□ SPECIAL LECTURE □

Physiology of Man under High Pressure

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Since the first experiments in saturation diving using animals were undertaken in 1957 at the U. S. Naval Submarine Research Laboratory to prove the safety of long exposures to normoxic mixtures of helium-oxygen at depth, many saturation dives using human divers have been successfully conducted by many different laboratories in the world. In one of such dives, human divers were exposed to a simulated depth of nearly 700 m (Bennett and McLeod, 1983) which represents the current diving depth record for humans. There are two basic questions regarding saturation dives: 1) what is the ultimate depth human divers may reach, and 2) how long may human divers be exposed to a hyperbaric environment?

During last 15 years I have been involved in seven saturation dives conducted in either Honolulu, Hawaii or Yokosuka, Japan. The two Hawaii dives were sponsored by the University of Hawaii and the five Japan dives by the Japan Marine Science and Technology Center (JAMSTEC). All of these dives were conducted as the integral part of the U.S.-Japan Cooperative Diving Research Program supported by the U.S.-Japan Cooperative Program in Natural Resources (UJNR). Although all dives were conducted to study the physiology of human divers during a prolonged exposure to hyperbaric helium-oxygen environment, the results obtained from the three dives (Table 1), in which more comprehensive physiological studies were conducted, will be extensively used in this presentation.

Many changes in physiological functions have been observed during saturation diving. These include high pressure nervous syndrome (HPNS), disturbances of body heat balance, alteration of cardiorespiratory functions, diuresis and body fluid disturbances associated with changes in endocrine functions and in circadian rhythms.

All of these changes will be briefly discussed in this presentation, except for the HPNS and the body heat balance. There is no question that HPNS constitutes a major risk for the divers, especially during the rapid compression phase, but it can be controlled by manipulating the compression rate. In fact, in all dives I was involved with, the HPNS was deliberately avoided by applying a slow compression and/ or by imposing several compression stops. Moreover, unless the chamber temperature was deliberately lowered to study the responses to cold at high pressure, the chamber temperature was kept at thermoneutral level in all dives I was involved with. These maneuvers have allowed us to study various physiological functions under high pressure, independent of complications associated with the HPNS and/or subtle cold stress.

Energy Balance

According to Webb et al. (1977), in 14 of 15

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Table 1. Profiles of three research dives conducted under the aegis of the U.S.-Japan Cooperative Diving Research Program

Code Name	Saturation Press. (ATA)	Bottom Time(Days)	No. of Divers	Year	Location
Hana Kai II	18.6	17	5	1975	Hawaii
Seadragon IV	31	14	4	1978	Japan
Seadragon VI	31	7	4	1983	Japan

saturation dives where body weight has been measured, most subjects lost weight; in the 15th dive there was no weight loss. Calorie counting of food intake was done in six of these studies and the intake was reported to be 2500-3500 kcal/day. In the other nine dives, food intake was said to be between 3500 and 6000 kcal/day. Despite the high food consumption, weight losses of 0.6 to 4 Kg were observed in 14 dives.

In order to study the mechanism for the persistent weight loss during saturation diving, a comprehensive study of energy balance was undertaken during the Hana Kai II dive by Webb et al. (1977); all food, urine, and feces for five divers were analyzed by bomb calorimetry while 24-h energy expenditure was measured from continuous oxygen intake, while CO_2 output and urine N; body weight, total body water and body composition were also assessed.

The results indicated that food inntake was about 3500 kcal/day while fecal and urinary losses were a normal 6-8% of intake; more importantly, there was no evidence to indicate that energy expenditure increased significantly during the hyperbaric condition as long as the chamber temperature was thermoneutral. In fact, the average body weight decreased by only 0.8 Kg during 17 days of exposure to 18.6 ATA. The above weight loss was attributed to a loss of adipose tissue, since the total body water volume remained unchanged.

Body weight was also carefully monitored in subsequent dives to a simulated depth of 300 msw (or 31 ATA): Seadragon IV (Nakayama et al., 1981) and Seadragon VI (Shiraki et al., 1987). The body weight decreased, on the average, by 0.7-1.0 Kg during these dives.

