# Effect of air diving exposure generally encountered by recreational divers: Oxidative stress?

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Lemaitre F, Meunier N, Bedu M, Effect of air diving exposure generally encountered by recreational divers: Oxidative stress? Undersea Hyper Med 2002; 29(1): 39-49. Long term effects on respiratory function have been found in air divers and have indicated the development of small-airway disease. These effects have been attributed to oxygen toxicity or to venous gas micro emboli (VGM). The airway obstructions observed in air divers raise fundamental questions about whether these alterations exist after one simulated dive.
The aim of this report was to study the oxidative stress induced by brief normobaric hyperoxia ($FiO_2$ = 0.6 for 30 min) by measuring breath-exhaled compounds. Oxidative stress was measured by pentane in the expirate of 7 subjects ventilated with hydrocarbon-free air (HFA) before and after the hyperoxic exposure. NO concentration allowed us to determine the inflammatory response in the airway. Venous blood was drawn before and after the $O_2$ breathing period for measurements of malondialdehyde (MDA).
In all seven subjects, pentane elimination rates on 60%$O_2$ do not increase after hyperoxia. NO rates during the HFA and hyperoxic exposures are significantly increased ($p<0.05$). MDA concentrations are not changed after the hyperoxic exposure. Pulmonary function parameters obtained 225 minutes after hyperoxia are not changed.
These results provide evidence that a dry gas and oxygen breathing ($FiO_2$ = 0.6) for 30 min can raise exhaled NO. Oxidative stress assessed by pentane and MDA does not exist. We conclude that dry gas and the mild, 30 minute hyperoxic exposure, frequently encountered by recreational divers may be responsible for an airway inflammation. The consequences of such chronic exposure remains to be established.

*oxidative stress, pentane, NO*

## INTRODUCTION

Previous work has demonstrated the effects of saturation diving on human pulmonary functions (1). Decreases in vital capacity (2) and in diffusing capacity (3), pulmonary obstruction (4) have been found in professional divers and attributed to oxygen toxicity (3, 5) or to venous gas micro emboli (VGM) during ascent (6). Although hyperoxia or VGM seems to be negligible in air divers who dive in shallow water, i.e. 0-50 meters (7, 8), recent longitudinal studies have shown possible chronic effects of air diving on pulmonary function (9-11). Therefore, we can observe a significant reduction in diffusing capacity (5, 12) and airway obstruction (11) that are

 

attributed to venous gas microembolism (VGM) (5, 12) and/or hyperoxia (11, 13). Moreover, inhalation of a cold and dry air during diving can provoke airway inflammation responses (14-17). These effects observed during one single dive can induce a long term effect on respiratory function. It remained unclear until today, if the long term pulmonary changes in air divers are the result of inflammatory processes induced by chronic exposure to mild hyperoxia and/or by cold and dry air.

Therefore, the aim of this study was to investigate whether an oxidative stress or an inflammatory process could be induce by a single period of dry air breathing, corresponding to an air dive of 20 meters ($FiO_2$ = 0.6 for 30 min).

## METHODS

### *Subjects*

Seven healthy non-smoking subjects (26.6 ± 4.8 years; 176.6 ± 7.4 cm; 67.6 ± 11.8 kg) participated in this study. Only six of them participated in the NO procedure. Written consent for participation in the study was obtained from all subjects.

### *Materials and procedure*

Because they have been shown to be dependent on oxygen tension (18-20), Malondialdehyde (MDA), pentane and NO were measured. During the breathing tests, subjects were connected to a pneumotachograph (Godart-Staham, Holland) and a two-way non-rebreathing valve (Hans Rudolph) through a mouthpiece. The inspiratory circuit was connected by a two-way valve to hydrocarbon-free air (HFA) or hydrocarbon-free 60% $O_2$ ($HFO_2$) contained in 25-L Tedlar bags supplied from a gas cylinder. During quiet ventilation, the exhaled gas is collected into a 10-L bag (Tedlar) for subsequent analysis or connected to room air by a two-way valve. Before collecting, the bags were flushed three times with pure nitrogen gas.

