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Body Fluids After CO_2 Inhalation: Insight into Panic Mechanisms?

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Summary. Blood gases and electrolyte fluctuations were studied in arterial blood, after a single 35% CO_2–65% O_2 inhalation, which is known to trigger panic attacks in patients with panic disorder. The immediate effect of this maneuver was a brief hypercapnic acidosis followed by a slight alkalotic rebound, with shifts in Ca^{2+} and K^+. The possible effect of these changes on neuronal membrane excitability is discussed, referring to recent experimental findings in panic provocation.

Key words: Panic attacks – CO_2 – pH – CNS

Introduction

Increasing experimental evidence suggests that patients with anxiety attacks display a high vulnerability to inhalation of carbon dioxide (CO_2). Single inhalations of 35% CO_2–65% oxygen (O_2) mixtures, which were once curiously believed to be anxiolytic (Wolpe 1973), proved to elicit panic attacks (PA) in panic disorder (PD) patients. This effect has been well documented in a recent controlled study (Griez et al. 1987). Following a double blind cross-over design, 12 PD patients and 11 normal controls were given a vital capacity inhalation of 35% CO_2 in oxygen and compressed air. Upon inhalation, subjects held their breath for 4 s, to enhance alveolar exchanges. Immediate changes were assessed, both in physical sensations and in the subjective state. Within 15 s, the panic patients presented acute symptoms of panic, such as hyperventilation, dizziness, paresthesias, faintness, shaking, etc. To a somewhat lesser extent, this was also observed in the controls. However, the patients additionally reported an instantaneous increase in subjective anxiety, mimicking the experience of a real life PA, while normals failed to mention noticeable changes in their internal state. The CO_2-elicited symptomatology subsided after approximately 1 min.

The above results, which have been replicated by others (Fyer et al. 1987), warrant considering a single inhalation of 35% CO_2 as a promising tool for exploration into the mechanisms underlying panic anxiety. If a 35% CO_2 challenge triggers panic, the mechanisms at work in this intervention may help to shed light on those involved in real-life PA.

Inhalation of a mixture which is 35% CO_2 will induce a transient, but significant hypercapnia. Actually, such an intervention triggers the chemoreceptors, eliciting an episode of hyperventilation which induces a slight residual hypocapnia. This rebound pattern has been evidenced in a group of normal volunteers by registration of the end-tidal pCO_2 ($pACO_2$) (van den Hout and Griez 1985). Since hyperventilation and its correlate, hypocapnia have traditionally been linked to anxiety (Lum 1981; Margarian 1982), it seemed obvious that the 35% CO_2 challenge triggered panic in predisposed patients by indirectly inducing a state of hypocapnic alkalosis. However, both physical symptoms and feelings of panic appear within the very first seconds after CO_2 intake.

To gain insight into this problem, we undertook a precise documentation of the blood gas shifts induced by a single inhalation of a 35% CO_2–65% O_2 mixture. The present study was designed to determine both the nature and the magnitude of the shifts in arterial pH, pCO_2 ($paCO_2$), K+, and Ca^{2+} induced by the single 35% CO^2 inhalation challenge. Venous blood proved unsuitable, since in pilot studies it showed only a delayed and flattened rise as compared to changes in arterial values.

Method

Six healthy young volunteers, three males and three females ranging in age from 21 to 40 years, gave their informed consent to participate in this study. A catheter was introduced into the radial artery to withdraw blood during the experiment; the catheter was kept patent by infusion of a 5% glucose solution. Subjects were instructed in how to use the demand valve mask (Entonox) for supply of the 35% CO_2–65% O_2 mixture. Before the experiment began, 2 blood samples were taken for baseline values. For 1.5 min after CO_2 inhalation, arterial blood samples were taken every 10 s in order to follow the time course of $paCO_2$, pH, K^+, and Ca^{2+}. The $paCO_2$ and pH were measured with sensitive electrodes (ABL-3, Radiometer, Copenhagen), K^+ by flame photometry, and ionized calcium with a Ca^{2+}-sensitive electrode. A gas volume of the size of the vital capacity was in contact with the pulmonary circulation for 4 s, the instructed breath-holding time. After exhalation of the gas, subjects resumed breathing normal room air. This method was intentionally identical to that used by Griez et al. (1987), in order to allow reference to the latter study as to the time course of the CO_2-induced panic symptoms. Throughout the experiment, $pACO_2$ was monitored by a capnograph (Gould-Godart MK II).