These studies indicate that human divers are able to maintain their energy balance reasonably well under high pressure. Although it is not clear why the magnitude of the body weight loss was as high as 4 Kg in some earlier dives, it is possible that there may have been a caloric deficit in these dives for some unidentified reason.

Cardiovascular Functions

In the majority of saturation dives conducted so far, a definite bradycardia was found in both resting and exercising divers (Shilling et al., 1976). Although the degree of bradycardia appeared to be correlated to the predive heart rate, the average heart rate reduction during saturation diving amounts to about 15% of the predive heart rate (Fig. 1). However, it is interesting to note that the relative magnitude of the bradycardia was not correlated with the (simulated) depth over a wide range of 140-1150 ft. Although the mechanism underlying the hyperbaric bradycardia has not yet elucidated, it should be noted that hydrostatic compression of the isolated cardiac pacemaker cell alone also induces a reduction of the beating frequency (Ornhagen and Hogan, 1977), strongly suggesting that the high hydrostatic pressure *per se* may act directly at the level of the pacemaker cell membrane and play an important role in modulating heart rate in diving man. The latter finding also suggests an arterial baroreceptor-mediated bradycardia may not be a major mecha-

nism although it may make a contribution. Whatever the mechanism, the hyperbaric bradycardia is also a time-dependent phenomenon in that it slowly disappears within 1-3 days of exposure to high pressure, possibly suggesting a baroreceptor resetting.

In the Hana Kai II dive, impedance cardiography was utilized in order to determine the stroke volume and the thoracic conductive volme (Smith et al., 1977). In general, stroke volume changed inversely as a function of heart rate and tended to be increased early in the dive when the bradycardia was present. Consequently, the cardiac output remained relatively constant during various dive periods. On the other hand, the thoracic conductive volume tended to increase during compression to about 10.5 ATA (350 fsw) and then fell. If we accept the generally held notion that the thoracic conductive volume reflects the thoracic blood volume, we may speculate that the latter increases during compression as the density of the breathing gas increases. It may be parenthetically mentioned in this regard that the increased density of the breathing gas significantly increased the peak inspiratory esophageal pressure with only a slight increase in peak expiratory esophageal pressure, which is most likely responsible for the intrathoracic blood pooling during compression.

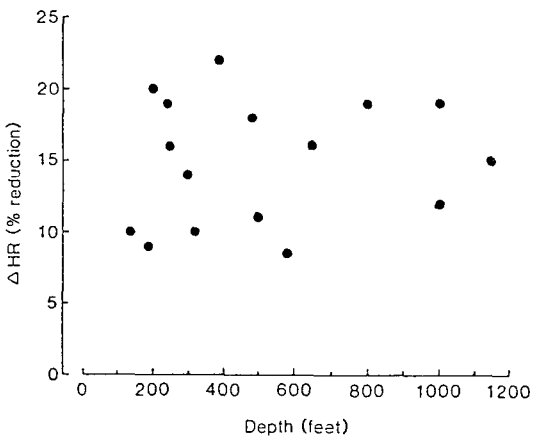

Fig. 1. Percent decreases in the heart rate during the early phase of dry saturation dives to different simulated depth. Data points are computed from the heart rate data reported for nine different dives.

Regardless of the mechanism for the increased thoracic conductive (or blood) volume during compression, it is interesting to speculate about the potential physiological significance of this phenomenon. The most likely consequence of an increased thoracic blood volume would be distention of the atrium, resulting in a release of atrial natriuretic peptide (ANP) as well as cause simultaneous inhibition of both antidiuretic hormone (ADH) and renal sympathetic tone. The latter changes would be expected to indue a diuresis and/or natriuresis during compression. Indeed, significant increases in urinary excretion of water and Na are observed during the compression phase of saturation diving (Hong et al., 1977), but it is not yet clearly established that these early renal responses to high pressure are due to the increase in ANF and/or the inhibition of ADH (see below).

