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**N-TERMINAL PRO BRAIN NATRIURETIC PEPTIDE INCREASES AFTER ONE-
HOUR SCUBA DIVES AT TEN-METERS DEPTH**

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ABSTRACT

Objectives: The N-terminal pro brain natriuretic peptide (N-BNP) is a promising cardiac natriuretic peptide used as clinical hormonal marker in cardiac dysfunction. The main stimulus for N-BNP synthesis and secretion is cardiac wall stress recognized as a common denominator of many cardiac diseases. Diving is associated with environmental factors leading to variations in thoracic blood volume and haemodynamic changes. The purpose of the present study was to examine the changes in the concentration of N-BNP in healthy men during and after scuba diving

Method: 10 healthy-military divers (mean age 33 years) performed a dive in the sea for 1 hour at 10 meters depth. Venous blood samples were taken at timed intervals allowing to evaluate plasma level of N-BNP at different steps, namely at T0 (before immersion), at T30 minutes (during the dive, after short surfacing), at T60 minutes (right now after surfacing), at T300 (post-dive) and finally at T24 hours. Peptide blood concentrations were determined by electrochemoluminescence immunoassay. Data were analyzed using parametric statistics.

Results: When compared to T0, the results show a significant increase of N-BNP levels (in % of baseline levels) at T60 ($128 \pm 5\%$, $p < 0.043$,) and at T300 ($149 \pm 8\%$, $p < 0.001$).

Conclusion: This preliminary study reveals that N-BNP rises with scuba diving. Our findings suggest that diving involves a mechanical strain on the heart with a persistent endocrine myocardial activity post-dive.

Key words: natriuretic peptides, brain natriuretic peptide, immersion, diving

INTRODUCTION

Scuba diving is associated with environmental factors that may affect haemodynamics and cardio-vascular function in diver. Indeed, while immersion tends to increase the preload, cold exposure also tends to increase the afterload. Similarly, ventilation of a high density gas mixture disturbs left cardiac chambers filling [1].

The natriuretic peptides, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), belong to the cardiac-derived mediators' family. By affecting both blood volume and pressure regulation, they play a key role in cardiovascular homeostasis [10]. The role of ANP in the development of diuresis and natriuresis following the head-out immersion is well established. ANP is stored in atrial myocytes granules and distension of the atria constitutes the major stimulus for ANP release induced by central hypervolemia [5].

BNP is mainly secreted from the left ventricular myocytes. Its measurement causes an increasing interest for this peptide as biological hormonal marker in the diagnosis and prognosis of ischemic cardiac dysfunction and heart failure [3].

N-terminal pro brain natriuretic peptide (N-BNP) is the N-terminal part of the prohormone proBNP which is cleaved into two subsections in cardiac myocytes. The biological effects of N-BNP on its own are unknown but its level correlates with increased BNP level in cardiovascular diseases [17]. In healthy subjects, N-BNP is continuously released by the heart and can be detected in the venous blood at picomolar concentrations. N-BNP has a longer plasma half-life than BNP (120 minutes versus 20 minutes) and is stable in EDTA plasma for 3 days at room temperature [16].

To date, no work concerning plasma changes of N-BNP in water immersion have been completed. Thus, it appeared relevant to study the course of this peptide in healthy subjects during and after scuba diving.

MATERIAL AND METHODS

Ten trained healthy men (military divers), aged from 24 to 39 years (mean 33), performed dives in the sea for 1 hour at 10 meters depth without stops. All subjects gave their written consent and procedures were conformed to the declaration of Helsinki. The water temperature was 16°C. The divers were asked to avoid excessive physical exertion during the two hours that preceded the dive and also during the dive (i.e. moderate fin swimming).

At different times intervals, five blood samples were drawn from a antebachial vein through a 18-gauge needle and injected into EDTA-tubes: T0 (before immersion), T30 minutes (during the dive, after short surfacing), T60 minutes (right now after surfacing), T300 minutes and finally T24 hours. Immediately after being sampled, each blood tube was shipped to the laboratory and peptide levels were determined in 20 minutes by using a highly sensitive and specific automated analytical system, the Elecsys N-BNP test (Roche Diagnostics). The normal values are estimated to be under 110 ng/l.