Results

Each sampling of arterial blood lasted approximately 10 s, with the result that the sampling could not be performed

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Table 1. Raw data: mean and SD

Sample	Time (s)	$pACO_2$ (vol%)	$paCO_2$ (KPA)	pH	CA^{2+} (m*M*/l)	K^+ (m*M*/l)
I	Baseline	3.93 (0.6)	4.59 (0.47)	7.45 (0.03)	1.07 (0.031)	4.4 (0.17)
II	Baseline	3.93 (0.6)	4.69 (0.49)	7.45 (0.03)	1.03 (0.09)	4.47 (0.2)
III	10.24 (0.3)	6.33 (1.99)	15.01 (1.92)	7.09 (0.04)	1.25 (0.12)	4.6 (0.18)
IV	20.3 (1.1)	2.74 (0.39)	6.1 (3.33)	7.41 (0.14)	1.08 (0.06)	4.58 (0.21)
V	31.4 (1.4)	3.09 (0.29)	3.2 (0.18)	7.55 (0.01)	0.99 (0.03)	4.7 (0.22)
VI	41.8 (1.8)	3.26 (0.47)	3.42 (0.33)	7.53 (0.02)	1.03 (0.04)	4.72 (0.26)
VII	53.2 (2.9)	3.35 (0.55)	3.8 (0.46)	7.51 (0.03)	1.01 (0.05)	4.62 (0.19)
VIII	63.4 (3.6)	3.51 (0.52)	3.81 (0.5)	7.51 (0.03)	1.05 (0.06)	4.53 (0.23)
IV	74.6 (4.2)	3.44 (0.68)	3.96 (0.6)	7.50 (0.04)	1.05 (0.07)	4.55 (0.14)
X	85.8 (6.1)	3.75 (0.58)	4.01 (0.5)	7.50 (0.04)	1.05 (0.06)	4.47 (0.19)
			$F = 49.87$*	$F = 40.69$*	$F = 7.15$*	N.S.

* $P < 0.0001$
$df = 9.45$

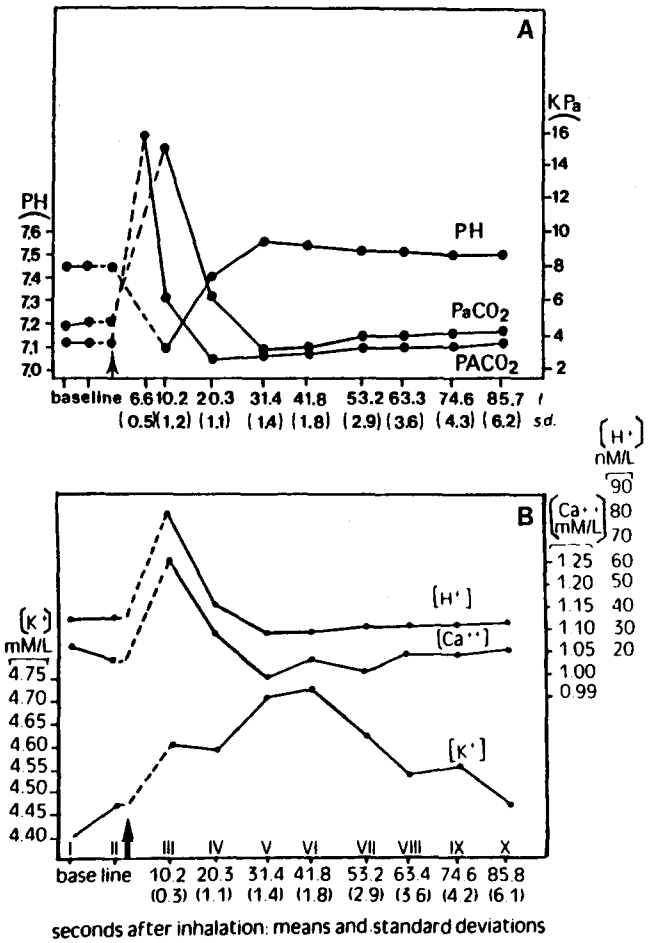

Fig. 1. a Effects of a full 35% CO_2–65% O_2 inhalation on pH alveolar (pA) and arterial (pa) CO_2 (*arrow* indicates the onset of inhalation). **b** Electrolyte fluctuations in arterial blood: potassium (K^+) ionized calcium (Ca^{2+}) and hydrogen (H^+) after a vital capacity inhalation of 35% CO_2–65% O_2

exactly at 10-s intervals in every case. For that reason, the means of sampling times appear in the presentation of the data (Table 1). The $pACO_2$ read on the capnogram at the time of completion of each blood sample collection has also been included. In Fig. 1a, the time course of $paCO_2$ and arterial pH are plotted against that of $pACO_2$. Fig. 1b shows the electrolyte fluctuations.

