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Short communication

Modification of apparent intracerebral hematoma volume on T2*-weighted images during normobaric oxygen therapy may contribute to false diagnosis

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ABSTRACT

It was previously reported that normobaric oxygen therapy (NBO) significantly affected T2*-weighted imaging in a mouse model of intracerebral hemorrhage (ICH). However, it is unclear whether a similar phenomenon exists in large volume ICH as seen in human pathology. We investigated the effects of NBO on T2*-weighted images in a pig model of ICH. Our data show that NBO makes disappear a peripheral crown of the hematoma, which in turn decreases the apparent volume of ICH by 18%. We hypothesized that this result could be translated to ICH in human, and subsequently could lead to inaccurate diagnostic.

Magnetic resonance imaging (MRI) is the most recommended modalities to evaluate hemorrhagic and ischemic stroke patients [1]. As an important part of these patients requires normobaric oxygen therapy (NBO) [1], the MRI related NBO impact has to be investigated. It was reported that NBO dramatically decreased the sensibility of T2*-weighted imaging to detect intracranial hemorrhage (ICH) in a rodent model [2]. However, ICH volume in mice is very limited, so the generalization of this finding to human pathology was not possible. In the present study, we investigated the effects of NBO on standard T2*-weighted imaging in a pig model of ICH. The report was carried out in accordance with the ARRIVE guidelines, the European Directives and the French Legislation on Animal Experimentation, and also approved by the local ethic committee (#7754 CENOMEXA, N°51, 2657–01). A total of 13 Langrace pigs (35–40 kg) were included. During the surgical and imaging procedures, anesthesia was maintained with propofol (80–120 μg/kg/min) and sevoflurane (1.5–2.0%). For ICH induction, a 3-mm burr hole was drilled at +2.4 cm anterior and +0.6 cm to the right of the bregma, and the dura mater was opened. The tip of a Fogarty catheter was introduced into the right frontal lobe and the balloon was inflated for 1 min. A catheter was then inserted into the preformed cavity and five ml of autologous arterial blood were injected (1.5 ml/min). The catheter was then removed and the wound closed [3].

Pigs were first exposed to normoxia (fraction of inspired oxygen, FiO_2 = 20%) during ICH induction and for an additional 30 min. A first MRI acquisition was performed, then pigs were exposed to NBO (FiO_2 = 100%, NBO group, n = 7) or normoxia (CTRL group, n = 6) during 30 min. A second set of MRI acquisition was then performed. At each stage, O_2, CO_2 and pH arterial blood levels were measured using an automatic gas analyzer (Rapidlab, Siemens) (Fig. 1A). Experiments were performed in a 3 T scanner with the R3.2.3 release (Achieva quasar dual, Philips Healthcare; Amsterdam; The Netherlands) using small two elements flexible surface coil (FlexS, Philips Healthcare; Amsterdam; The Netherlands). The protocol consisted of a T2-weighted FFE sequence with these following sequence parameters: TR = 828.530 ms; TE = 16.1 1 ms; matrix size = 288 × 227; FOV = 230 × 182 × 71 mm;

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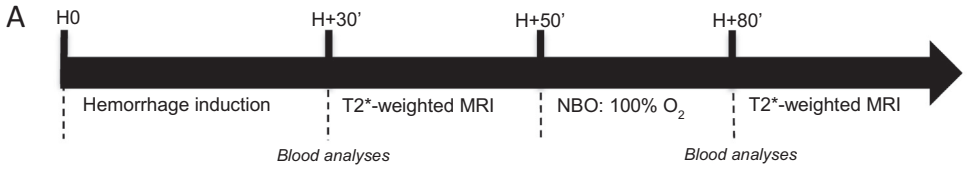

B

Pig	PO_2	PO_2 +30min	Wilcox.	$SatO_2$	$SatO_2$ +30min	Wilcox.	pH	pH +30min	Wilcox.	PCO2	PCO2 +30min	Wilcox.
					CTRL							
1	88.9	87		97.6	97.2		7.56	7.54		41.4	42.9	
2	67.9	69.8		94.1	94.4		7.5	7.5		42	41	
3	85	85.8		97.2	97.2		7.5	7.5		37.9	38.8	
4	104.7	107.8		98.2	98.1		7.53	7.54		43.5	42.8	
5	113.3	110		98.5	98.6		7.53	7.58		37.6	33.1	
6	159	85		99.3	96.5		7.58	7.43		38.8	47	
Average	103.13	90.9	p=0.463	97.48	97	p=0.345	7.53	7.51	p=0.715	40.2	40.93	p=0.753
±SD	± 31.62	± 15.30	ns	± 1.81	± 1.47	ns	± 0.03	± 0.05	ns	± 2.43	± 4.69	ns
					NBO							
1	110.5	279.2		98.1	99.7		7.41	7.465		38.5	42.5	
2	174.2	524.8		nd	nd		nd	nd		44.3	56.1	
3	121.5	398.2		98.5	99.8		7.45	7.405		49.7	61.8	
4	115.4	542		98.4	99.9		7.464	7.425		49.6	58.1	
5	272.1	585.8		99.7	99.9		7.608	7.615		34.9	33.4	
6	116	519.8		98.9	99.9		7.59	7.57		31.3	34.7	
7	64.5	214.3		95.2	99.5		7.51	7.525		46.5	43.5	
Average	139.17	437.72	p=0.018	98.13	99.78	p=0.028	7.50	7.50	p=0.753	42.11	47.15	p=0.063
±SD	± 66.71	± 143.60	*	± 1.53	± 0.16	*	± 0.07	± 0.08	ns	± 7.29	± 11.50	ns

