

Effect of administration of water enriched in O₂ by injection or electrolysis on transcutaneous oxygen pressure in anesthetized pigs

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Background: Oral administration of oxygenated water has been shown to improve blood oxygenation and could be an alternate way for oxygen (O₂) supply. In this experiment, tissue oxygenation was compared in anesthetized pigs receiving a placebo or water enriched in O₂ by injection or a new electrolytic process.

Methods: Forty-two pigs randomized in three groups received either mineral water as placebo or water enriched in O₂ by injection or the electrolytic process (10 mL/kg in the stomach). Hemodynamic parameters, partial pressure of oxygen in the arterial blood (PaO₂), skin blood flow, and tissue oxygenation (transcutaneous oxygen pressure, or TcPO₂) were monitored during 90 minutes of general anesthesia. Absorption and tissue distribution of the three waters administered were assessed using dilution of deuterium oxide.

Results: Mean arterial pressure, heart rate, PaO₂, arteriovenous oxygen difference, and water absorption from the gut were not significantly different among the three groups. The deuterium to protium ratio was also similar in the plasma, skin, and muscle at the end of the protocol. Skin blood flow decreased in the three groups. TcPO₂ slowly decreased over the last 60 minutes of the experiment in the three groups, but when compared to the control group, the values remained significantly higher in animals that received the water enriched in O₂ by electrolysis.

Conclusions: In this protocol, water enriched in O₂ by electrolysis lessened the decline of peripheral tissue oxygenation. This observation is compatible with the claim that the electrolytic process generates water clathrates which trap O₂ and facilitate O₂ diffusion along pressure gradients. Potential applications of O₂-enriched water include an alternate method of oxygen supply.

Keywords: transcutaneous oxygen partial pressure determination, tissue oxygenation, oxygenated water, water clathrate

Introduction

Adequate tissue oxygenation is a major issue in the management of anesthesia and intensive care in hypoxemic or shock state patients. It can also prevent surgical wound infection¹ or postoperative nausea and vomiting.² It is usually obtained by using mechanical ventilation and increased fraction of inspired oxygen (FIO₂). Other procedures include intravenous administration of oxygen (O₂),³ enteral administration of O₂,^{4,5} and enteral administration of water enriched in O₂ (O₂ waters).⁶ The present experiment further explores this route of O₂ supply and compares the effects of two types of O₂ water to those of a placebo (100 mg versus [vs] 10 mg O₂/L, respectively) administered intragastrically in anesthetized pigs. Enrichment in O₂ was obtained by injection of O₂ at high oxygen pressure (PO₂) and by an electrolytic process⁷

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(see Methods). It has been suggested that this process of enrichment in O_2 generates water clathrates which are able to trap solutes such as O_2^{8-10} and can facilitate O_2 diffusion along PO_2 gradients. A previous study of this O_2 water obtained by electrolytic process shows an improvement of mitochondrial respiration *ex vivo*, in oxidative saponin-skinned fibers isolated from soleus muscles of rats, for O_2 concentration lower than $150 \mu\text{mol/L}$ (Zoll et al, unpublished data, 2012).

The purpose of the present experiment was to verify *in vivo* the ability of these O_2 waters to improve O_2 diffusion to the peripheral tissues, by monitoring the transcutaneous oxygen pressure ($TcPO_2$), which is a convenient way to assess tissue oxygenation during anesthesia.¹¹⁻¹⁴ We hypothesized that in a condition of hemodynamic and respiratory stability, $TcPO_2$ will be higher with the water enriched in O_2 by electrolysis.

Methods

Animals

The experiments, which were conducted on three groups of 14 male pigs (Large White, 6 months old, 22.5 ± 0.8 kg; no significant difference between the three groups) were carried out at Institut de recherche contre les cancers de l'appareil digestif – European Institute of Telesurgery (IRCAD-EITS, University of Strasbourg, France). The protocol was conducted in accordance with the American Physiological Society's Guiding Principles in the Care and Use of Animals and was approved by the local Institutional Animal Ethics Authority (authorization number 67-147).