Ventilatory and Exercise Capacity

As the environmental pressure increases, the density of breathing gas increases in direct proportion as well, which, in turn, decreases diffusive mixing of gas in the lung and increases air flow resistance on both inspiration and expiration (Van Liew, 1983). Despite these respiratory factors associated with high density gas breathing, rapid compression to high pressure does not seem to impair respiratory homeostasis in man at rest breathing CO_2-free gas over the pressure range 1-50 ATA (gas density range 0.4-25 g/l) (Gelfand et al., 1983). However, the maximal ventilatory capacity is very sensitive to density of breathing, as shown in Table 2.

Despite the decreased ventilatory capacity as indicated by ~30% reduction in the maximal voluntary ventilation at 18.6 ATA, it was interesting to note that the maximal aerobic power (and the endurance time) either remained unchanged or even slight-

ly increased under the same pressure, depending upon the PO_2 level of the chamber gas(Table 2) (Dressendorfer et al., 1977). When the PO_2 level was maintained at 0.3 ATA, a level slightly above normoxic level of 0.2 ATA, the maximal aerobic power increased by ~3% ($p<0.05$) as compared to the 1 ATA predive level. However, when the PO_2 level at 18.6 ATA was artificially lowered from 0.3 to 0.2 ATA, the maximal aerobic power at 18.6 ATA was identical to that at the predive 1 ATA level. Evidently, it is advantageous to raise the level of PO_2 in the hyperbaric environment to a level above normoxia in order to maintain the physical exercise capacity at moderate ambient pressure.

However, such advantages of slight hyperoxia were not evident at 31 ATA at which the maximal voluntary ventilation decreased by about 45%. Although PO_2 of the chamber gas was raised to 0.4 ATA (rather than 0.3 ATA), the maximal aerobic power decreased by 13% ($p<0.05$) at 31 ATA as compared to the predive 1 ATA value (Table 2) (Ohta et al., 1981). These observations indicate that the maximal aerobic power is affected at higher pressure despite the increased PO_2 level. Although the data of Dwyer et al. (1977) also support this conclusion (Table 2), they should be interpreted with caution because of the fact that these experiments were carried out in the wet hyperbaric environment.

Since water immersion *per se* is known to induce alterations in cardiorespiratory functions, it is not clear to what extent the data of Dwyer et al. (1977) are influenced by the act of immersion.

In recent years, deep saturation dives using "trimix" (5-10% N_2 present in the chamber gas) have been conducted at the F.G. Hall Laboratory of Duke University as an attempt to attenuate or ameliorate HPNS by counterbalancing the effects of rapid changes in pressure. Although the use of trimix allowed the diver to reach a simulated depth of nearly 700 m, it should be realized that the addition of N_2 to heliox (He-O_2) gas mixtures increases the density of the mixture at a given depth and consequently may limit the ventilatory capacity. Therefore, Salzano et al. (1984) have conducted a series of studies designed to ascertain the physiological condition of the subjects performing graded exercise in a dry chamber while breathing trimix gases ($PO_2=0.5$ ATA) at pressures of 47-66 ATA (with densities varying from 7.9-17.1 g/l). These investigators noted that dyspnea was evident at both rest and

Table 2. Maximal voluntary ventilation (MVV), maximal aerobic power (VO_2 max) and maximal exercise endurance time (ET).

P_B (ATA)	PO_2 (ATA)	MVV (l/min, BTPS)	VO_2 max (l/min, STPD)	ET (min)
		-Hana Kai II (Dressendorfer et al., 1977)-		
1	0.2	137	3.10	4.19
18.6	0.3	101*	3.20*	6.22*
18.6	0.2	108*	3.10	4.88
		-Seadragon IV(Ohta et al., 1981)-		
1	0.2	178	3.11	-
31	0.4	95-100*	2.71*	-
		-Duke Wet Dive (Dwyer, et al., 1977)-		
1.5	0.3	123	2.86-3.00	-
43.4	0.4	72*	1.81-2.36	-

*Significantly different ($p<0.05$) from the corresponding 1 ATA value.

during exercise and was predominantly inspiratory in nature. Moreover, compared with surface measurements, moderate work at depth was associated with alveolar hypoventilation, arterial hypercapnia, very large physiological dead space, high levels of arterial lactate, and signs of simultaneous respiratory and metabolic acidosis. In fact, acidemia at depth was more severe, and its onset occurred at lesser work rates than at 1 ATA. The increase of ventilation that accompanies the onset of acidemia at the surface was not present at depth. Based on these observations, Salzano et al. (1984) cautioned that maximal work tolerance may be an insufficient assessment of the physiological condition of a diver exposed to these high pressures.