An expired gas sample was collected for 30 seconds whilst the subject breathed ambient air (TO). Then all subjects breathed HFA for 30 min before and for 165 min after breathing a hyperoxic mixture ($FiO_2$ = 0.6 for 30 min). Expired gas samples were collected before (at 30 min: T30) and after (at 60 min: T60) the hyperoxic mixture, and at 95 min (T95), 125 min (T125), 155 min (T155), 175 min (T175), 195 min (T195) and 225 min (T225) (figure 1). During collection, flow signals from the pneumotachograph were stored on a PC and integrated to obtain volumes of expired gas and ventilation in $l.min^{-1}$ STPD.

### *Lung function tests*

Flow-volume curves were obtained before and 225 min after breathing oxygen and allowed us to determine: forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_1$), $FEV_1$/FVC, peak expiratory flow (PEF) as well as maximal expiratory flow rates at 75%, 50% and 25% of FVC ($MEF_{75\%}$, $MEF_{50\%}$, $MEF_{25\%}$). For each parameter, the best values from at least three consecutive manoeuvers differing by no more than 5% were chosen (21). All of these parameters were measured or calculated with a pneumotachograph (Medical Graphics). Volume calibration was done before each test, and the results were corrected to BTPS conditions.

### *Hydrocarbon breath tests*

In order to analyse pentane in expired air, gas samples were concentrated using "trap-and-purge" method. The hydrocarbons were trapped into thermal desorption tubes packed with standard adsorbent traps (with carbotrap B and carbosieve S-III). Just before use, the adsorbent traps were cleaned by thermal desorption (350°C, 25min, helium flow 30 ml/min). The gas, collected in the bag, was aspirated through the adsorbent trap using a pump (Buck I.H. Pump™

certified, Sigma Aldrich, France). The pump used to aspirate gas through the tube was downstream of the tube. The flow rate of gas through the traps (or adsorbent tubes) depends on the adsorbent packing. With a flow meter placed between the bag and the tube, we determined the flow rate ($ml.min^{-1}$) in the traps to calculate how long the pump took to concentrate 1L of expired gas. The pentane was desorbed from the trap by a thermal desorption unit (TDU 890, Sigma Aldrich, France) as soon as possible after collection, to avoid contamination. Compounds were separated by gas chromatography (3400 Varian, France) using an $Al_2O_3$/KCl plot column 50 m * 0.53 mm (Chrompack, France). Pentane calibration curves were obtained from hydrocarbon standard gas mixture using adsorbent tubes (Sigma Aldrich, France) (15.7 ppm n-pentane in nitrogen) (19). Direct injections of standard gas pentane in TDU 890-gas chromatograph gave the same calibration curves as dilutions of standard pentane in HFA which were trapped and purged from adsorbent tubes. The limit of detection for pentane is 1 pmol. Pentane flows were calculated as the product of respiratory minute ventilation (STPD) and pentane production (pmol) and expressed in $pmol.min^{-1}kg^{-1}$.

***Nitric oxide measurements: single breath***

Following a full inspiration, seated subjects were asked to exhale slowly from total lung capacity. Subjects wore a nose clip and maintained mouth pressure at 17 $cmH_2O$ (expiratory flow at $100ml.s^{-1}$) by using biofeedback visual display. This constant pressure is sufficient to keep the soft palate closed preventing the contamination of exhaled air with nasal NO (22). Expirate was continuously sampled by a NO analyser (SIEVERS) and the NO profile and pressure versus time are captured and displayed in real time on a computer. Three consecutive readings were made at each measurement point during nasal occlusion (figure 1).

