

*Pathophysiological and diagnostic implications of cardiac biomarkers and antidiuretic hormone release in distinguishing immersion pulmonary edema from decompression sickness*

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# Pathophysiological and diagnostic implications of cardiac biomarkers and antidiuretic hormone release in distinguishing immersion pulmonary edema from decompression sickness

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## Abstract

Immersion pulmonary edema (IPE) is a misdiagnosed environmental illness caused by water immersion, cold, and exertion. IPE occurs typically during SCUBA diving, snorkeling, and swimming. IPE is sometimes associated with myocardial injury and/or loss of consciousness in water, which may be fatal. IPE is thought to involve hemodynamic and cardiovascular disturbances, but its pathophysiology remains largely unclear, which makes IPE prevention difficult. This observational study aimed to document IPE pathogenesis and improve diagnostic reliability, including distinguishing in some conditions IPE from decompression sickness (DCS), another diving-related disorder.

Thirty-one patients (19 IPE, 12 DCS) treated at the Hyperbaric Medicine Department (Ste-Anne hospital, Toulon, France; July 2013–June 2014) were recruited into the study. Ten healthy divers were recruited as controls. We tested: (i) copeptin, a surrogate marker for antidiuretic hormone and a stress marker; (ii) ischemia-modified albumin, an ischemia/hypoxia marker; (iii) brain-natriuretic peptide (BNP), a marker of heart failure, and (iv) ultrasensitive-cardiac troponin-I (cTnI), a marker of myocardial ischemia.

We found that copeptin and cardiac biomarkers were higher in IPE versus DCS and controls: (i) copeptin: 68% of IPE patients had a high level versus 25% of DCS patients ( $P < 0.05$ ) (mean  $\pm$  standard-deviation: IPE:  $53 \pm 61$  pmol/L; DCS:  $15 \pm 17$ ; controls:  $6 \pm 3$ ; IPE versus DCS or controls:  $P < 0.05$ ); (ii) ischemia-modified albumin: 68% of IPE patients had a high level versus 16% of DCS patients ( $P < 0.05$ ) (IPE:  $123 \pm 25$  arbitrary-units; DCS:  $84 \pm 25$ ; controls:  $94 \pm 7$ ; IPE versus DCS or controls:  $P < 0.05$ ); (iii) BNP: 53% of IPE patients had a high level, DCS patients having normal values ( $P < 0.05$ ) (IPE:  $383 \pm 394$  ng/L; DCS:  $37 \pm 28$ ; controls:  $19 \pm 15$ ; IPE versus DCS or controls:  $P < 0.01$ ); (iv) cTnI: 63% of IPE patients had a high level, DCS patients having normal values ( $P < 0.05$ ) (IPE:  $0.66 \pm 1.50$   $\mu$ g/L; DCS:  $0.0061 \pm 0.0040$ ; controls:  $0.0090 \pm 0.01$ ; IPE versus DCS or controls:  $P < 0.01$ ). The combined “BNP-cTnI” levels provided most discrimination: all IPE patients, but none of the DCS patients, had elevated levels of either/both of these markers.

We propose that antidiuretic hormone acts together with a myocardial ischemic process to promote IPE. Thus, monitoring of antidiuretic hormone and cardiac biomarkers can help to make a quick and reliable diagnosis of IPE.

**Abbreviations:** ADH = antidiuretic hormone, AU = arbitrary units, BNP = brain natriuretic peptide, CRP = C-reactive protein, DCS = decompression sickness, H+6 = 6 hours after admission to the hospital, H0 = time of emergency admission to the hospital, IMA = ischemia-modified albumin, IPE = immersion pulmonary edema, us cTnI = ultrasensitive cardiac troponin I.

**Keywords:** antidiuretic hormone, cardiac biomarkers, decompression sickness, diving, immersion pulmonary edema

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Ethical Approval: informed consents were obtained before inclusion. The Ethics Committee at the university hospital gave its agreement. The protocol followed the guidelines of the 1975 Declaration of Helsinki.

Alain Boussuges and Emmanuel Fenouillet contributed equally to this work.