Body Fluid Balance

Maintaining a constant body fluid volume and composition is on of the major requirements to support divers' activities during a prolonged dive. However, in one of the earlier dry saturation dives conducted by Hamilton et al. (1966), a significant increase in urine flow was observed at a simulated depth of 650 ft. A similar hyperbaric diuresis was reported in many subsequent dives to various depths (Hong, 1975). Although the presence of a subtle cold stress in many early saturation dives could account for the diuresis, more recent dives conducted in the absence of any cold stress indicated that a sustained diuresis could be induced even in a thermoneutral hyperbaric environment.

The average daily urine flow computed from eleven different dives (4-49.5 ATA) increased from approximately 1,500 ml predive to 2,000 ml at pressure (Hong, 1975). In all cases, the diuresis was accompanied by a reduction in urine osmolality with or without a small increase in osmolal clearance. Hence, the negative free water clearance tended to decrease in most dives. A more consistent increase in the urinary excretion of osmotic particles (e.g., Na and K) is usually observed during exposure to a pressure greater than 25 ATA (Nakayama et al., 1981). The endogenous creatinine clearance is gener-

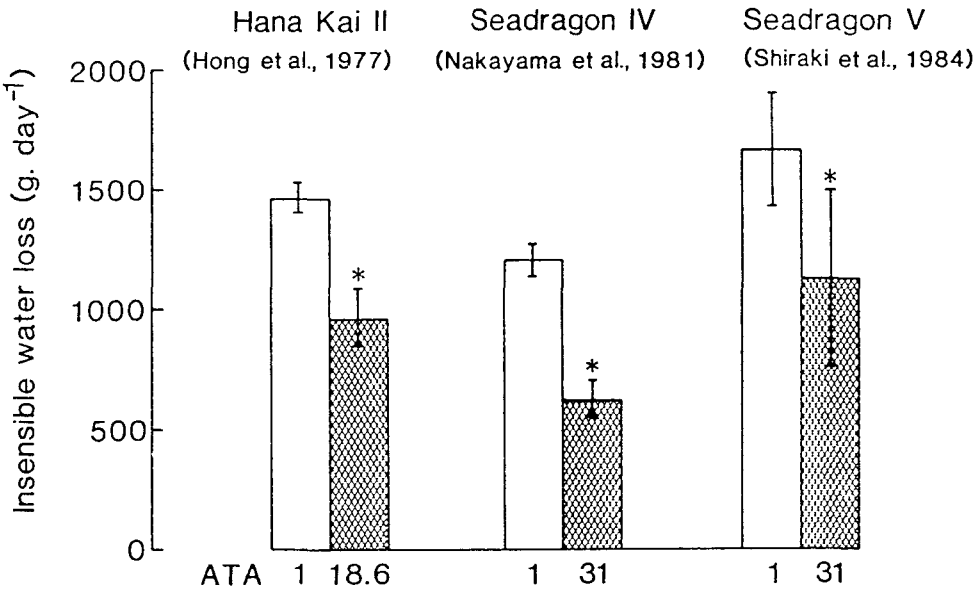

Fig. 2. Insensible water loss during predive 1 ATA and at high pressure in three different dives. *Significantly different ($p<0.01$) from the corresponding 1 ATA data.

ally found to be unchanged at pressure (Hong et al., 1977; Shiraki et al., 1987), indicating that the hyperbaric diuresis results from the inhibition of the tubular reabsorption of filtered water and/or Na/K. In general, the hyperbaric diuresis and natriuresis are not accompanied by an increased intake of water and Na.