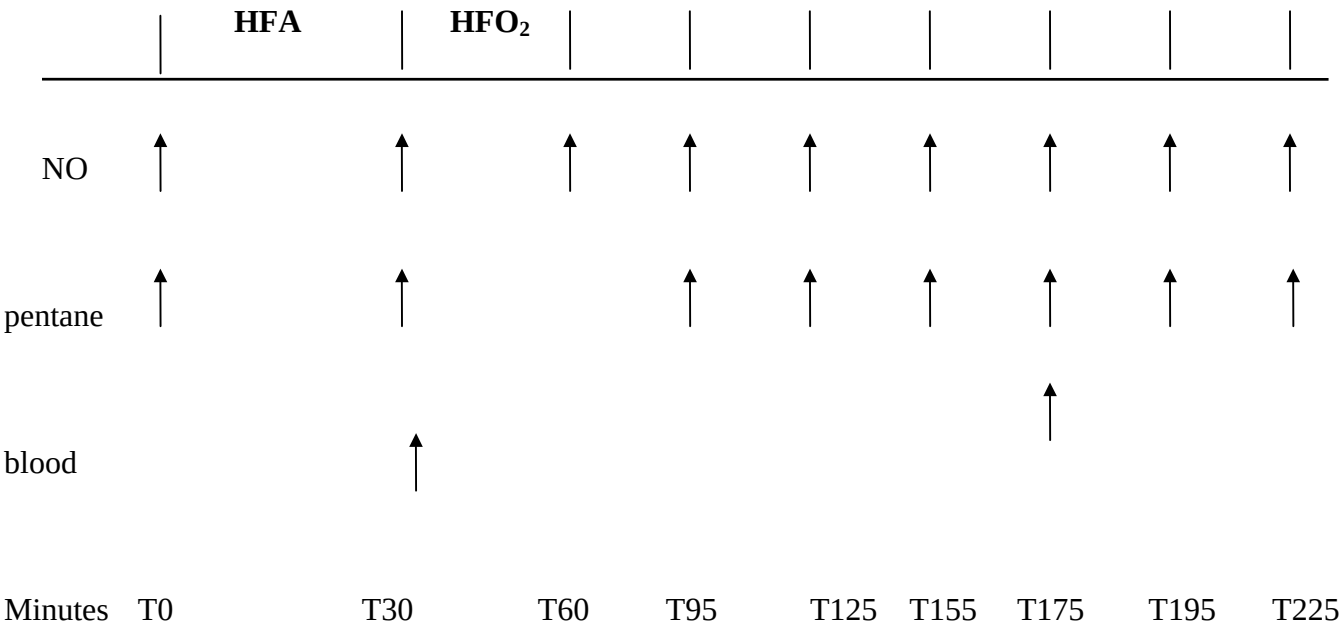


**Figure 1** : Technical procedure for sampling. The exhaled air is collected before the washout with hydrocarbon-free air (HFA) while the subject breath ambient air (TO). Then, expired gas samples are drawn at T30 (Washout), T60, T95, T125, T155, T175, T195 and T225 minutes.

Venous blood samples are drawn before and 115 min after the $O_2$ breathing period ($HFO_2$) (at T175) for measurements of malondialdehyde (MDA).

***Blood samples***

Blood samples obtained by venous puncture were collected into 3 ml evacuated tubes containing one ml of thiobarbituric acid (EDTA). The Conti's method (17) was used to analyse blood samples. After centrifugation, lipid peroxides in the supernatant were measured by fluorescence (excitation 532 nm – emission 553 nm). Venous blood samples were drawn before and 115 min after the $O_2$ breathing period for measurements of malondialdehyde (MDA). Normal values were established in our laboratory (19); plasma MDA levels of 60 healthy subjects gave a mean of 1.54 $\mu M.l^{-1} \pm 0.45$ (coefficient of variation: 6.3%).