Study protocol

The animals were housed at the research facility, at constant temperature (21°C) and with a 12:12 day/night cycle, with food and water *ad libitum* for 3 days before the experiment. Following premedication with intramuscular ketamine (20 mg/kg) and azaperone (2 mg/kg), a 20-gauge catheter was placed in an ear vein for normal saline infusion at 5 mL/kg/h . The animals were intubated (Portex Blue Line 6 mm; Smith Medical, Kent, UK) under laryngoscopy after injection of propofol (2 mg/kg) and pancuronium (0.2 mg/kg). A 20G arterial catheter (Leader-cath, Vygon, Ecouen, France) was then placed in the femoral artery by Seldinger technique, and a venous catheter was inserted in an internal jugular vein and advanced into the right ventricle under continuous pressure monitoring. Anesthesia was maintained using isoflurane up to a maximum of 2.5% end-tidal concentration, with 21% oxygen delivered using a ventilator (Aisys Carestation; GE Healthcare, Little Chalfont, UK). Tidal volume was set at

10 mL/kg , with a 4 cm H_2O positive end expiratory pressure (PEEP), and end tidal PCO_2 was kept constant between 36 and 40 mmHg by adjusting the respiratory rate between 14 and 18 cycles/minute. Body temperature was maintained with an isolation blanket. For the administration of waters, an orogastric tube was also put in place, and the gastric content was aspirated before the beginning of the procedure.

Measurement

Heart rate, ECG, continuous arterial pressure, esophageal temperature (esophageal probe, Odam Physiogard SM 785TM; Schiller, Baar, Switzerland), and oxygen consumption (VO_2) (CPX, SensorMedics, Yorba Linda, CA, USA) were monitored throughout the experiment. Skin perfusion was explored from phase shift of a laser light beamed by a fiber optic on moving red blood cells (Doppler flowmetry, Periflux PF4; Perimed AB, Stockholm, Sweden). The laser Doppler flowmeter probe was placed on the internal portion of the right thigh. Although precise quantifications cannot be made, it has been shown that changes in skin microcirculation can be monitored with this technique during sedation or anesthesia.^{15,16}

Measurement of $TcPO_2$ (Tina TCM4 series, Radiometer, Denmark) was performed on the internal portion of the right thigh, close to the Doppler flowmeter probe. For this purpose, following two calibrations, the electrode (heated at 43°C) was placed on the skin, which had been shaved and cleaned with alcohol. A stabilization period of 20 minutes ($TcPO_2$ changes $<2 \text{ mmHg}$ within 5 minutes) was allowed before recording basal preingestion values.

Water administered

Three types of water were used: remineralized water used as placebo and waters enriched in O_2 by injection and electrolysis. The waters were prepared from demineralized water which was remineralized with Na^+ (200 mg/L), SO_4^{2-} (250 mg/L), and PO_4^{2-} (240 mg/L). The water ingested as placebo was enriched in O_2 by injection at a level of $10 \text{ mg } O_2/L$ (ie, close to the value at equilibrium with atmospheric O_2 at sea level at the temperature of ingestion [$\sim 8 \text{ mg/L}$ at 5°C – 10°C]).¹⁷ The two other waters were enriched at $100 \text{ mg } O_2/L$ ($PO_2 \sim 1,220$ – $1,350 \text{ mmHg}$) by injection or the electrolytic process. In this process, the remineralized water was pumped between two electrodes separated by a membrane permeable to electrical charges but not to gases and the water enriched in O_2 , which was recovered on the negative electrode (pH = 7.1–7.2, conductivity = 750 – $770 \mu\text{S/cm}$, $4,375$ – $5,000 \mu\text{mol } O_2/L$) was used to prepare the final

product, which was kept in glass bottles with a narrow neck. Upon opening, and keeping the bottle unagitated at 20°C, the half-life of the decrease in O₂ content was 5.5 days. Accordingly, only negligible loss of O₂ should be expected within the short delay (<1 minute) between opening of the bottle and administration of the water. It is worth mentioning that Nestle et al¹⁸ also examined the disappearance of O₂ from an O₂ water with an initial content of ~100 mg/L using nuclear magnetic resonance relaxometry. The half-life measured was also large (~100 minutes), although lower than that measured in the present experiment, probably because the water was poured in drinking beakers with a much larger and more ventilated surface for O₂ to escape than that in a bottleneck.