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## 1. Introduction

Immersion pulmonary edema (IPE) is a serious environmental illness caused by water immersion, cold, and exertion, and occurs during popular water sports such as SCUBA diving, snorkeling, and swimming. Cases are also reported among professional divers, military swimmers, and triathletes.<sup>[1–4]</sup> IPE pathophysiology is unclear and its incidence is difficult to determine accurately because many cases are thought to be misdiagnosed. IPE is characterized by dyspnea, cough, haemoptysis, hypoxemia, and extreme fatigue.<sup>[1–4]</sup> Most patients recover from IPE with rest and oxygen and/or betamimetic therapy, but IPE is sometimes associated with myocardial injury and/or loss of consciousness, which may have a fatal outcome in a water environment.<sup>[4–9]</sup> The fragmented knowledge of IPE pathophysiology is a hurdle to deducing new approaches to prevent the disorder and identifying patients with IPE as soon as possible in a context where established biochemical markers are not available.

First, the pathogenesis of IPE is thought to imply hemodynamic and cardiorespiratory disorders that induce leakage of fluid out of the lumen of the capillary into the interstitial space, and eventually into the alveolar airspace.<sup>[1–4]</sup> Various events are involved in fluid leakage including (i) increased capillary pressure resulting from increased cardiac preload following blood redistribution from peripheral to thoracic vessels induced by exertion in immersion conditions, and afterload following vasoconstriction induced by cold and/or emotional stress,<sup>[2,10,11]</sup> (ii) decreased alveolar pressure resulting from ventilatory constraints when breathing dense gas, and (iii) changes in lung capillaries' permeability.<sup>[2–4]</sup> These elements are consistent with the clinical manifestations described above<sup>[1–4]</sup> and suggest that acute heart failure occurs during IPE. They also suggest that an investigation in IPE patients of cardiac biomarkers such as the brain natriuretic peptide (BNP, a marker of heart failure) and troponin (a marker of myocardial ischemia) might be informative to support an unambiguous diagnosis.

Second, the pathogenesis of IPE is often associated with hypoxemia,<sup>[1,2,12]</sup> suggesting a hypoxic/ischemic component to the illness, which could be monitored by ischemia-modified albumin (IMA), a marker produced by hypoxemic/ischemic tissues when O<sub>2</sub> supply does not meet tissue demands following limited O<sub>2</sub> supply or excessive O<sub>2</sub> demand.<sup>[13]</sup>

Third, the pathogenesis of IPE implies environmental (e.g., pressure and cold) and emotional stressors that induce hemodynamic and volumic changes via the release of various effectors, notably the antidiuretic hormone vasopressin (ADH).<sup>[1,2,10,11,14,15]</sup> Because ADH controls volemia and affects the cardiovascular system,<sup>[14,15]</sup> it may be a key player in IPE and its measure via a surrogate marker, copeptin, the stable C-terminal domain of the hormone precursor,<sup>[16–19]</sup> is feasible. Additionally, copeptin is a nonspecific but early marker of severe stress reactions,<sup>[16,17]</sup> and its release has been described in acute coronary syndrome,<sup>[18]</sup> congestive heart failure, and lung injury.<sup>[19]</sup>

In this prospective study, the situation with regard to these markers in IPE was compared with that observed in decompression sickness (DCS), another diving-related disorder that is caused by the formation of gas bubbles in tissues.<sup>[20]</sup> DCS symptoms include mechanical and embolic manifestations.<sup>[20]</sup> The initial diagnosis of IPE and DCS is on their typical clinical presentation, but the distinction between them is sometimes difficult in an emergency situation, at an early stage or in some environmental conditions (e.g., long/deep diving, cold water).<sup>[1,2,10,20,21,22]</sup> We, therefore, also sought to help

distinguish IPE from DCS in some challenging conditions by characterizing the biomarkers outlined above in each disorder.

In summary, the present observational study was aimed at understanding the pathophysiology of IPE by evaluating cardiac function, kidney function, and hypoxia biomarkers, and to review the resulting data to improve the reliability of IPE diagnosis, particularly to distinguish IPE from DCS.

