Hyperbaric Diuresis and Nocturia—A Review

Keizo SHIRAKI¹, Sueko SAGAWA¹, Nobuhide KONDA¹ and Suk Ki HONG²

¹*Department of Physiology, University of Occupational and Environmental Health, Japan.
Kitakyushu 807, Japan*

²*State University of New York at Buffalo. Buffalo, New York, U. S. A.*

Abstract : Human divers are now able to engage in a multi-day dive to a considerable depth using the mixed gas saturation diving technique, however their daily activities are somewhat limited in the depth. One of the major problems that has not been generally appreciated is the potential for body fluid disturbances at high pressure due to the development of a sustained diuresis. In addition, a marked nocturia has been observed in recent saturation dives at 26–31 atmospheres absolute (ATA), which disturbs divers' sleep during the night. In this review, we will briefly discuss the basic characteristics and mechanisms of these disturbances of renal functions observed during hyperbaric exposure.

Key words : hyperbaric diuresis, nocturia, body fluid balance, ADH.

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Human divers are now able to engage in a multi-day dive to a considerable depth using the mixed gas saturation diving technique. In a dive recently carried out at Duke University, several divers reached a simulated depth of nearly 690 m (70 ATA) and then safely returned to sea level. Apparently, human divers seem to be able to cope with such high pressure and can perform their daily activities albeit on a somewhat limited basis.

One of the major problems associated with hyperbaric exposure is the occurrence of the high pressure nervous syndrome (HPNS) which can severely limit the performance of divers. Fortunately, however, one can attenuate HPNS by slow compression or by using a "trimix" (He-N₂-O₂) (Bennett & McLeod, 1983). Another problem that has not been generally appreciated is the potential for body fluid disturbances at high pressure due to the development of a sustained diuresis (Hong, 1975; Hong *et al.*, 1977). In addition, a marked nocturia has been observed in recent saturation dives at 26–31 ATA (Nakayama *et al.*, 1981), which disturbs divers' sleep during the night.

In this review, we will briefly discuss the basic characteristics and mechanisms of these disturbances of renal functions observed during hyperbaric exposure. Since the hyperbaric diuresis as a phenomenon has already been extensively reviewed by Hong (1975) and Hong *et al.* (1983), it will be discussed briefly and a greater emphasis will be placed on the phenomenon of hyperbaric nocturia.

Hyperbaric Diuresis

In practically all multi-day saturation dives conducted during the last 25 years, a sustained diuresis has been observed (Hong, 1975). Because of the high gas density and the presence of helium at high concentration, the body heat loss is greatly accelerated in the hyperbaric environment. As a result, a subtle cold stress was present in many early saturation dives, which could account for the diuresis. However, later dives were carried out in the absence of any cold stress and yet a significant diuresis was still observed, indicating that thermoneutral hyperbaric conditions induce a sustained diuresis.

The average daily urine flow computed from eleven dives (4 to 49.5 ATA) increased from approximately 1,500 ml pre-dive to 2,000 ml at pressure (Hong, 1975). In dives with bottom time (i.e., under high pressure) of longer than 7 days, the magnitude of diuresis was somewhat greater during the early phase as compared to the later steady state phase of the hyperbaric exposure (Hong *et al.*, 1977). 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. The endogenous creatinine clearance was generally found to be unchanged at pressure, although it decreased approximately 15% in a recent dive at 31 ATA (Nakayama *et al.*, 1981). The latter dive (code-named "Seadragon IV") was conducted at the Japan Marine Science and Technology Center in 1979, and the results obtained from this dive are shown in Fig. 1 to illustrate the general characteristics of a hyperbaric diuresis.

Despite the sustained diuresis during a prolonged exposure to the hyperbaric environment, the daily fluid intake (drinks, water in food, and water of oxidation) showed small but consistent decreases at pressure (Hong *et al.*, 1983; Nakayama *et al.*, 1981).

These results rule out the increased fluid intake and glomerular filtration rate as the reason(s) for the hyperbaric diuresis. Moreover, the results predict that the sustained diuresis in the absence of increased fluid intake should induce a progressive dehydration during a prolonged hyperbaric exposure. However, evidence for such dehydration was found only during the early phase (5–6 days) of the hyperbaric period (Hong *et al.*, 1977; Nakayama *et al.*, 1981). 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 pre-dive value (Hong *et al.*, 1977). These findings indicate that the overall body fluid balance is still maintained at high pressure.