The waters, which were prepared by Danone Research (Palaiseau, France), were administered through the orogastric tube. Each animal received 10 mL/kg of water.

Experimental procedure

The animals were studied for 90 minutes following water administration (T0). At each measurement point blood samples were simultaneously drawn from the femoral artery and the right ventricle. The arteriovenous oxygen difference (avDO₂ mL O₂/dL) was calculated from arterial and venous O₂ contents (in mL/dL of blood) computed as $[(1.34 \times [\text{Hb}] \times \text{SaO}_2) + (0.003 \times \text{PO}_2)]$, where [Hb] is the hemoglobin concentration in g/dL and SaO₂ the saturation of hemoglobin.

At the end of experiments the gastric content was aspirated through the orogastric tube, ~3 g samples of skin and gracilis muscle were quickly dissected in the vicinity of the TcPO₂ electrode, and the animal was killed by an intravenous injection of potassium chloride.

Water absorption and distribution

Absorption and distribution in the body water pool of the waters administered were assessed using D₂O in eight animals in each group. For this purpose, the waters were labeled by adding 10 mL of D₂O/L in order to obtain a final deuterium to protium ratio (D/H) ~10,000 ppm (actual values: 9,276±135 ppm). The D/H ratio was then measured 1) in plasma (separated from the blood by centrifugation) at selected intervals following water administration, 2) in the gastric content recovered at the end of experiment, and 3) in fluids recovered from the skin and muscle samples after homogenization and centrifugation. The D/H ratio was measured by mass spectrometry in water purified from the various fluids by reverse lyophilization; ie, the sample is freeze-dried and the water removed in the process is recovered in a cold trap.

Statistical analysis

Data are presented as mean ± SEM. After testing for normality and homogeneity of variance, data were compared using parametric (one-way or two-way analysis of variance) or nonparametric tests (Kruskal–Wallis). For each parameter, except blood gas, the reference mean during the basal period is the average of the values recorded over successive 2.5-minute intervals during the steady state period of 20 minutes. A *P* value <0.05 was regarded as statistically significant. Statistical analysis was performed by GraphPad Prism 5.0.

Results

As shown in Table 1, heart rate, mean arterial pressure, PaO₂, avDO₂, and VO₂ were stable throughout the experiment and not significantly different in the three groups. The temperature was also similar in the three groups and the small decrease did not reach statistical significance. Skin

Table 1 Data observed before and at 30-minute intervals following administration of the three waters

	Min	Placebo	Injection	Electrolysis
Temperature (°C)	0	35.6±0.3	35.7±0.3	35.8±0.4
	30	34.9±0.4	35.1±0.4	34.9±0.6
	60	34.9±0.4	35.6±0.4	35.1±0.5
	90	34.9±0.4	35.1±0.4	35.0±0.6
Heart rate (beats/min)	0	87±7	77±5	78±6
	30	83±7	96±12	79±7
	60	87±9	89±7	84±7
	90	101±8	85±7	83±6
Mean arterial pressure (mmHg)	0	53±2	52±2	55±2
	30	53±2	51±2	54±2
	60	54±3	51±2	51±3
	90	54±2	50±2	52±3
PaO ₂ (mmHg)	0	95.3±3.0	96.8±2.3	102.8±5.3
	30	97.5±4.5	102.8±8.3	108.8±8.3
	60	96.0±5.3	104.3±8.3	104.3±9.0
	90	99.0±6.0	108.0±6.8	105.8±7.5
avDO ₂ (mLO ₂ /dL)	0	27.8±2.5	28.1±1.7	29.5±2.3
	30	27.0±2.2	28.9±1.6	29.0±2.0
	60	29.9±3.4	27.0±1.9	29.8±2.0
	90	27.4±2.4	27.1±1.3	28.5±2.0
VO ₂ (mL/kg/min)	0	5.2±0.5	5.7±0.7	5.0±0.6
	30	4.9±0.6	6.0±0.7	5.2±0.7
	60	5.4±0.6	6.0±0.8	5.1±0.8
	90	5.5±0.6	5.5±0.8	5.0±0.5
Skin blood flow (perfusion unit)	0	44±4	38±4	33±5
	30	38±4	32±5	31±5
	60	34±4*	28±4*	25±3*
	90	30±4*	23±2*	22±3*

