different from the control. It appears that, under normoxic conditions, a 30-fold change in gas density and 10 fold change in ambient pressure did not affect the heart rate (**Fig. 5**, top panel).

4. Inert Gases

The bradycardiac effect of hyperoxia was indistinguishable between helium and nitrogen environments (Fig. 5, middle panel). So far, we know hyperoxia lowers the heart rate to a similar degree in a nitrogen, helium, or hydrogen environment. Similarly, in humans, Ceamitrun *et al.* (1993) also reported that the HB in saturation dives with nitrogen and in helium gas mixtures was indistinguishable. This graph also showed that breathing 100% oxygen at the sea level depressed the heart rate by 12% in rats (Fig. 5, lower panel). This result was similar to those reported for humans. It strongly favors hyperoxia as responsible for HB rather than pressure, inert gas, or gas density.

5. Sleep

The heart rate varies greatly depending of the time of day, mental conditions, physical activities and other stimuli. One must institute a strict protocol in determining HB to minimize potential factors affecting it. For examples, Matsuda *et al.* (1975) adopted a procedure of recording ECG 4 times daily at a specific time of day. Consistent data should

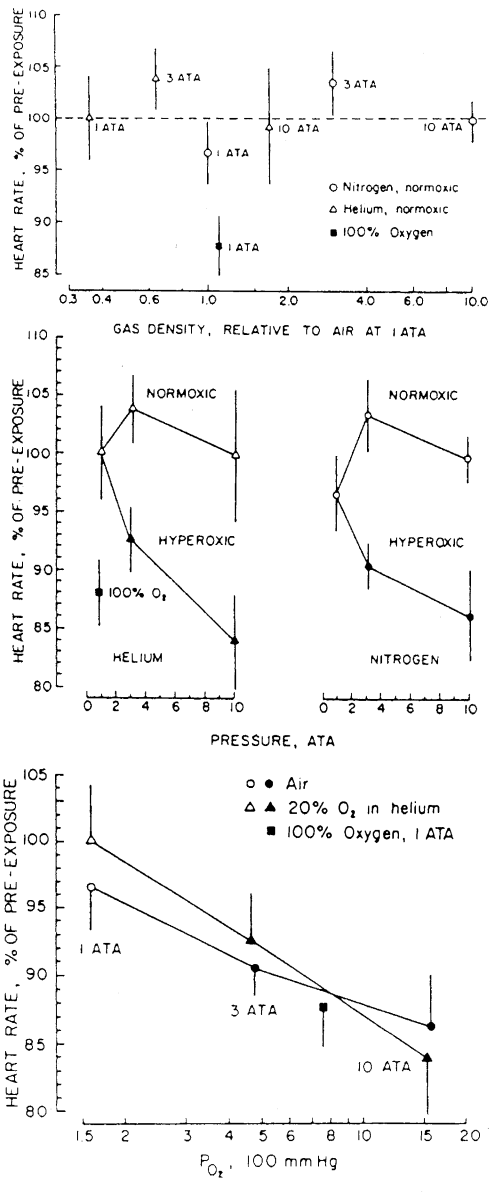

Fig. 5 Effect of gas density, inert gases and inspired Po_2 on the heart rate in rats
(modified from Shida and Lin, 1981)

emerge if the protocol does not require the cooperation in the part of the subjects. One such protocol is to continuously record the R-R intervals of sleeping subjects.

In July 1997, JAMSTEC started recording R-R intervals for 10 minutes every hour on the hour from 23:00 until 07:00 the next morning, in their 20-30-m N_2-O_2 saturation dives (Po_2 = 0.4 atm). When we averaged the heart rate throughout the night, we saw a persisting bradycardia. In three out of four subjects, the heart rate decreased modestly, around 10%, a statistically significant change (**Fig. 6**).

6. Diminishing Bradycardia

Matsuda *et al.* (1975) recorded heart rates 4 times daily at the same time each day. Their data indicated that the HB was maintained for the first 4 days at 7 ATA then rose gradually toward the predive level. Even so, the pooled basal data (the first recording of the day) clearly showed a persistent bradycardia throughout pressure phases. Average results of 7 young males showed that the heart rate decreased by approximately 20% from the predive value of 74±1 bpm.

In some cases, the hyperbaric bradycardia tended to diminish over time. In a nitrox 7-ATA dive, Wilson and colleagues (1977) showed the bradycardia occurred initially for at least 4 days before it drifted back toward the predive level. Nevertheless, the heart rate was still lower than the predive value at the end of the 7 days of saturation and 2 days of decompression. Interestingly, they obtained similar results in all 4 dives where hyperoxia (Po_2 = 0.51-0.61 atm) was present in 3 dives but not in the fourth (Po_2 = 0.23 atm).

MECHANISMS OF HYPERBARIC BRADYCARDIA

In a hyperbaric environment, the P_{O2} is usually high, approximately double that of the sea level condition. Pressure and gas density are also elevated and inert gases may become active. These factors, individually or in combination with other factors, may be responsible for producing HB. Confined and noisy conditions may also be a factor. As summarized above, hyperoxia is the dominant factor responsible for HB while other factors play a minor role.

