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Letter to the Editor

Plasma adenosine release is associated with bradycardia and transient loss of consciousness during experimental breath-hold diving

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During breath-hold diving, transient loss of consciousness (T-LOC) is frequent [1,2]. During competition, T-LOCs resolve without sequelae due to quick rescue by the medical staff. However, in the absence of supervision, like during spare time activities, the consequences of T-LOC might expose subjects to the risk of drowning and death.

Adenosine is implicated in the mechanism of some forms of T-LOC like vasovagal syncope (VVS, [3,4]). Adenosine is a purine derivative that comes from the dephosphorylation of ATP and that strongly impacts the cardiovascular system via the activation of four G-protein coupled receptors namely A_1 R, A_{2A} R, A_{2B} R, and A_3 R, depending on their pharmacological properties [5]. The activation of A_1 R leads mostly to bradycardia while the activation of A_{2A} R leads to vasodilation [5,6]. High adenosine plasma concentration (APC) is associated with T-LOC because of bradycardia and/or vasodilation. T-LOC during breath-hold diving is secondary to hypoxemia [2]. Hypoxemia leads to a release of adenosine in the extracellular spaces [7], which may participate in the occurrence of T-LOC. The aim of this study was to evaluate the kinetics of APC in elite breath-hold divers with or without previous breath-hold induced T-LOC events, during experimental breath-holding.

Twenty international breath-hold divers (19 men and one woman, mean age 37 ± 8 years), who participated in the 2012 free diving world championship in Nice, France, voluntarily accepted to be included in the study and gave written informed consent and the study was approved by the local ethics committee. The authors of this manuscript have certified that they comply with the principles of Ethical Publishing in the International Journal of Cardiology. Ten non-diver subjects from our medical staff (9 men and 1 woman, mean age 38 ± 9 years) served as controls for basal APC measurement.

Six ECG leads, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were monitored and recorded continuously. Arterial blood oxygen saturation (SpO_2) was measured continuously with a pulse oximeter fixed on the left median finger. An intravenous catheter was inserted before the onset of the experiment for safety reasons and blood sampling.

Subjects began the experiment by resting and breathing normally in ambient room conditions (25 ± 2 °C) for 10 min. After this resting period, control values were assessed and blood samples were collected. Then, subjects were asked to perform a sequence of five short static breath-holdings separated by 5-min recovery periods as warm-up. These short breath-holds were used as a warm-up to maximize the diving reflex and to decrease the stress effect.

Then subjects were instructed to perform a single sub maximal static breath-hold, then rested lying on their back to recover for 10 min.

Breath-hold divers and control subjects were placed in the supine position during sample collection. Control subjects did not perform breath-hold. For divers, venous blood samples were collected at rest before the warm-up (basal, T0), at the end of the maximal static breath-hold (T1), and after 10 min of recovery (T2). Blood samples were collected and processed as described previously [4,8] and APC was determined as previously described [4,8].

Quantitative variables were expressed using median and interquartile range (IQR) values. Correlation between APC and quantitative variables

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Table 1
Characteristics of subjects included in the study: Subjects were asked to perform a submaximal static breath-hold.