***Statistical analysis***

The results are given as means and standard deviation (±SD). Comparisons between each point were carried out using Wilcoxon-tests. A p-value <0.05 was considered significant. Analyses were performed using the Statview software (Abacus Concepts, Inc., Berkeley, CA, 1992).

## RESULTS

***Lung function tests***

All values were within the normal range of recommended reference values predicted by the ECCS standard. No significant differences were found in lung volumes or maximal expiratory flows (at 75, 50 and 25% of FVC) between pre and post exposure (225 min) to oxygen (table 1).

| | Before $O_2$ | p | After $O_2$ |
|---|---|---|---|
| FVC (l) | 6.1 ± 0.8 | ns | 6.03 ± 0.8 |
| $FEV_1$ (l) | 5 ± 0.7 | ns | 4.9 ± 1.5 |
| $MEF_{75\%}$ ($l.s^{-1}$) | 8.9 ± 1.5 | ns | 9 ± 1.5 |
| $MEF_{50\%}$ ($l.s^{-1}$) | 5.4 ± 1.5 | ns | 5.4 ± 1.5 |
| $MEF_{25\%}$ ($l.s^{-1}$) | 2.6 ± 0.7 | ns | 2.6 ± 0.8 |
| PEF ($l.s^{-1}$) | 10.1 ± 1.6 | ns | 9.9 ± 1.5 |
| $FEV_1$/FVC (%) | 82 ± 6 | ns | 81 ± 8 |

**Table 1** : Lung function parameters before and 225 min after 62 kPa normobaric $PO_2$ breathing during 30 minutes. FVC: forced vital capacity; $FEV_1$: forced expiratory volume in one second; PEF: peak expiratory flow; $MEF_{75\%, 50\%, 25\%}$ maximal expiratory flow at 75%, 50% and 25% of vital capacity. Values are means±SD. Ns: non significant.

***Breath biomarkers***

***Pentane:*** Mean values of pentane flows and concentrations and the mean pentane curve are presented in table 2 and in figure 2 respectively. Pentane flows decreased by 42% in the first 30 min after the lung washout period, but these changes were not significant. After hyperoxia (in reference to T30), pentane flows increased by 27% at T175 but the changes were still non significant. Pentane concentrations provide the same results.


| **Sampling times (min)** | **T0** | **T30** | **T60** | **T95** | **T125** | **T155** | **T175** | **T195** | **T225** |
|---|---|---|---|---|---|---|---|---|---|
| **NO (ppb)** | 12.1 ±6.5 | 13.5* ±6.6 | 14.9*+ ±6.5 | 15.2* ±7.4 | 14.4* ±7.4 | 13.7* ±6.5 | 13.1 ±5.5 | 13.3 ±5.3 | 11.8 ±5.4 |
| **Pentane flows ($pmol.min^{-1}.kg^{-1}$)** | 1.34 ±0.91 | 0.78 ±0.30 | / | 0.72 ±0.20 | 0.84 ±0.30 | 0.91 ±0.32 | 0.99 ±0.53 | 0.77 ±0.27 | 0.85 ±0.37 |
| **Pentane concentrations (pmol)** | 10.83 ±5,83 | 7.53 ±2.83 | / | 6.71 ±1.80 | 8 ±3.71 | 8.31 ±2.79 | 8.30 ±3.80 | 7.22 ±2.72 | 8.35 ±2.66 |

**Table 2** : Evolution of NO's and pentane's exhalation rates in expired air before (TO) and after washout (T30) and after 60%$O_2$ breathing for 6 subjects. HFA: Hydrocarbon-free air. Values are means ± SD. *: $p<0.05$ vs TO; +: $p<0.05$ vs T30.