O_2-Dependent Mechanism

Hyperoxia reduces the heart rate at rest and dur-

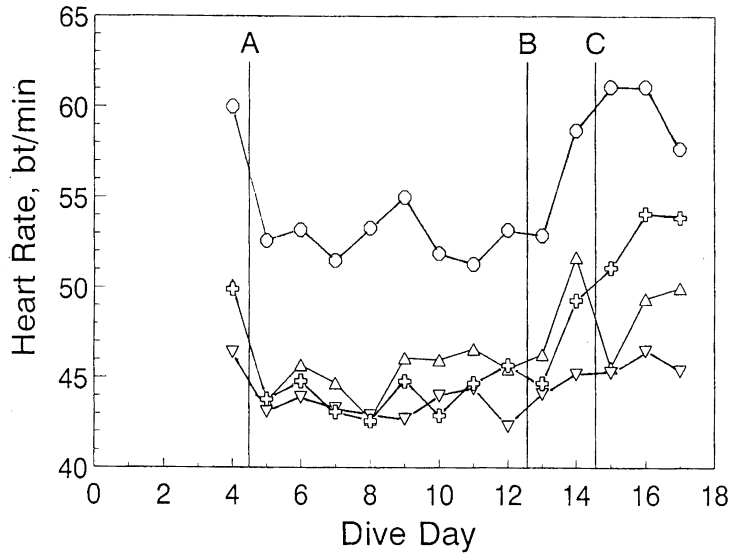

Fig. 6 Over night average of heart rates in 4 sleeping subjects during a 4 ATA N_2-O_2 (Po_2 = 0.4 atm) saturation dive

Each point represent the average of R-R intervals recorded in approximately 10 minutes (Lin *et al.*, 1999)

ing exercise this can be demonstrated at the sea-level condition. Daly and Bondurant (1962) demonstrated a linear reduction in heart rate as O_2 concentration rises. According to them, the heart rate fell approximately 1 bt/min for every 10% increase in oxygen. Breathing 100% O_2 , the heart rate decreased by about 10% compared to breathing air. By using a parasympathetic blocker, it was shown that the O_2-induced bradycardia is mediated through the vagus nerve (Albano, 1970; Daly & Bondurant, 1962).

Bradycardia also occurs during exercise while breathing O_2 at sea level. Margaria *et al.* (1972) compared heart rate responses to maximum and submaximum exercise while breathing either air or 100% O_2 at sea level. They reported a relative bradycardia during exercise approximately 10% lower when breathing oxygen versus breathing air.

In 1984, Eckenhoff and Knight conducted a variety of air saturation dives with depth ranging from 18 to 40 msw. Their purpose was to quantify the effects of confinement and the chamber environment. Hyperoxia was present in all dives, except AIRSAT C. In AIRSAT C, 3 subjects were exposed to a depth of only 0.6 m for 8 days under conditions similar to other dives, but no hyperoxia. Bradycardia was not observed in AIRSAT C, whereas the heart rate fell significantly by 14-23% in other dives. These experiments demonstrated hyperoxia lowers the heart rate.

Lin and Shida (1988) assembled data on HB in rats, rabbits, and dogs and established a relationship between % reduction in heart rate and inspired Po_2 by the equation:

$$\%\Delta HR = -10.47\ (Po_2) + 102.63\ (n = 22, r = 0.8993, p < 0.01)$$

Where HR is the heart rate and P_{O2} is the inspired partial pressure of O_2 . In dogs as in humans, the HB was mediated by the vagus nerve according to Bean & Whitehorn (1941).

Taking this data and experimental results cited earlier, along with results from animal experiments, it is clear that hyperoxia is responsible for a majority of HB. It is most likely that hyperoxia causes bradycardia indirectly by peripheral vaso-

constriction and baroreceptor reflex.

Baroreceptor Mechanisms. Bradycardia occurs in general vasoconstriction, which raises arterial blood pressure and stimulates baroreceptors. General vasoconstriction is evident while breathing hyperoxic gases (Andersen & Hillestad, 1970; Daly and Bondurant, 1962; Eggers *et al.,* 1962; Kenmure *et al.,* 1972; Plewes & Farhi, 1983; Torbati *et al.,* 1979; Whalen *et al.*, 1965). Hyperoxia causes peripheral vasoconstriction by:

1. Interference with CO_2 Transport. Hyperoxia reduces the amount of deoxygenated hemoglobin, which lowers the buffer capacity of the blood, raising tissue [H^+] concentration. Breathing 100% O_2 raises venous P_{CO2}, and breathing O_2 in hyperbaria exaggerates this effect (Lambertsen.1968). The effect of central hypercapnia initiates hyperventilation, lowers P_{CO2}, and raises pH. A general vasoconstriction follows. The centrally mediated sympathetic vasoconstriction overcomes the peripheral effects of acidosis and hypercapnia. Experience from hyperbaric oxygen therapy shows that hyperoxia reduces blood flow in most tissues by 10-20%.