Subjects	Age (years)	Weight (Kg)	Height (cm)	Apnea practice (years)	Number of T-LOC during the past 2 years	Experimental apnea (sec)	HR TO	HR T1	HR T2	SBP T0	SBP T1	SBP T2	DBP T0	DBP T1	DBP T2	SpO_2 T0	SpO_2 T1	SpO_2 T2
1	36	84	193	6	4	225	72	45	73	126	145	125	86	89	85	100	71	99
2	34	74	182	13	3	225	72	50	71	138	159	137	78	93	75	99	70	100
3	26	69	176	20	0	150	75	72	80	138	182	138	61	75	66	99	88	99
4	45	62	163	19	0	300	69	67	70	140	192	140	80	90	80	100	92	99
5	51	82	169	40	0	225	71	70	69	138	136	138	61	75	63	98	91	99
6	36	77	176	8	3	225	69	46	70	138	145	136	79	85	80	99	71	100
7	35	73	184	2	0	225	70	60	70	129	140	130	83	90	78	100	89	99
8	31	74	181	16	0	187	78	80	80	125	150	124	86	90	85	99	80	99
9	36	71	180	2	1	262	72	56	80	134	163	134	85	106	85	99	86	99
10	32	74	181	12	2	225	75	70	70	130	149	127	60	65	65	100	78	99
11	45	105	184	10	0	225	80	78	76	121	145	122	60	48	58	98	91	100
12	48	85	190	22	0	300	80	76	78	125	135	125	58	70	60	100	84	99
13	40	69	175	30	2	225	60	50	80	135	155	137	83	90	80	99	79	100
14	34	60	166	2	1	375	60	45	67	111	130	112	57	68	60	99	92	99
15	35	88	187	29	0	300	75	55	65	124	153	125	68	90	70	100	90	98
16	30	77	185	15	3	375	56	50	60	107	144	108	70	76	70	99	80	99
17	41	92	188	24	1	300	71	60	69	148	163	145	78	87	75	99	88	99
18	53	88	178	37	5	337	69	48	70	124	124	123	69	71	72	100	74	99
19	27	74	175	15	0	375	63	50	77	126	181	135	69	110	70	98	79	100
20	25	68	176	5	1	300	70	70	68	138	166	138	65	78	60	100	73	100
Median	35.5	74	180.5	15	1	243.5	71	58	70	129.5	149.5	132	69.5	86	71	99	82	99
IQR	31–44	69.5–84.7	175–193	6.5–23.5	0–2.75	225–300	69–75	50–70	69–77.5	124–138	141–163	124.3–137.8	61–82.5	72–90	63.5–80	99–100	75–89.7	99–100

HR: heart rate SpO_2, blood pressure, and APC were evaluated before apnea (T0), at the end of apnea (T1), and after 10 min of recuperation. SpO_2: pulsatile saturation in arterial O2 APC: adenosine plasma concentration; SBP: systolic blood pressure DBP: diastolic blood pressure; IQR: interquartile range.