## 2. Methods

### 2.1. SCUBA divers' inclusion

In this prospective approach, all the 31 patients (19 IPE, 12 DCS) treated at the Emergency Unit of the Department of Hyperbaric Medicine (Sainte-Anne Hospital, Toulon, France) between July 2013 and June 2014 were consecutively included. None of the patients refused to participate, and none were excluded. Ten healthy divers were recruited as controls for biochemical analysis, and blood samples were collected after SCUBA diving. The Ethics Committee at the university hospital gave its agreement, informed consents were obtained before inclusion, and the protocol followed the guidelines of the 1975 Declaration of Helsinki. Blood pressure measurement and venous blood sampling (5 mL of whole blood on sodium heparinate, or on sodium EDTA for the BNP assay) were performed on hospital admission for all groups. Blood gas analysis was performed on admission for IPE patients only (2 mL of arterial blood). An additional biochemical check-up was performed 6 hours later for the IPE group, sufficient time to enable significant changes to occur in the biomarkers monitored. Circulating bubble detection was performed by pulsed Doppler echocardiography for all symptomatic divers. IPE diagnosis was based on interstitial infiltrates on chest computed tomography scan ( $n=10$ ), or on lung comets by chest sonography ( $n=9$ ). DCS diagnosis was based on paraesthesia with sensitive/motor defect.

### 2.2. Copeptin measurement

Copeptin was measured using the BRAHMS Copeptin US KRYPTOR assay (Thermo Fischer) (detection threshold: 1 pmol/L; inter- or intra-assay variation: <10%; normal value: <13 pmol/L).<sup>[23]</sup>

### 2.3. Albumin and IMA measurement

Albumin was measured on a COBAS 8000 apparatus (Roche, Switzerland). IMA was measured using the Albumin Cobalt Binding test, a quantitative *in vitro* diagnostic assay (Ischemia Technologies, Denver, CO) that detects IMA by measuring the cobalt-binding capacity of albumin in serum using a Synchron LX20 analyzer (Beckman Coulter, France) (expressed in arbitrary units, AU; detection threshold: 10 AU; intra-assay variation: <5%; normal value: <100 AU).<sup>[24]</sup>

### 2.4. Measurement of cardiac troponin-I (cTnI)

cTnI was measured on an ADVIA Centaur apparatus (Siemens, Germany) using an immunochemical method (range: 0.005–50 µg/L; intra-assay variation: <10%; normal value: <0.05 µg/L).

### 2.5. BNP measurement

BNP was measured on an ADVIA Centaur apparatus using a 2-site sandwich immunoassay (range: 2–2000 ng/L; intra-assay variation: 10%; normal value: <100 ng/L).

## 2.6. C-reactive protein (CRP) measurement

The Ultra-Sensitive CRP (US-CRP) marker was measured using a COBAS 8000 apparatus (detection threshold: 0.05 mg/L; intra-assay variation: <10%; normal: <5 mg/L).

## 2.7. Statistical analysis

Quantitative variables were expressed as means  $\pm$  standard deviation (SD) or medians and interquartile range (IQR). The ANOVA 2-way analysis was used for intergroup comparisons and the Wilcoxon test for intraindividual comparisons. For age, sex, and dive parameters between groups, *t* test of Fischer-test was used. Statistical tests were 2-sided and  $P < 0.05$  was considered significant. Analyses were performed using R-Software (Project for Statistical Computing; v.2.8.1). The sensitivity and specificity of each biomarker were calculated for predicting IPE.

## 3. Results

### 3.1. Characteristics of the subjects

Clinical characteristics of the subjects are given in Table 1. Among the 31 patients, we recruited, 19 were diagnosed with IPE and 12 with DCS. The patient groups did not differ significantly in age, gender, dive duration, or dive depth (Table 1). Circulating bubbles were not detected in IPE patients, which suggests that no

diver with “chokes” or both IPE and DCS was included. All IPE patients were treated with oxygen for 2 hours and 8 with betamimetics and/or aerosol. Systolic blood pressure was higher in IPE patients versus DCS and controls. It is of note that in DCS patients, Cutis Marmorata was observed in 1 patient and vestibular disorder was diagnosed in another patient (presence of vertigo). DCS patients were treated with oxygen (2.8 ATA for  $3 \pm 1$  hours). There were no procedural errors (e.g., missing decompression, emergency ascent). The mean time for admission of patients, between symptoms and emergency admission, was  $90 \pm 15$  minutes. No sequelae were observed among the patients of either group.