Since the urine flow increases at pressure without increasing the fluid intake, it is predicted that a state of net fluid loss (i.e., dehydration) should develop during a multi-day dive. However, evidence for such dehydration was found only during the early phase (5-6days) of the hyperbaric period (Hong et al., 1977; Shiraki et al., 1987). Surprisingly, the total body fluid volume measured during the steady state phase of exposure to pressure (18.6 ATA) was not significantly different from the predive value (Hong et al., 1977), indicating that the overall body fluid balance is still maintained at high pressure.

These paradoxical phenomena (i.e., no dehydration despite a sustained diuresis in the absence of an increased water intake) can be explained only if there is a reduction in the insensible water loss, corresponding to the magnitude of the increase in daily urine flow at pressure. This has been experimentally verified at least in three dives (Fig. 2) (Hong et al., 1977; Nakayama et al., 1981; Shiraki et al., 1984). On this basis, Hong et al. (1977) proposed that the primary mechanism for the hyperbaric diuresis is the suppression of the insensible water loss, which should result in water retention with a subsequent inhibition of antidiuretic hormone (ADH) system. Such an inhibition of the ADH system has also been experimentally established (Claybaugh et al., 1984; Hong et al., 1977; Shiraki et al., 1987).

The reduction of insensible water loss has been explained by the fact that the diffusivity of water vapor is inversely proportional to ambient pressure or the gas density (Paganelli and Kurata, 1977). As stated above, the diuresis observed during the early phase of exposure to high pressure was accompanied by a transient dehydration (equivalent to 500-800 ml) and an increase in the excretion of osmotic substances. Therefore, it appears that factors other than the inhibition of ADH may also be involved in inducing the early diuresis. Hong (1975) speculated that both a gas osmotic effect and the high density of the breathing gas may play a role. As described above (Section B) the thoracic conductive volume increased during the compression phase of the Hana Kai II dive, strongly implying that the low pressure volume receptors located in the atrium are most likely stimulated and, as a result, that atrial natriuretic peptide (ANP) could be released. Under a variety of

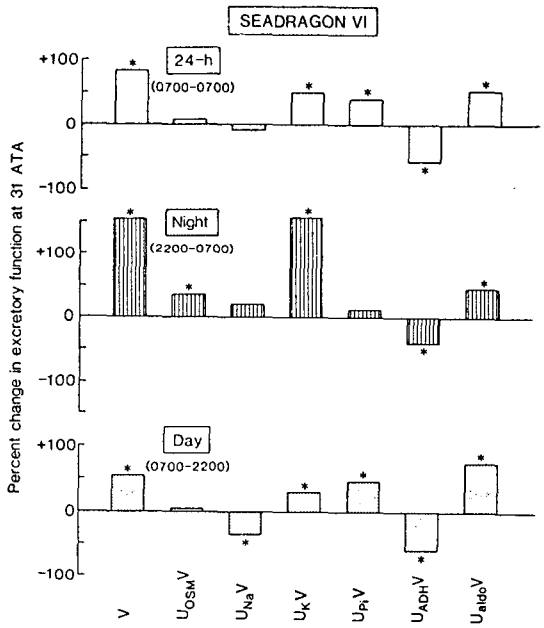

Fig. 3. Percent changes in urinary excretions of water (V), total osmotic substrates ($U_{osm}V$), Na($U_{Na}V$), K($U_{R}V$), inorganic phosphate ($U_{Pi}V$), antidiuretic hormone ($U_{ADH}V$) and aldosterone ($U_{aldo}V$) at 31 ATA as compared to predive 1 ATA. Top, middle and bottom panels indicate the excretory functions per whole day (24-h), daytime (0700-2200 h), and night time (2200 -0700 h), respectively. *significant change at 31 ATA ($p<0.05$). The data are from the Seadragon VI dive (Claybaugh et al., 1987; Shiraki et al., 1987).

experimental conditions in which central blood pooling is induced, the plasma ANP level is known to increase, which is thought to be responsible for the subsequent diuresis and natriuresis. However, there were no consistent increases in the level of plasma ANF during either early or steady-state phase of three different dives to 300-600 msw, in which a significant natriuresis was observed (Moon et al., 1987; Claybaugh et al., unpublished data).