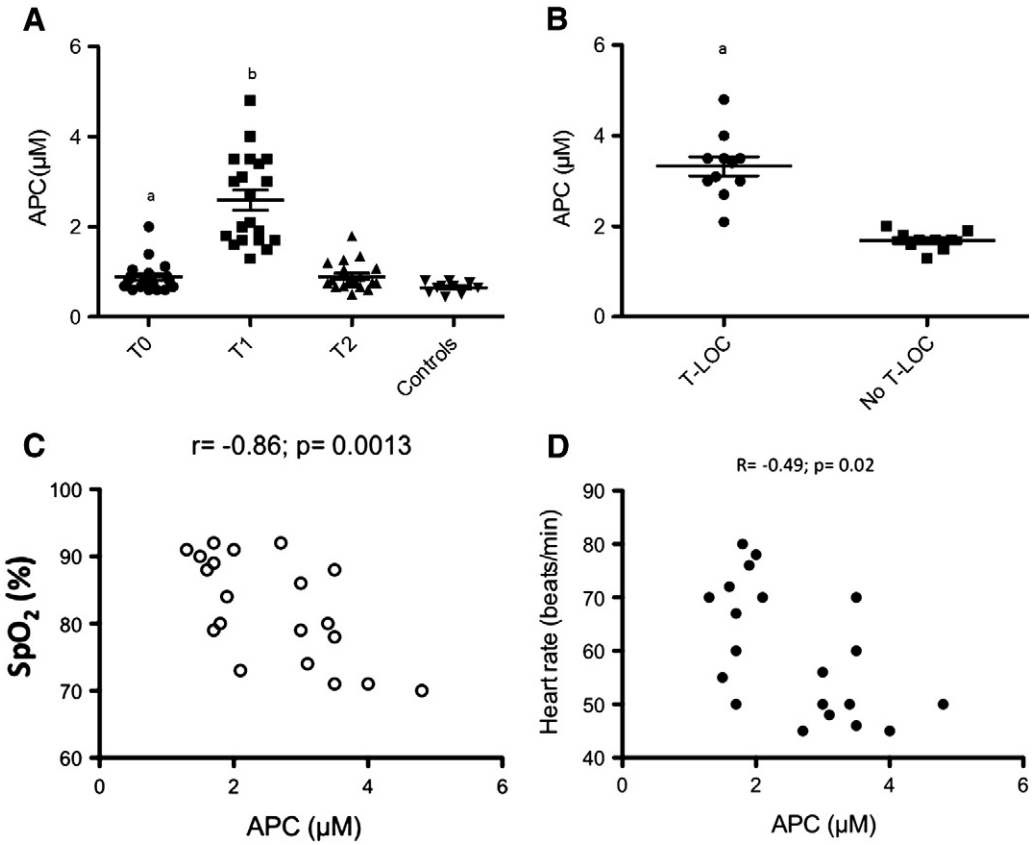

Fig. 1. A. Adenosine plasma concentration (APC) in the diver population (n = 20) in basal state (T0), at the end of the breath-holding (T1), and after 10 min of recovery (T2); a: $p < 0.05$ compared with controls; b: $p < 0.01$ compared with T0 or T2. Divers were asked to perform a submaximal static breath-holding. B. Adenosine plasma concentration (APC) at the end of breath-holding evaluated in the two groups of divers. a: $p < 0.001$. Divers were asked to perform a sub maximal static breath-holding. T-LOC: divers with previous transcient loss of consciousness during diving. C–D. Correlation (Spearman's R) between adenosine plasma concentration (APC) and Sp02 (Fig. 1-C) and heart rate (HR, Fig. 1-D) in 20 divers, during experimental breath-holding. APC was evaluated at the end of the breath-holding experimental procedure.

was assessed using the Spearman test. Quantitative variables were compared using the non-parametric Mann–Whitney *U* test. The non-parametric Wilcoxon test was used for intra individual comparisons. Statistical tests were two-sided and P-values less than 0.05 were considered significant.

Characteristics of breath-hold divers are given in Table 1. Breath-hold divers were separated into two groups: 11 had already experienced at least one episode of loss of consciousness (T-LOC divers) during the previous 2 years; 9 had never experienced any episode of loss of consciousness (non T-LOC divers). T-LOC divers and non T-LOC divers had similar age, weight, size, breath-hold performance, and breath-hold duration practice. None of the subjects had T-LOC during the experimental breath-hold.

In basal conditions (T0), heart rate (HR) was lower in the T-LOC divers than in the non T-LOC divers (median [IQR]: 70 [60–72] vs 75 [69.5–79]; $p = 0.05$). At the end of the breath-hold period, HR and SpO_2 were lower than basal values (HR: 71 bpm [69–75] vs 58 bpm [50–70], $p < 0.01$; SpO_2: 99% [98–100] vs 82% [75–89.7], $p < 0.01$). HR decreased much more in the T-LOC group than in the non T-LOC group (50 bpm [46–60] vs 70 bpm [57.5–77], $p < 0.01$).

DBP and SBP were higher than basal values (DBP: 69.5 mm Hg [61–82.5] vs 86 mm Hg [72–90], $p = 0.01$; SBP: 129.5 mm Hg [124–138] vs 149.5 mm Hg [141–163], $p < 0.01$). No significant difference was found in SBP or DPB between the T-LOC group and the non T-LOC divers either at baseline or during breath-holding. The T-LOC group and the non T-LOC group did not differ significantly in SpO_2 at the end of breath-holding (78 [71–86] vs 89 [82–91], $p = 0.07$). Blood pressure and SpO_2 returned to baseline values within 10 min after the test.

Baseline APC was higher in divers than in controls (0.82 μM [0.67–0.95] vs 0.67 μM [0.53–0.76], $p = 0.04$; Fig. 1A). However, this difference was restricted to the T-LOC divers (0.9 μM [0.82–1.12], $p = 0.01$). The Non T-LOC divers had APC values similar to controls (0.68 μM [0.63–0.86], $p = 0.1$ ns). At the end of breath-hold, APC increased significantly in all divers, compared with basal 2.4 μM [1.7–3.4], $p < 0.01$ (Fig. 1A), but the increase was much higher in the T-LOC group than in the non T-LOC divers (3. 4 μM [3–3.5] vs 1.7 μM [1.55–1.85], $p < 0.01$; Fig. 1B). APC values returned to baseline within 10 min of recovery. APC pattern was inversely correlated with HR (Spearman's $r = -0.49$, $p = 0.02$; Fig. 1C) and with SpO_2 (Spearman's $r = -0.86$, $p = 0.001$; Fig. 1D).

The main finding of this study is that high baseline APC and high APC and low HR during breath-hold are associated with the occurrence of T-LOC. This suggests a role of adenosine release, via its bradycardic properties leading sometimes to AV block [9], in T-LOC in divers. Basal HR and APC measurement, could be useful for screening patients who dive.

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