Notes: Values are presented as mean ± SEM. **P*<0.05 (T0 versus T60 and T0 versus T90 in each group).

Abbreviations: avDO₂, arteriovenous oxygen difference; min, minutes; PaO₂, partial oxygen pressure in the blood; SEM, standard error of the mean; T, time; VO₂, oxygen uptake.

blood flow significantly decreased during the experiment in the three groups between T0 and T90 ($P < 0.05$) (Table 1). Figure 1 shows changes in TcPO₂ vs the mean of basal pre-ingestion. From minute 0 to 30 following water administration, TcPO₂ was stable and not significantly different between the three groups. Beginning at minute 30, TcPO₂ slowly but significantly decreased until the end of experiment in the three groups. However, when compared to the control group, the decrease in TcPO₂ was significantly lower in animals that received the water enriched in O₂ by the electrolytic process (two-way analysis of variance: main effect of time [$P < 0.001$] and water [$P < 0.001$]) (Figure 1).

No significant difference was observed between the three groups for plasma D/H observed in the basal period (149±1, 157±2, and 149±1 ppm before administration of the placebo and the waters enriched by injection and electrolysis, respectively), and for the progressive increase in plasma D/H over background values, following administration of waters labeled with D₂O (Figure 2). Based on the actual D/H and volume of O₂ water administered in the stomach, and on the D/H and volume of the fluid aspirated from the stomach at the end of experiment, the volume of water which was emptied in the small intestine was computed and was found not significantly different in the three groups (Table 2). The D/H ratio in water purified from the skin and skeletal muscle at the end of experiment were also not significantly different, respectively, in the three groups, but the values were ~91%–92%, those simultaneously observed in plasma (Table 2).

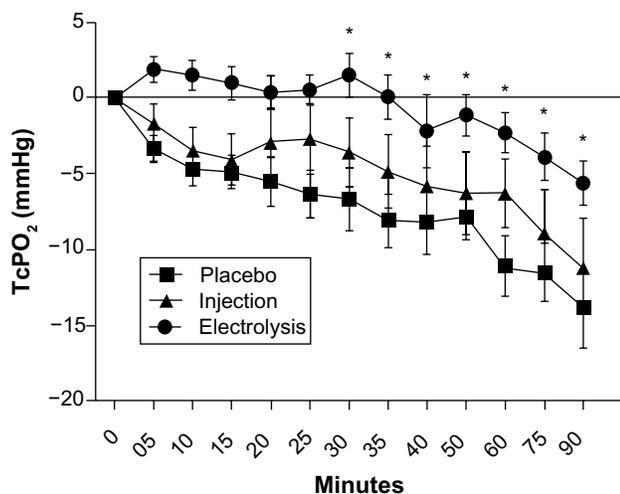


Figure 1 Changes versus baseline in TcPO₂ from T0 to T90 in the three groups. **Notes:** TcPO₂ decreased in the three groups but remained significantly higher (* $P < 0.001$) from T30 to T90 with the water enriched in O₂ by electrolysis than in control. Values represent mean ± SEM. **Abbreviations:** SEM, standard error of the mean; T, time; TcPO₂, transcutaneous oxygen pressure.