### 3.2. Natremia, albuminemia, CRP

At the time of admission to the emergency unit (H0), mean albuminemia did not significantly differ between IPE, DCS, and controls although the mean concentration tended to be lower in the IPE group than in the 2 other groups (Table 1). Mean natremia was slightly lower in the IPE group than in the 2 other groups. The mean CRP level tended to be higher in the IPE group than in the 2 other groups.

### 3.3. Copeptin

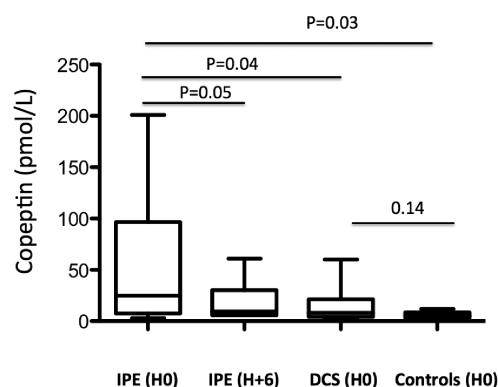
At H0, the level was higher in the IPE group than in the DCS group and in the controls (Data expressed as mean  $\pm$  SD:  $53 \pm 61$ ,

**Table 1**  
Diving parameters and clinical characteristics.

Characteristics	Immersion pulmonary edema n = 19	Decompression sickness n = 12	Controls n = 10
Age (y)	50 (24–74)	51 (32–66)	45 (28–56)
Gender (M/F)	14/5	10/2	7/3
Diving duration (min)	34 (15–90)	41 (21–63)	35 (20–45)
Depth (m)	30 (3–59)	38 (25–55)	39 (20–50)
Breathing gas	Air	Air	Air
Clinical manifestations	Anxiety n = 18 Dyspnea n = 18 Cough n = 11 Hemoptysis n = 9 Blood-tinged sputum expectoration n = 7 Cyanosis n = 2 Fainting n = 1	Medullar injuries: n = 10 Paraparesia n = 5 Tetraparesia n = 1 Paraesthesia n = 6 Dysesthesia n = 7 Cutaneous injuries n = 1 Stroke n = 1 (Hemiparesia) Inner ear n = 1 (Vertigo)	
Systolic blood pressure	153 (95–190)*	140 (125–180)	136 (110–135)
Diastolic blood pressure (mm Hg)	81 (57–115)	80 (69–110)	70 (68–85)
Albumin (g/L)	34 (31–37)	36 (29–37)	38 (30–40)
Natremia (mmol/L)	131 (129–137)*	138 (135–140)	141 (140–145)
C-react. prot. (mg/L)	3.6 (0.3–26)	1.15 (0.3–4.5)	1.3 (0.3–3)
pO <sub>2</sub> (Pa) (art. blood)	9199 (4399–17,331)	Not performed	Not performed
Sat (%)	94 (83–100)		
pH	7.40 (7.34–7.48)		
Lactates (mmol/L)	1.7 (0.6–4.5)		
Medical history	Hypertension n = 3 Dyslipidemia n = 3 Smoker n = 2 Coronary artery disease n = 1 Migrainous n = 1	Hypertension n = 1 Dyslipidemia n = 1 Smoker n = 1 Coronary artery disease n = 1	

Data were expressed as median (range). Biological data were compared using ANOVA 2-way analysis. For age, sex, and diving parameters, *t* test of Fischer-test was used. Statistical tests were 2-sided. The R-Software (Project for Statistical Computing; v.2.8.1) was used.

\*  $P < 0.05$  compared with decompression sickness or control subjects.