Like $pACO_2$, $paCO_2$ showed a biphasic pattern, rising to 15 kilopascal (KPA) during the first 10 s, then dropping to 6.1 KPA after 10 s to cross the baseline with a maximum decline to 3.2 KPA after 30 s. While there was an identical pattern, the time course of blood values appeared somewhat delayed with regard to alveolar air values, especially during the hypercapnic phase. This delay can obviously be attributed to the procedure of blood sampling. While the $pACO_2$ was read on the capnogram at the end of each blood collection and represented a punctual value at precisely every 10th s, the $paCO_2$ obtained from each blood sample was actually an integration of a rapidly dropping value, reflecting the varing pCO_2 over the preceding 10 s. The pH of arterial plasma was acid during the first phase and became slighty alkaline after the hypocapnic overshoot. Changes in ionized calcium followed the pattern of $[H^+]$ changes. $[Ca^{2+}]$ was elevated during acidosis and then droped by 20%, while $[K^+]$ showed a gradual and steady increase which began during hypercapnia and continued after $paCO_2$ had dropped.

Discussion

Not surprisingly, the most striking change after the 35% CO_2 intake was an immediate hypercapnic acidosis. While this phenomenon was very short lived, it must be remembered that the effects of the intervention in patients appeared instantaneously. Panic was recorded within 15 s of the gas intake (Griez et al. 1987) which places its onset definitely in the hypercapnic phase. The alkalotic overshoot was subsequent. It is therefore warranted to consider the phase of hypercapnic acidosis as the most relevant in the genesis of the clinical picture induced by the 35% CO_2 procedure. Hence, this is perfectly consistent with several recent observations that continuous breathing of 5% CO_2 enriched air (which does not induce hypocapnia) is also anxiogenic in PD patients (Gorman et al. 1984, 1987; Woods et al. 1986).

Reviewing recent data on experimental provocation of panic Carr and Sheehan (1984) suggested a defect in the intracellular redox regulation system in panic patients, making some chemoreceptive central neurones overly sensitive to a disequilibrium of the intracellular acid-base balance. They point out that CO_2, crossing the blood-brain barrier and penetrating the cellular membranes, may lower intraneuronal pH, producing, in this way, a "redox challenge". This conjec-

ture could be particularly pertinent in the case of massive, abrupt pCO_2 changes, such as those induced by a single inhalation of 35% CO_2–65% O_2. After pCO_2 has been temporarily elevated, transient transmembrane pH disequilibria are known to occur (De Weer 1978). Such transients disequilibria affect conduction velocity and membrane potentials in excitable tissues (Marranes et al. 1981). They are thought to account, at the cellular level, for some physiological phenomena observed upon rapid variations in pCO_2. Such phenomena are expected (1) to rise abruptly and (2) to abate gradually (de Weer 1978). The CO_2-elicited panic symptoms (as do naturally occurring PAs)(1) appear abruptly and (2) subside gradually.

Maybe the steady rise in arterial K^+ reflects outward movements from the intracellular compartment, a well-known phenomenon in the case of hypercapnia (Nunn 1977).

As for the changes in ionized calcium, it is interesting to note that, after an initial rise, there was a drop of about 20%. This drop is of the same magnitude as the Ca^{2+} drop quoted during lactate infusion (Fyer et al. 1984). The exact significance of Ca^{2+} shifts in panic provocation is not established. However, the observation that two different panicogenic interventions affect ionized calcium is reminiscent of Pitts and McClure's finding two decades ago, that adding Ca^{2+} to the perfused solution lowered the incidence of lactate-elicited panic (Pitts and McClure 1967).

In conclusion, the present study agrees with a recent hypothesis that acidosis and/or hypercapnia within the CNS may evoke panic. It provides data on the synchronous occurrence of ionic shifts which may reflect transmembrane movements that influence neuronal excitability. However, the precise locus of the genesis of panic remains a matter for future research.

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