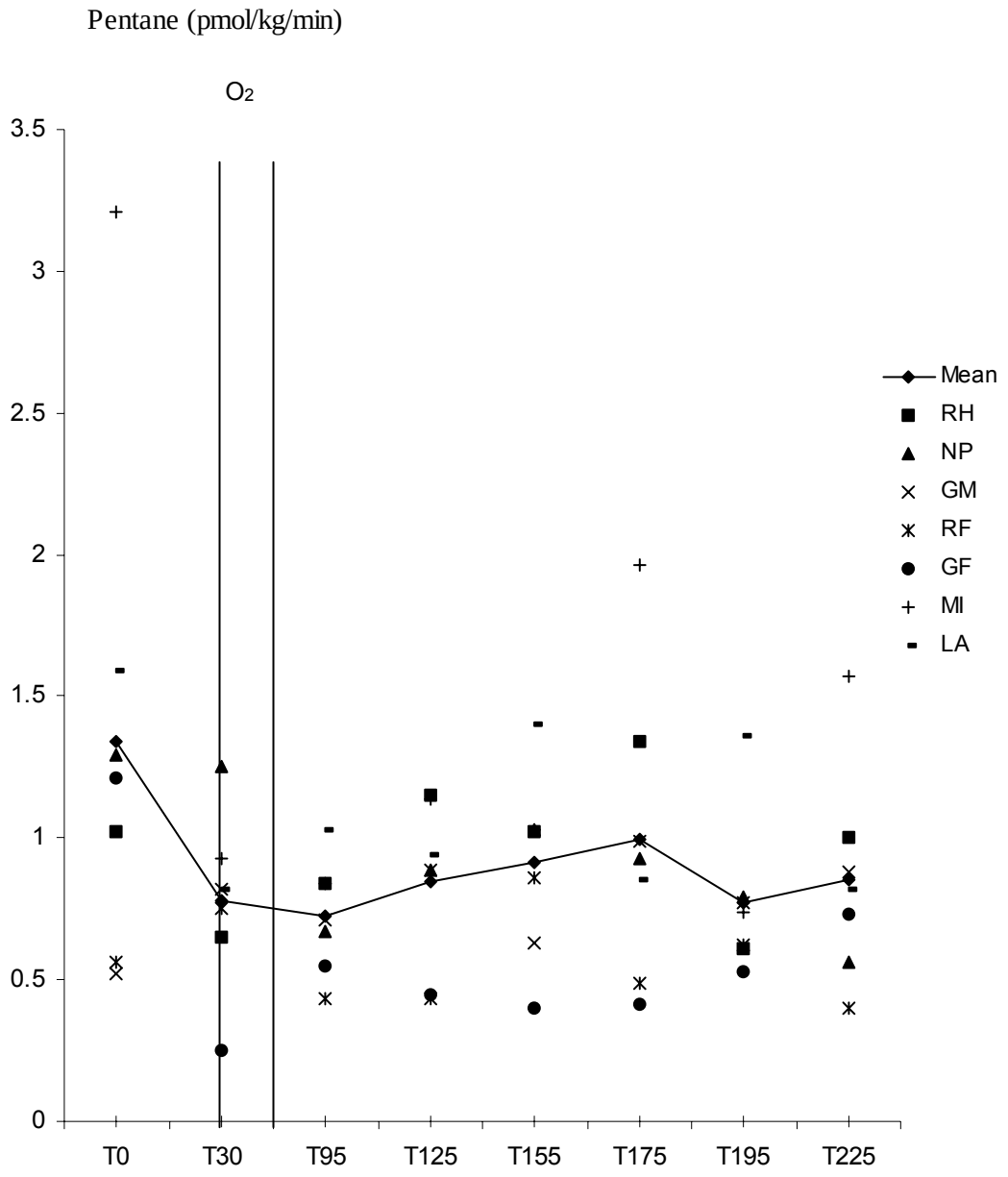


**Figure 2 :** Individual pentane flow values and the mean pentane curve. The exhaled air is collected before the washout with hydrocarbon-free air (HFA) while the subject breathed ambient air (TO), at 30 min (T30), 60 min (T60), 95 min (T95), 125 min (T125), 155 min (T155), 175 min (T175), 195 min (T195) and 225 min (T225).