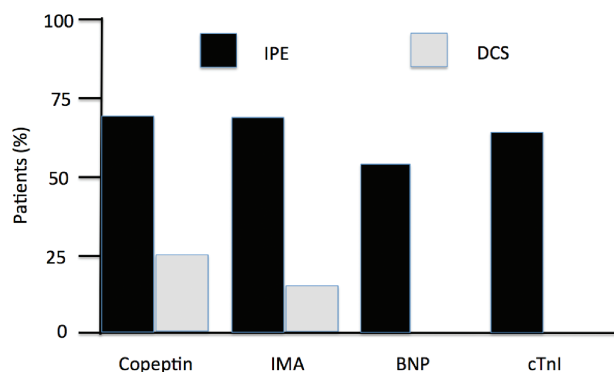


**Figure 1.** Copeptin. Copeptin (pmol/L), a surrogate marker for the antidiuretic hormone and a stress marker, was evaluated in patients with immersion pulmonary edema (IPE;  $n=19$ ) or decompression sickness (DCS;  $n=12$ ), and in healthy divers (Controls;  $n=10$ ). Biological parameters were evaluated on admission to the emergency unit (H0) for all patients and 6 hours later (H+6) for IPE patients. Data are expressed as median, interquartile range, min, max. DCS=decompression sickness, IPE=immersion pulmonary edema.

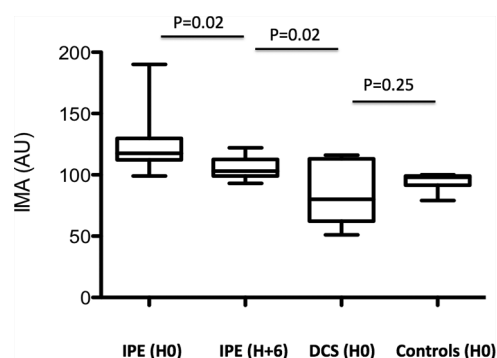
$15 \pm 17$ , and  $6 \pm 3$  pmol/L, respectively; IPE versus DCS or controls:  $P < 0.05$ ) (data are also expressed as median and interquartiles (IQRs) and presented in the figures thereafter, e.g., Fig. 1 for the copeptin level). Among the IPE patients, 68% (13/19) had an abnormal level ( $>13$  pmol/L) compared with 25% (3/12) of DCS patients ( $P < 0.05$ ; Fig. 2). Six hours after admission (H+6), the level decreased in IPE ( $19 \pm 21$  pmol/L), but it remained higher than in DCS (Fig. 1). No significant difference was found between the DCS patients and the controls.

### 3.4. IMA

At H0, the level was higher in the IPE group than in the DCS group and in the controls (mean  $\pm$  SD:  $123 \pm 25$ ,  $84 \pm 25$ , and  $94 \pm 7$  AU, respectively; IPE versus DCS or controls:  $P < 0.05$ ; median and IQRs are given in Fig. 3). Among the IPE patients, 68% (13/19) had an abnormal level ( $>100$  AU) compared with 16% (2/12) of DCS patients ( $P < 0.05$ ; Fig. 2). At H+6, the level decreased in IPE ( $105 \pm 9$  AU), but it remained higher than in DCS (Fig. 3). No significant difference was found between the DCS patients and the controls.



**Figure 2.** Marker levels in the patients' population. Percentage of patients' population with level above a given threshold value on admission to the emergency unit is given (Copeptin:  $>13$  pmol/L; IMA:  $>100$  AU; BNP:  $>100$  ng/L; cTnI:  $>0.05$   $\mu$ g/L).



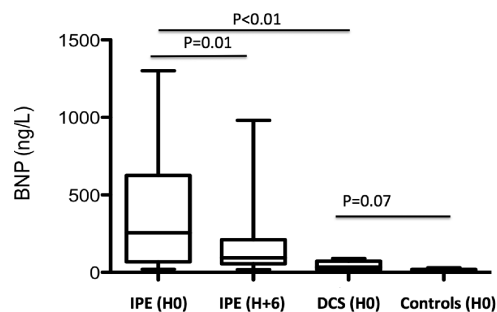
**Figure 3.** Ischemia-modified albumin. IMA (arbitrary units, AU), an ischemia/hypoxia marker, was evaluated in patients with immersion pulmonary edema (IPE;  $n=19$ ) or decompression sickness (DCS;  $n=12$ ), and in healthy divers ( $n=10$ ; controls) (AU: arbitrary units). Biological parameters were evaluated on admission to the emergency unit (H0) for all patients, and 6 hours later (H+6) for IPE patients. Data are expressed as median, interquartile range, min, max. AU=arbitrary units, IMA=ischemia-modified albumin, IPE=immersion pulmonary edema.