First, the statistical analysis was accomplished using one-way repeated measures analysis of variance test after passing normality test (power of performed test with alpha = 0.05: 0.992) and equal variance test (p = 0.088). Second, a pairwise multiple comparison procedure (using the Holm-Sidak method) allowed comparing each kinetic group with each other. This method is more powerful than the Tukey test and is recommended at the first line procedure for most multiple comparison testing. For statistic processing, we used the Sigmastat software program (Systat software inc, CA 94804 Richmond).

All data are presented as mean +/- SEM. Differences are considered statistically significant if $p < 0.05$.

RESULTS

All measurements are below the normal cut-off value: 20,05 ng/l (5,83-35,63) at T0; 22,98 ng/l (9,06-43,03) at T30; 25,63 ng/l (11,10-49,51) at T60; 29,99 ng/l (9,83-56,81) at T300 and 15,92 ng/l (5,01-30,99) at T24H. There are statistically significant differences ($p < 0.001$) in the mean values among the blood samples times. When compared to T0, we can observe a significant increase of N-BNP (in % of baseline levels) at T60 ($128 \pm 5\%$, $p < 0.043$) whereas the most significant difference is noticed at T300 ($149 \pm 8\%$, $p < 0.001$), long time after the dive. No significant differences between groups comparison T0-T30, T30-T60, T60-T300 and T0-T24H are observed (**Fig. 1**).

[Figure 1 here]

DISCUSSION

The plasma levels of N-BNP before diving are similar with those found in the literature for individuals in good health and the variability in basal levels of the peptide is typical for a normal population [9]. Factors influencing plasma natriuretic peptides levels in individuals without cardiovascular pathology are poorly described. Few reports have suggested that N-BNP levels may be dependant on covariates as age, gender or heart rate. However, a recent study demonstrated that N-BNP was not significantly affected by a submaximal or maximal physical activity (in contrast to BNP) [2].

In our study, the increase of N-BNP remains on the physiological level with values below the appropriate decision cut-off for heart dysfunction. It appears long after the immersion during the dive (60 minutes), then subsides long after the end of the dive, at least until the 5th hour and returns to baseline the following day, i.e. after 24 hours.

Considering the plasma half-life of N-BNP, these results suggest that diving acts as a mechanical strain on a healthy myocardium with a persistent endocrine activity, even when the pressure and the volumetric stretch due to the immersion and ventilatory loads have stopped. The peripheral vasoconstriction due to cold exposure, with consequent increase in arterial blood pressure, plays probably a potential role on the levels of this peptide, but no data are available to confirm this assumption.

So far, no other work exists on the N-BNP during the immersion or when diving, therefore excluding any possibility to compare our results with accepted references. Only two studies on the BNP in immersion exist and they seem to demonstrate that the plasma level of BNP does not rise significantly after one hour of experiment, head-out of the water [8, 12].

If one compares the course of the N-BNP versus ANP studied in immersion alone, one can see that the ANP is quickly released in the blood (approximately 15 minutes) and its concentration remains high as long as the immersion is prolonged (up to three hours). As soon as the body gets out of the water, it returns to its level before immersion within less than one hour [14]. This observation allows us to consider that the N-BNP and the ANP have a distinct metabolism and regulation system.

The immunocytochemical analysis of the human myocardium shows a proportion of BNP in the secretory granules smaller than of ANP [13], while in vitro studies reveal that the activation of the ANP gene is slower than in the case of BNP [11]. The endocrine heart seems to react to hemodynamic changes by processes of synthesis, storage and secretion which are specific to each of two natriuretic peptides: the ANP is stored in great quantities in the auricles, is quickly released into the blood circulation in case of acute cardiac overload, and then slowly rebuilt afterwards; while the BNP secretion increases especially under conditions of chronic myocardial stimulation with fast induction of its gene expression [4].