2. Reduced Production of Vasodilating Metabolites. Hyperoxia reduces the production of vasodilating metabolites, which are vasodilators. Vasoconstriction occurs passively by the fall of vasodilating metabolites.

Chemoreceptor Mechanism. Hyperoxia reduces the tonically activity chemoreceptor drive on the sympathetic, resulting in lowering the sympathetic efferent activity to the heart. Hyperoxla suppression of sympathetic drive occurs both at rest and during exercise (Hesse *et al.,* 1981 ; Ruhle *et al.,* 1978; Smith, 1974).

O_2 -Independent Mechanisms

As summarized above, oxygen-independent mechanisms are difficult to evaluate because pressure, gas density, inert gases, and hyperoxia cannot be separated cleanly in most studies involving humans. Doubts always remain about which factor causes the effect. However, it is certain that pressure, gas density, and inert gases produce a minor effect on HB. Other O_2 independent factors that may also have bearing on HB are:

1. Autonomic Nervous State

Spectral analysis of the variability of R-R intervals showed two distinct peaks, one centered at 0.25 Hz and the other at 0.1 Hz. They are known respectively as the high frequency (HF) and low frequency (LF) bands. Research in the past decade has clarified the physiological significance of R-R spectra. For, example, tachycardia occurs during a head-up tilt, which is caused by increased sympathetic and decreased parasympathetic activities. These changes correspond to an elevated LF amplitude and a fall in HF amplitude. It is now accepted that the sympathetic activity is best correlated with the amplitude ratio of LF to HF rather than LF alone (Mukai & Hayano, 1995). In our study in a 3 ATA N_2-O_2, saturation dive, we found in the morning records that the amplitude of HF doubled during saturation compared to the predive value suggesting a greater parasympathetic tone, while that of LF was unchanged. This means the LF-to-HF ratio must have decreased, suggesting a reduced sympathetic tone (Lin *et al.,* 1996).

2. Respiratory Arrhythmia

For normal breathing frequencies, the heart rate rises with inspiration and falls with expiration. Normally, expiration lasts slightly longer than inspiration. The vagus nerve mediates this respiratory-coupled heart rate change. However, in a hyperbaric environment, breathing a gas mixture with elevated gas density prolongs expiration. An overall lowering of the heart rate occurs. Therefore, a prolonged expiratory phase may be a contributory factor to HB.

3. Cardiovascular Deconditioning

Cardiovascular deconditioning (CD) occurs during and following exposure to weightlessness, bed rest, and head-out water immersion (Greenleaf, 1977; Lin, 1984). Indications of CD include orthostatic intolerance, reduced cardiac dimensions, functional (blood volume redistribution) or actual (diuresis) hypovolemia, and diminished exercise

capacity. For astronauts, these changes were predicted from ground-based weightlessness simulations and confirmed by measurements made during space flights. Divers exhibit many of the same characteristics during and following exposure to a hyperbaric environment (Arita *et al.,* 1987; Lin, 1987; Ohta *et al.,* 1981). These diverse conditions have in common an expanded central blood volume. In hyperbaria, divers breathe a high-density gas mixture elevating the airway resistance. This necessitates a greater intrathoracic negative pressure during inspiration, resulting in expanded central blood volume. Under such conditions, there is a diuresis throughout the period of hyperbaric exposure (Hong *et al.,* 1996; Shiraki *et al.,* 1984; Shiraki *et al.,* 1987), just as that which would occur In head-out water immersion, during bed rest, and other ground-based space simulations. These similarities led us to suspect CD may also exist during hyperbaric exposure. This hypothesis has been confirmed repeatedly.

The occurrence of CD was confirmed in *Seadrag on VI* (Arita *et al.,* 1987), *New Seatopia-85* (Lin *et al.,* 1987; Lin *et al.,* 1995) at the Japan Marine Science and Technology Center (JAMSTEC), Yokosuka, Japan, and in dive series (Holthaus, 1988; Lin *et al.,* 1991) in the German Underwater Simulator (GUSI), Geesthacht, Germany. Of particular interest here is that a resting heart rate in CD is higher than that of the control (Lin, 1999). However, the existence of HB counteracts this CD-induced tachycardia and it emerges only after the completion of decompression. We postulate that this relative tachycardia attenuates the expression of HB resulting in a diminishing or canceling of HB during a prolonged saturation dive.

SUMMARY AND CONCLUSION

In summary, hyperoxia is the most significant factor contributing to HB. Hyperoxia interferes with CO_2 transport and consequently a centrally mediated vasoconstriction. The heart rate is lowered through baroreceptor reflex. In addition, hyperoxia suppresses chemoreceptor activity and lowers the sympathetic drive that the heart rate also lowers. Results from spectral analysis of R-R intervals suggest a state of lowered sympathetic and elevated parasympathetic activity in hyperbaric environments.

In conclusion, the existence of hyperbaric bradycardia invalidates the use of heart rate-work relationships obtained at sea level for use in hyperbaric environments. Independent calibration must be made to avoid underestimating the work intensity in hyperbaria.

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