### 3.5. BNP

At H0, the level was higher in the IPE group than in the DCS group and in the controls (mean  $\pm$  SD:  $383 \pm 394$ ,  $37 \pm 28$ , and  $19 \pm 15$  ng/L, respectively; IPE versus DCS or controls:  $P < 0.01$ ; median and IQRs are given in Fig. 4). Although 53% (10/19) of IPE patients had an abnormal level ( $>100$  ng/L), none of the DCS patients had an abnormal level ( $P < 0.05$ ; Fig. 2). At H+6, the level decreased in IPE ( $132 \pm 105$  ng/L), but it remained higher than in DCS (Fig. 4). No significant difference was found between the DCS patients and the controls.

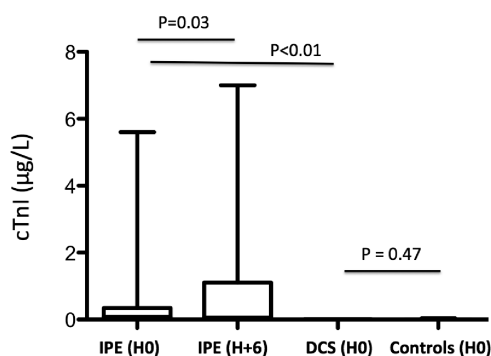
### 3.6. cTnI

At H0, the level was higher in the IPE group than in the DCS group and in the controls (mean  $\pm$  SD:  $0.66 \pm 1.50$ ,  $0.0061 \pm 0.004$ , and  $0.009 \pm 0.01$   $\mu$ g/L, respectively; IPE versus DCS or controls:  $P < 0.01$ ; median and IQRs are given in Fig. 5). Although 63% (12/19) of IPE patients had an abnormal level ( $>0.05$   $\mu$ g/L), none of the DCS patients had an abnormal level ( $P < 0.05$ ; Fig. 2). At H+6, the level increased in IPE ( $1.3 \pm 2.4$   $\mu$ g/L) versus the level measured at



**Figure 4.** Brain natriuretic peptide. BNP (ng/L), a marker of heart failure, was evaluated in patients with immersion pulmonary edema (IPE;  $n=19$ ) or decompression sickness (DCS;  $n=12$ ), and in healthy divers ( $n=10$ ). Biological parameters were evaluated on admission to the emergency unit (H0) for all patients, and 6 hours later (H+6) for IPE patients. Data are expressed as median, interquartile range, min, max. BNP=brain natriuretic peptide; DCS=decompression sickness, IPE=immersion pulmonary edema.





**Figure 5.** Cardiac troponin I. Us-cTnI ( $\mu\text{g/L}$ ), a marker of myocardial ischemia, was evaluated in patients with immersion pulmonary edema (IPE;  $n=19$ ) or decompression sickness (DCS;  $n=12$ ), and in healthy divers ( $n=10$ ). Biological parameters were evaluated on admission to the emergency unit (H0) for all patients, and 6 hours later (H+6) for IPE patients. Data are expressed as median, interquartile range, min, max. DCS=decompression sickness, IPE=immersion pulmonary edema.

**Table 2**

**Sensitivity and specificity of cardiac markers in divers with immersion pulmonary edema ( $n=19$ ).**

	BNP	cTnI	IMA	Copeptin
Sensitivity (%)	53	63	68	68
Specificity (%)	100	100	83	75

BNP=brain natriuretic peptide, cTnI=troponin I c, IMA=ischemia-modified albumin.

H0 (Fig. 5). No significant difference was found between the DCS patients and the controls.