When comparing these observations with our study, the fact that the N-BNP rises in the plasma later in time after the dive may be attributed to small quantities of this peptide in the myocytes before the immersion. Its secretion would occur secondarily with progressive mechanisms of intracellular synthesis, which are long in producing pro-BNP. This assumption seems to be compatible with other experimental results showing an increase in mRNA of BNP in the myocytes, in response to a mechanical stimulation, which has occurred in the hour [6].

We know that the hemodynamic modifications obtained under the experimental conditions of the immersion are similar to those observed in scuba diving, the consequences being a loss of weight, an increase in the diuresis and dehydration [7, 15]. Unfortunately, in our study, we could not evaluate the urine flow rate, nor that we could study other biological parameters such as the hematocrit. Further investigations including the analysis of these parameters would be useful to determine the level of hydration of the divers under the same conditions, many hours after diving. In particular, this could allow us to check whether the timed rise in N-BNP could be the reflection of a relative dehydration that subsides long after the emersion.

CONCLUSIONS

This preliminary study shows that N-BNP, a promising hormonal marker of myocardial dysfunction, rises with scuba diving. Peptide level starts to increase one hour after immersion and remains high until four hours after surfacing. Our findings suggest that diving associated with immersion and ventilatory loads involves a mechanical strain on the heart with a persistent endocrine myocardial activity post-dive.

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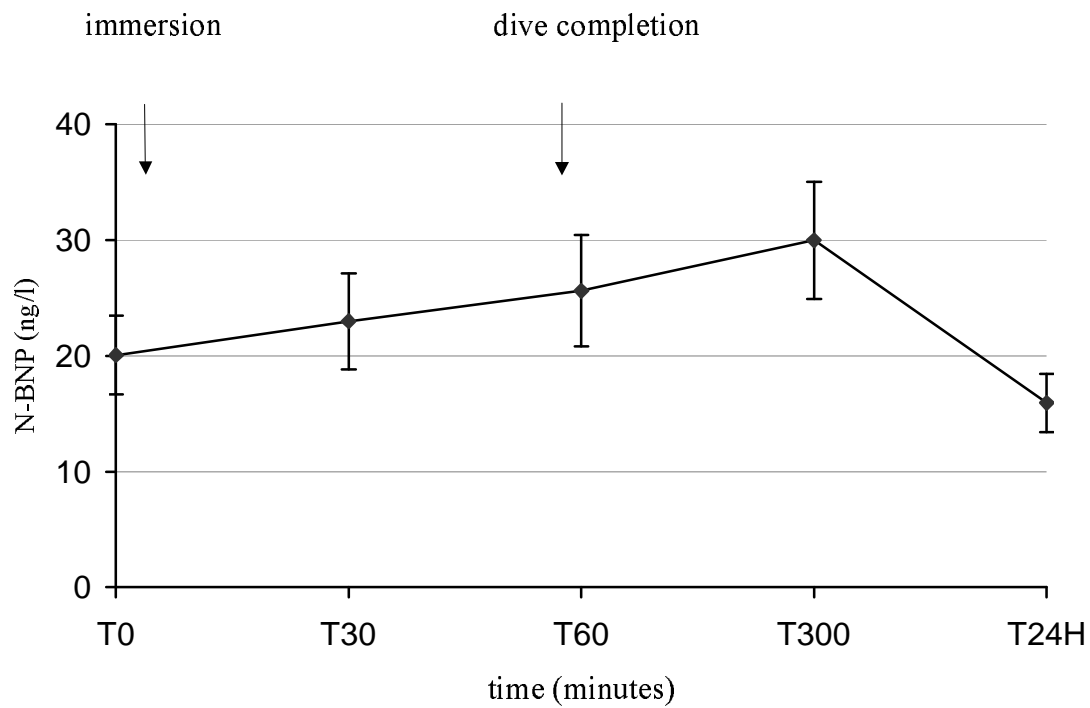


Figure 1: Course of plasma levels of N-BNP during and after 1-hour dive at 10-meters depth. Data are mean \pm SEM. * $p < 0.05$, versus baseline value. 1-way repeated measures anova test and post-anova test (holm-sidak) as appropriate.