These paradoxical findings 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 several dives (Hong *et al.*, 1977; Nakayama *et al.*, 1981). Therefore, the primary mechanism for the hyperbaric diuresis appears to be the suppression of the insensible water loss, which should result in water retention and subsequent inhibition of the antidiuretic hormone (ADH)

system. Such an inhibition of the ADH system has also been experimentally established (Claybaugh *et al.*, 1984; Hong *et al.*, 1977; Matsui *et al.*, 1983). The reduction of the insensible water loss has been explained by the fact that binary diffusivity of water vapor is inversely proportional to ambient pressure and also varies with the molecular species of the gas in the diffusive path (Paganelli & Kurata, 1977). In addition, there appears to be a secondary mechanism operating under higher pressure, which is responsible for the natriuresis shown in Fig. 1. Although the exact mechanism is still unknown, a high hydrostatic pressure inhibits active Na transport across the epithelium (Hong *et al.*, 1984).

The greater diuresis observed during the early phase of hyperbaric exposure appears to induce a transient dehydration and is attributed to both a gas osmotic effect and the high density of the breathing gas (Hong, 1975). A sudden exposure to a hyperbaric

Fig. 1. Urine flow (V), urine osmolality (U_{osc}), Osmolal clearance (C_{osc}), and endogenous creatinine clearance (C_{cr}) during various dive periods of Seadragon IV. Each period consists of 3 days, and each point represents the mean ($\pm$ SE) of 4 subjects.

environment (or high gas density) increases the thoracic blood volume, which increases the excretion of free water and Na. However, these postulates have not been experimentally verified. One unexplained finding is that the urinary excretion of ADH always increases during the early phase of hyperbaric exposure before it decreases (Hong *et al.*, 1977; Hong *et al.*, 1983; Matsui *et al.*, 1983). This clearly indicates that there must be other mechanisms for the early diuresis than the inhibition of ADH. It is possible that some factors counteracting the action of ADH (e.g., norepinephrine, prostaglandin, natriuretic hormone, etc.) may be activated during the early hyperbaric period. Regardless of the mechanism, the early diuresis results in a dehydration, which may be causally related to the increased plasma renin activity and urinary excretion of aldosterone (Hong *et al.*, 1977; Hong *et al.*, 1983; Matsui *et al.*, 1983).

As stated above, the diuresis observed during the steady hyperbaric exposure is generally associated with a reduced level of ADH excretion. Strangely, however, this reduction in ADH excretion is still maintained during the postdive period when the hyperbaric diuresis is no longer present (Hong *et al.*, 1977; Hong *et al.*, 1983; Matsui *et al.*, 1983). In other words, there appears to be a dissociation of ADH and renal responses after a dive. Although there could be many possibilities for this phenomenon, one might speculate that the renal tubule is sensitized to ADH during the prolonged hyperbaric period when the ADH level is kept suppressed.

Hyperbaric Nocturia

During the Seadragon IV dive (Claybaugh *et al.*, 1984; Nakayama *et al.*, 1981), it was unexpectedly observed that the major portion of the increase in daily urine flow at high pressure was accounted for by the increase in overnight urine flow (Fig. 2). This "nocturia" phenomenon has never been reported before and this mechanism is entirely unknown at present.

Circadian rhythms for various renal functions are also shown in Fig. 2 for pre- and post-dive 1 ATA and 31 ATA periods (Claybaugh *et al.*, 1984). It is evident that the diurnal rhythm for urine flow is the same in all periods, and the only difference was found in the nocturnal urine flow. This higher overnight urine flow was accompanied by significant increases in C_{osm} and $C_{\text{H}_2\text{O}}/C_{\text{osm}}$, but not by any increase in C_{cr} . This indicates that increases in the excretion of both osmotic substances and free water are responsible for the increase in overnight urine flow at high pressure. In other words, tubular reabsorption of solutes and water appears to be suppressed at night under high pressure. In fact, the urinary excretion of Na and K was higher at night at 31 ATA, although the basic pattern of the circadian rhythm remained the same in all periods (Fig. 3). However, despite such increases in the excretion of solutes and free water, the overnight excretion of both ADH and aldosterone at 31 ATA were comparable to that at 1 ATA (Fig. 3). On the other hand, the basic pattern of the circadian rhythm for the