The sustained natriuresis observed during a steady-state phase of exposure to a pressure greater than 25 ATA is usually accompanied by an increased, rather than reduced, level of plasma renin and aldosterone (Hong et al., 1977; Claybaugh et al., 1984; Claybaugh et al., 1987). This rules out aldosterone as a factor involved in inducing a hyperbaric natriuresis; nor is it likely that ANP is playing any role, as discusssed above. In this regard, it may be noted that the active Na efflux in human erythrocytes is significantly inhibited by a modest hydrostatic pressure of 30-50 ATA (Goldinger et al., 1980).

If such an inhibitory effect of high hydrostatic pressure exists for the active tubular Na reabsorption, it could account for the observed hyperbaric natriuresis. Recently, we reported that the active Na transport across the toad skin (which is widely used as a functional model for the distal nephron of the mammalian kidney) is progressively inhibited with the increase in hydrostatic pressure (Hong et al., 1984; Goldinger et al., 1986). The dose-response relationship indicated a 20% inhibition at 50 ATA. More recent studies indicated that this pressure-induced inhibiton of active Na transport across the toad skin is associated with corresponding derease in the apical membrane Na permeability (Wilkinson et al., unpublished data). However, it is still unknown if high hydrostatic pressure also inhibits the tubular Na-K-ATPase activity.

During the course of the Seadragon dive series a marked increase in the overnight urine flow was observed during exposure to 31 ATA (Nakayama et al., 1981; Shiraki et al., 1987). This hyperbaric nocturia could not be accounted for by nocturnal fluid intake or cold stress. Interestingly, the nocturia is largely due to an increased osmolal clearance whereas the diurnal (daytime) diuresis is largerly due to an increase in free water excretion (Fig. 3) (Shiraki et al., 1987). However, these differences in the characteristics of the hyperbaric diuresis between day and night could not be accounted for by concomitant circadian changes in endocrine functions such as the ADH or aldosterone system (Fig. 3). Evidently, the daytime diuresis appears to be associated with the suppression of the insensible water loss and the attendant inhibition of the ADH system. On the other hand, the nocturia appears to be due to the greater inhibition of active tubular reabsorption of Na through a mechanism yet to be elucidated.

Other Physiological Functions

During a multi-day (chamber) saturation dive the divers are confined to a limited space, often with minimal activities. Moreover, there is evidence to indicate that a modest dehydration develops during the early phase of compression when the divers start breathing a dense gas mixture. Therefore, it is not unreasonable to suspect that a state of cardiovascular deconditioning may occur during saturation diving. In the Seadragon VI dive, Arita et al. (1987) determined a cardiovascular index of deconditioning from the measurements of blood pressure and heart rate before and during 15 min of the 90° body tilt. The results indicated that a state of cardiovascular deconditioning is already evident within 24 h of exposure to 31 ATA. In fact, one diver fainted during the 90° body tilt at 31 ATA while no such episode occurred before or after the hyperbaric exposure. The fact that cardiovascular deconditioning occurs within 24 h of hyperbaric exposure suggests that the initial phase of cardiovascular deconditioning is unrelated to physical confinement. In these 90° body tilt experiments,

Matsui et al. (1987) also determined the changes in plasma renin and ADH levels and found that hyperbaria enhances renin but eliminates ADH responses to head-up tilt. These observations are very interesting, but if and how these differential endocrine responses to the 90° body tilt at 31 ATA are related to the above described cardiovascular deconditioning are not obvious.

It has been recognized for many years that animals breathing normoxic gas mixtures at high pressure have impaired work performance consistent with hypoxia. However, the cause for this hypoxia has not been clearly understood although a direct effect of high pressure on hemoglobin decreasing P-50 (Reeves and Morin, 1986; Stolp et al., 1984) has been suggested as a mechanism. Such an alteration of hemoglobin affinity at high pressure may be associated with the increase in the chloride distribution ratio across the red blood cell membrane observed at 31 ATA (Goldinger et al., 1981; Sagawa et al., 1987). Sagawa et al. (1987) also observed an increase in the 2,3-DPG level of the red blood cell of divers exposed to 31 ATA; a result which would be consistent with tissue hypoxia.

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