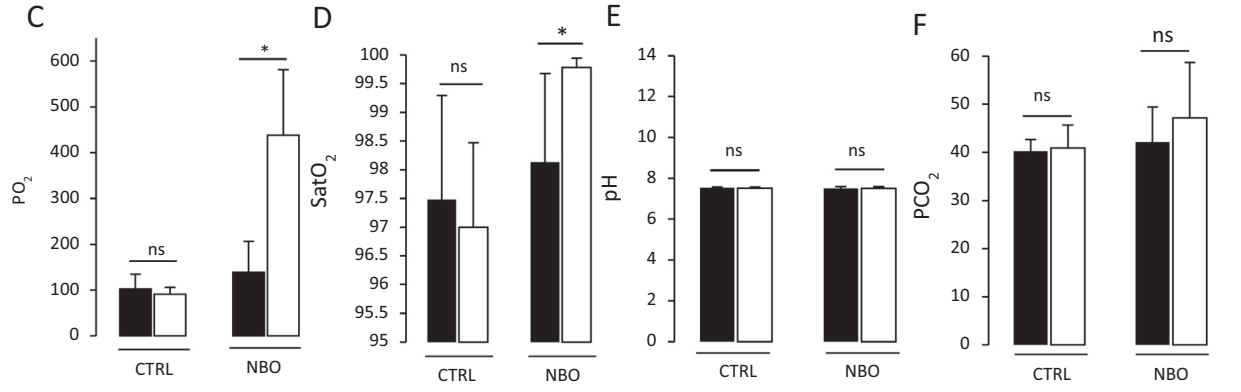

Fig. 1. NBO increases blood O_2 concentration. (A) Timeline of the performed experiments. (B) All the data are presented in the table. In comparison with CTRL group, NBO challenge increases (C) arterial blood PO_2 (139.17 ± 66.7 vs 437.72 ± 143.60, p = 0.018) and (D) $SatO_2$ (98.13 ± 1.53 vs 99.78 ± 0.16, p = 0.028). In both NBO and CTRL group, no significant changes were notice for (E) pH and (F) PCO_2. "nd" means no data available. Wilcoxon signed rank test, * = p < 0.05.

measurement time 151 s for 24 slices. Hemorrhagic volumes were then blindly quantified before and after normoxia or NBO challenge, using MRICron 6.6 (2013) software [4]. Wilcoxon signed rank tests were performed with the SYSTAT 13 software package.

Although not modified after 30 min of normoxia, PO_2 was 3 times higher after NBO (p = 0.018) (Fig. 1B, C) and the blood O_2 saturation significantly increased (p = 0.028) (Fig. 1B–D). General pH (Fig. 1B–E) and PCO_2 (Fig. 1B–F) did not differ after both conditions. Evolution of the hematoma volumes (Fig. 2A, B) revealed an 18% decrease of the apparent hematoma volume after 30 min of NBO (−18%, p = 0.028), although the apparent hematoma volume slightly increased in normoxia (+22%, p = 0.249) (Fig. 2C).

These data provide evidence in a large animal model that ICH signal on T2*-weighted imaging is significantly affected by NBO, which confirm our previous work in mice [2]. This phenomenon can be explained by the transformation of deoxyhemoglobin (paramagnetic) to oxyhemoglobin (diamagnetic) due to a higher increased tissue concentration of O_2 induced by NBO, leading to normalization of the tissue magnetic susceptibility and therefore to an increase in magnetic resonance signal on T2*-weighted images in hemorrhagic areas [5]. Interestingly, apparent hematoma volume in the normoxia group slightly increases. We hypothesized that this phenomenon is related to the transformation of oxyhemoglobin, present in the freshly induced hematoma, to deoxyhemoglobin. These results have several implications in preclinical studies. First, preclinical studies performed under anesthesia, involving measurement of hematoma volumes by T2*-weighted imaging, should be considered with caution, and the PO_2 should be carefully monitored and reported as previously recommended [6,7]. We also unveil potential pitfalls of NBO therapy for T2*-weighted imaging in patients, as our results suggest that T2*-weighted imaging could 1) underestimate by about 18% the hematoma volume in patients treated by NBO and 2) fail to identify hematoma growth, which is a major risk factor of poor outcome. This would be particularly relevant for patients requiring respiratory support which are frequently ventilated with 100% O_2 during transport to the MRI facilities.

Nevertheless, since NBO is safe after ICH [8], identification of the underlying cause which remains a radiological challenge, may benefit from NBO preparation for revealing the brain parenchyma at the periphery of the hematoma. However, we must discuss

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