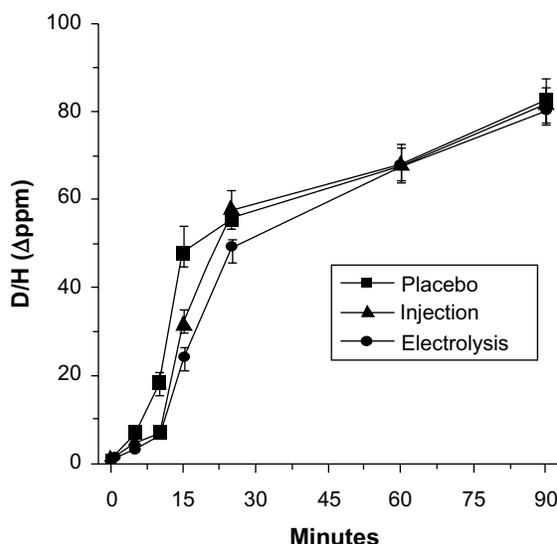


Figure 2 Plasma D/H ratio over the 90-minute period following ingestion of labeled water. **Notes:** Plasma D/H ratio: Δppm over baseline value before administration of water. D/H ratio increased significantly from T10 in the three groups. No significant difference was observed between the three groups for the progressive increase in plasma D/H over background values. Values represent mean ± SEM; n=8. **Abbreviations:** D/H, deuterium/protium; SEM, standard error of the mean.

Discussion

Results from the present experiment show that over the last hour of anesthesia, when compared to the placebo and the water enriched in O₂ by injection, TcPO₂ was maintained at a higher level with the water enriched in O₂ by the electrolytic process. When compared to the placebo, the progressive reduction in TcPO₂ observed between minute 30 and 90 was slightly smaller with both waters enriched in O₂, and the difference was significant for the water enriched in O₂ by electrolysis. This was not associated with any significant difference in water absorption and distribution. Indeed, no significant difference was observed for the amount of water emptied from the stomach, and the appearance of D₂O in plasma was fast and similar in the three groups, suggesting that in contrast to what was observed for CO₂,¹⁹ the presence

Table 2 Volume of water emptied from the stomach and D/H ratio measured at 90 minutes in the three groups

	Placebo	Injection	Electrolysis
Water emptied from the stomach (mL)	185±14	238±18	151±16
Final D/H in water from plasma (ppm)	92±4	93±3	94±4
D/H in water from skin (ppm)	78±5	67±3	77±4
D/H in water from muscle (ppm)	74±5	65±4	77±4

Notes: Values are presented as mean ± SEM. D/H ratio given in ppm above background values. No significant differences were detected between the three groups. **Abbreviations:** D/H, deuterium/protium; SEM, standard error of the mean.

of O₂ in the stomach does not delay gastric emptying. In addition, the kinetics of plasma D/H was not significantly different in the three groups, with a large increase within the first ~20 minutes followed by a more progressive rise until the end of experiment. As for D₂O appearance in muscle and skin, it was also remarkably similar in the three groups but slightly lagged behind D₂O appearance in plasma. This result suggests that water ingested is well distributed to various body compartments. Due to technical reasons, there is a paucity of data on the kinetics of distribution of labeled water ingested or administered in the blood²⁰ and we are not aware of any data concerning the skin. As for the skeletal muscle, Schwartz²¹ showed that in mice, the D/H in this tissue with a low perfusion at rest was slow to equilibrate with that in plasma and tends to plateau at about 90% of the plasma value for at least 30 minutes. Our data are well in line with this observation, and suggest that the perfusion was small in both skeletal muscle and skin.

During general anesthesia, the skin is a tissue of choice to monitor because it is readily accessible, quickly vasoconstricts under shock states, and is the last to be reperfused in shock and resuscitation states.¹⁴ Skin oxygenation can be monitored using TcPO₂, which might better reflect PaO₂ than SaO₂.²² Indeed, TcPO₂ is closely related to PaO₂ during anesthesia²³ and accurately reflects local ischemic suffering and global shock.^{14,24} It is also a sensitive and reliable index in the diagnosis of peripheral arterial disease.²⁵ The location and temperature of the electrode might affect the value of TcPO₂ recorded.^{22,26,27} For these reasons, we consistently positioned the electrode on the internal portion of the upper thigh and the electrode was heated at 43°C, which allows for a better diffusion of O₂, probably by shifting to the right the HbO₂ dissociation curve.²⁸