urinary excretion of ADH and aldosterone at 31 ATA changed markedly in that the early afternoon peak clearly identifiable at 1 ATA disappeared totally at 31 ATA (Claybaugh *et al.*, 1984). As stated above, however, there was no difference in the daytime excretion of free water and solutes between 1 and 31 ATA. These observations suggest that both ADH and aldosterone do not play any major role as primary determinants of solute and free water excretion at high pressure. Most likely, there are other heretofore unidentified

Fig. 2. Circadian rhythms for urine flow, endogenous creatinine clearance (C_{cr}), osmolal clearance (C_{osc}) and free water to osmolal clearance ratio (C_{H_2O}/C_{osc}) during predive 1 ATA (●—●), 31 ATA (●—●—●), and postdive 1 ATA (○—○) periods of Seadragon IV. Each point represents the mean ($\pm$ SE) of the results obtained from 4 subjects. Measurements were made for only 1 day for each of three periods. * $P < 0.05$ compared to predive values. The data obtained from Claybaugh *et al.* (1984).

Fig. 3. Circadian rhythms for urinary excretion of antidiuretic hormone (U_{ADH} V), aldosterone (U_{aldo} V), Na (U_{Na} V) during various periods of Seadragon IV. See Fig. 2 legend for other relevant information. The data obtained from Claybaugh *et al.* (1984).

factors, neural and/or humoral, significantly contributing to the body fluid homeostasis at pressure. Alternatively, these results are also consistent with a view stated above that the sensitivity of the renal tubules to these hormones may be altered under high pressure (Claybaugh *et al.*, 1984; Hong *et al.*, 1977). However, it is needless to say that the exact role of ADH and aldosterone should be defined on a more definitive basis by analyzing plasma levels of these hormones.

In the dive described above, the hyperbaric chamber temperature was maintained at $31.0 \pm 0.2^\circ\text{C}$ at 31 ATA, which was considered to be thermoneutral (Webb *et al.*,

1977). However, there was a reduction of the mean skin temperature by 1°C at 31 ATA (Nakayama *et al.*, 1981), and it was felt that there may have been a subtle cold stress at night, which could lead to a mild cold diuresis at pressure (Shiraki *et al.*, 1982). Consequently, the chamber temperature was raised to 31.5°C in the subsequent dive to 31 ATA ("Seadragon V"). There was no change in the mean skin temperature in the latter dive (Shiraki *et al.*, 1983). However, an essentially identical nocturia was again observed at 31 ATA (Fig. 4). Only the overnight urine flow was significantly higher at pressure as compared to 1 ATA.

As in the previous dive, this hyperbaric nocturia was not associated with any renal hemodynamic changes (Fig. 5). However, unlike the previous finding, this nocturia was entirely due to an increase in the free water clearance, with little change in C_{osm} during the night. As shown in Fig. 6, the urinary excretion of total osmotic substances and Na also remained unchanged during the night at 31 ATA (Fig. 6). A small (but significant) increase in the overnight K excretion was observed, which may be related to the increased aldosterone level (see below). These results indicate that the hyperbaric nocturia observed in "Seadragon V" is basically a water diuresis while that observed in "Seadragon IV" consists of both water and osmotic diuresis (Nakayama *et al.*, 1981).

The urinary excretion of ADH and aldosterone in "Seadragon V" also showed circadian rhythms similar to those observed in the earlier dive (Matsui *et al.*, 1983). However, more importantly, the level of overnight urinary ADH excretion was essentially the

Fig. 4. Circadian rhythms for urine flow during various phases of Seadragon V. Each point represents the mean ($\pm$ SE) of measurements for 3 days in 4 subjects. See Fig. 2 legend for other relevant information. The data obtained from Shiraki *et al.* (1983).