Most importantly, when we examined BNP (see also §3.5 and Fig. 4) and cTnI (see also §3.6 and Fig. 5) levels in each individual patient, we found that all IPE patients had elevated levels of either/both of these markers (Fig. 2 and Table 2), contrary to the DCS patients who all had normal values.

#### 4. Discussion

We observed here that most IPE patients had higher levels of copeptin, IMA, BNP and/or cTnI than DCS patients. Conversely, we found no significant difference between DCS patients and the control subjects. The level of cTnI and/or BNP provided most discrimination between IPE and DCS: all IPE patients, and none of the DCS patients, had elevated levels of either/both of these markers.

The first major finding of this study is that a high copeptin level is associated with IPE, which can be put in perspective with the observation that copeptin is elevated in heart failure.<sup>[19,25]</sup> The increase in the copeptin level, and hence in ADH production, in IPE supports a role of ADH via its well-known capacity of inhibiting diuresis and inducing renal vasoconstriction.<sup>[14,15]</sup> More specifically, we propose that IPE occurs in a context of decreased diuresis, which increases volemia and eventually blood pressure. The situation observed in IPE contrasts with that observed in healthy divers for whom water immersion is associated with increased diuresis.<sup>[15]</sup>

That ADH promotes hypervolemia in IPE is consistent with 2 observations: (i) our findings that natremia and albuminemia tended to be lower in IPE patients, and blood pressure higher (Table 1); (ii) a previous report that pre-dive hydration prevents bubble formation within body tissues in DCS.<sup>[26]</sup> The contrasting

volemic status in IPE and DCS may explain why these disorders only rarely coexist.<sup>[21,22]</sup>

The second major observation of this study is that IPE involves both heart failure processes and myocardial ischemia as shown by the high BNP- and cTnI-level, respectively. BNP was reported to increase during SCUBA diving and high BNP and troponin levels were found also in previous IPE studies that did not compare IPE to DCS patients.<sup>[7,10,11,27]</sup> We confirmed here that IPE patients typically had high BNP levels, which is consistent with an increased filling pressure. Regarding ultrasensitive-cTnI, our results can also be interpreted pathophysiologically: taking into account the time necessary (i) for ultrasensitive-cTnI to rise after myocardial ischemia (2–3 hours),<sup>[28]</sup> (ii) the mean diving-duration (34 minutes; Table 1), and (iii) the mean time between symptoms and hospital admission (90 minutes), our data suggest that IPE originates from a myocardial ischemia process beginning early in the diving session, with decompensation and symptoms occurring when the diver surfaces. This hypothesis is in agreement with a recent report showing that triathletes experience IPE quickly (within about 10 minutes) after water immersion.<sup>[4]</sup>

The third major point of our study is the high level of IMA in IPE. This characteristic reflects an ischemia/hypoxia process as IMA levels increase during experimental hypoxia,<sup>[29]</sup> but also during acute coronary syndrome or chronic heart failure.<sup>[30,31]</sup> As expected, the high level observed here in IPE patients decreased after the oxygen treatment that reduced hypoxia (H+6; Fig. 3).

Four main considerations necessarily limit this study: (i) we included during 1 year all patients treated at the Hyperbaric Department of an hospital that covers ~30% of the French Mediterranean shore, and it would be useful to increase the size of the panel to improve the significance of our findings; (ii) we did not include divers with “chokes” or patients presenting both IPE and DCS due to the very low incidence of such cases,<sup>[21,22]</sup> and it would be interesting to study these patients for the same markers if possible; (iii) we did not specifically address diuresis in the subjects followed here, and this could be important to directly address the effect of ADH in IPE; (iv) although we used biochemical analysis apparatus in hospital conditions after emergency admission, it would be interesting to compare our results with those obtained using the new generation of portable diagnostic equipment that can be installed on dive boats in order to examine whether measurement of cTnI and BNP soon after the dive has finished can help in the management of patients with diving disorders.

We conclude that the increase in ADH and troponin-I levels indicates that antidiuretic effects increasing blood pressure act in the context of myocardial ischemia and promote IPE. Accordingly, measuring cardiac biomarkers could be helpful for early identification of IPE or, in some conditions, to distinguish IPE from DCS.

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