During the first 30 minutes following administration of water, TcPO₂ remained fairly stable. In contrast, over the subsequent 60 minutes, TcPO₂ values consistently decreased in the three groups. This was not related to a reduction in PaO₂. Indeed, in spite of the low FiO₂ value used (21% as found in atmosphere versus the higher values commonly used in general anesthesia [30%–60%]), PaO₂ was stable over the duration of experiment (Table 1). The progressive reduction in TcPO₂ was, thus, probably due to vasoconstriction, and this was confirmed by the reduction in skin blood flow observed in the three groups. The reasons for this progressive reduction in skin blood flow are difficult to pinpoint. Ingestion of water and stomach distension can induce skin vasoconstriction.^{29,30} Although the amount of water administered was small (~225±80 mL) and a large

portion was transferred to the small intestine and absorbed, this mechanism cannot be excluded. Another hypothesis is that the significant decrease in skin blood flow is due to the low body temperature of the pigs documented at the start of the experiment and at all time points (Table 1). This hypothermia is due to temperature regulation in the research facility, to ingestion of water at ambient temperature, and probably to the lack of efficacy of the isolation blanket. This experimental condition could be a limitation of this study, but it should be noted that hypothermia was comparable in the three groups, and that hypothermia is a condition often observed during general anesthesia.

The better tissue oxygenation observed with the water enriched by the electrolytic process cannot be accounted for by the low amount of O₂ which was supplied in the small amount of O₂ waters administered: 225 mL of O₂ waters with 100 mg of O₂/L provide only ~16 mL of O₂ vs an average VO₂ slightly larger than 100 mL/min in the 22.5 kg animals studied (~5 mL/kg/min; see Table 1). In addition, the same amount of O₂ was supplied by the waters enriched in O₂ by injection and the electrolytic process, and a better tissue oxygenation was only observed with the water enriched in O₂ by the electrolytic process.

Although it is difficult to speculate on the basis of the limited data from the present pilot experiment, the better maintenance of skin oxygenation as tracked by TcPO₂ with the water enriched in O₂ by the electrolytic process is consistent with the claim that this enrichment process could stabilize O₂ in solution, and favors its diffusion along PO₂ gradients.⁷ This phenomenon can be due to the fact that the electrolytic process generates supramolecular water structures, or water clathrates,⁹ which can trap O₂ molecules and could modify the local pressure/content relationship for O₂.⁷ This has been previously described with hemoglobin-based oxygen carriers, which should reduce the intracapillary resistance of O₂ transport, enhancing the supply of O₂ to the tissue.^{31,32} The possibility that water clathrates can increase O₂ delivery and correct hypoxemia has been investigated by Spears.³³ Unfortunately, in this experiment, intravenous administration of water clathrates was associated with transient episodes of fall in oxygen saturation, probably due to pulmonary capillary occlusion because of formation of large bubbles (>50 μm) generated by defects in the delivery system. In the study by Spears,³³ O₂ clathrate hydrates were produced at high pressures and low temperatures, but Ozeki and Otsuka have recently shown that these water superstructures can also be generated using a magnetic field⁸ and they could also be produced by the electrolytic process⁷ used in the present experiment.

Conclusion

In this protocol, O₂ water produced by electrolytic process lessens the decline of peripheral tissue oxygenation. Potential applications of O₂ water could be an alternate way of oxygen supply, for treatment of chronic or acute hypoxia. In the field of intensive care medicine or anesthesia, the possibility to administer intravenously O₂ fixed in clathrates in saline solution could lead to other indications similar to those advocated for lipidic oxygen-containing microparticles,³ like rescue of hypoxemic patients.

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Disclosure

François Péronnet and Ruddy Richard are occasional consultants for Danone Research. Alexis Klein and Liliana Jimenez are employees of Danone Research. The authors report no further conflicts of interest in this work.

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