Fig. 5. Comparisons of urine flow, endogenous creatinine clearance (C_{cr}), osmolal clearance (C_{osm}), and free water to osmolal clearance ratio (C_{H_2O}/C_{osm}) between the day time (0700–2200 h; open bars) and night (2200–0700 h; shaded bars) during various phases of Seadragon V. See Fig. 4 legend for other relevant information. The data obtained from Shiraki *et al.* (1984).

same at both 1 and 31 ATA while the overnight excretion of aldosterone increased at high pressure. In other words, the overnight increase in free water clearance associated with the hyperbaric nocturia in “Seadragon V” can not be explained by changes in the level of urinary ADH excretion.

In order to see if there is an alteration of circadian rhythms for other physiological variables, the circadian rhythm for the mean skin temperature in “Seadragon V” was determined. Although there were some minor variations from day to day, a basically identical circadian rhythm was observed throughout the dive (Shiraki *et al.*, 1984). These findings indicate that the hyperbaric nocturia observed in both dives at 31 ATA is totally independent of the body heat balance.

Interestingly enough, this phenomenon appears to be demonstrable only in Japanese subjects during exposure to a pressure greater than 25 ATA. In a similar study conducted at 51 ATA, Rostain *et al.* (1975) failed to observe this phenomenon in French divers, although they noted a small phase shift in circadian rhythms in the heart rate and

Fig. 6. Comparisons of urinary excretion of total osmotic substances ($U_{osc} V$), Na ($U_{Na} V$), and K ($U_K V$) between the day time and night during various phases of Seadragon V. See legends for Figs. 4 and 5 for other relevant information. The data obtained from Shiraki *et al.* (1984).

Fig. 7. A typical cosinor fitting of the circadian rhythm of urine flow for the predive 1 ATA of Seadragon V. Data points obtained from one subject (Y. T.). From Shiraki *et al.* (1984).

Fig. 8. A typical cosinor fitting of the circadian rhythm of urine flow (subject: Y. T.) for the 31 ATA period of Seadragon V. The solid wave represents a curve determined by the least square method. The broken wave shows a curve fitted by the same method, but the curve is filled by supposing that the urine volume at night is the same as that of pre-dive period. From Shiraki *et al.* (1984).

oral temperature. However, it is difficult to interpret these data because they did not determine the state of overall body fluid and energy balance of the subject, which determines the urine flow, heart rate and oral temperature at a given time.

The analysis of the Seadragon V data using a cosinor fitting method indicates the characteristic circadian rhythm for urine flow at 1 ATA, with the peak flow (i. e., the acrophase) appearing at about 1700 hour (Fig. 7) (Shiraki *et al.*, 1984). When the data points obtained at 31 ATA are analyzed in relation to this 1 ATA rhythm, all points with the exception of the overnight point are distributed along the 1 ATA rhythm (Fig. 8) (Shiraki *et al.*, 1984). This suggests that the basic circadian rhythm is still retained at 31 ATA but there is an alteration in the tubular reabsorption of solute and/or free water at night at high pressure. It may be speculated that cardiovascular reflexes attendant to postural changes (i.e., from standing to supine) may be altered at high pressure. Although experimental data in support of this view are lacking at present, it is well known that a high hydrostatic pressure induces disturbances in neurological functions (Hugon, 1983), which could potentially alter postural reflexes. Clearly, this interesting phenomenon requires intensive studies for delineation of its mechanism.

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高圧利尿および夜間利尿

白木 啓三¹・佐川 寿栄子¹・今田 育秀¹・Suk Ki Hong²¹産業医科大学第二生理学教室 ²ニューヨーク州立バッファロー大学生理学教室

要 旨： 人類はかなりの長期間に亘り深度数百メートルの高気圧環境での生存が可能であることが証明されている。このような環境では気圧そのものによる影響とガス組成が1気圧とは異なることによる物理的な因子が生体に種々な生理的な変化をもたらす。神経系統への影響（高圧神経症候群 HPNS）と、体液バランスへの影響が生理的には大きな変化であるといえる。前者についてはガス組成を改良することにより問題はほとんど解決することが可能であるが、後者については人類にとって全く新しい生理的な経験であるといえる。特に体液の分布のシフトが1気圧における正常なリズムとは異なることが見つかっている。これは尿量やその他体液量をコントロールする因子に反映される。ここでは特に体液をコントロールする因子のうち高気圧環境における腎機能の変化について概説し、その機序を解説するために現在まで蓄積された知識を用いて考察を加える。

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