***Nitric Oxide:*** Means values of NO concentrations and mean NO curves are presented in table 2 and in figure 3 respectively. In reference to T0, we observed a significant increase of NO concentrations after HFA at T30 ($p<0.05$). After $HFO_2$, NO increased significantly by 10.6%

from T30 to T60 ($p<0.05$). Thereafter, NO concentration stayed higher than basal condition (TO) until T155 ($p<0.05$). Both the pentane and the nitric oxide result show one subject with values higher than the others subjects. However, without the outliers the statistical analysis remained unchanged.

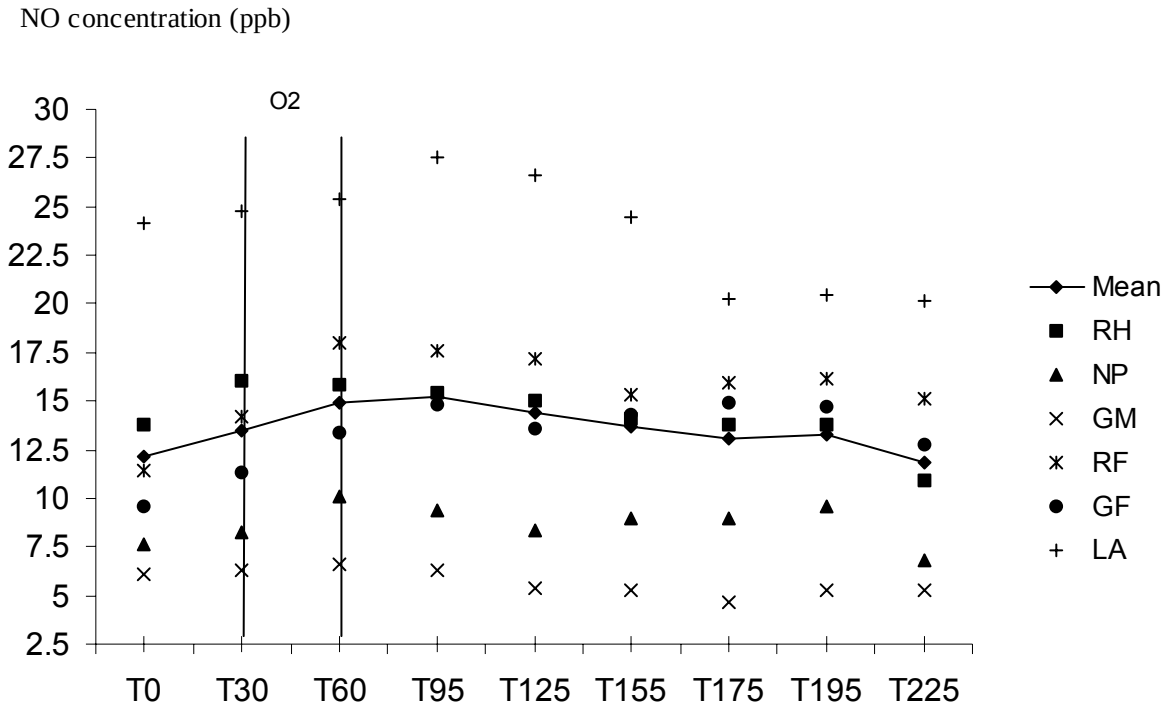


**Figure 3:** Individual NO curves. The NO concentration were analysed before the washout with hydrocarbon-free air (HFA) while the subject breathed ambient air (TO), at 30 min (T30), 60 min (T60), 95 min (T95), 125 min (T125), 155 min (T155), 175 min (T175), 195 min (T195) and 225 min (T225).

***MDA***

MDA curves are presented in figure 4. MDA concentrations were not significantly increased 115 min after hyperoxia (mean MDA before = 2.5 μM vs MDA after = 2.8 μM).

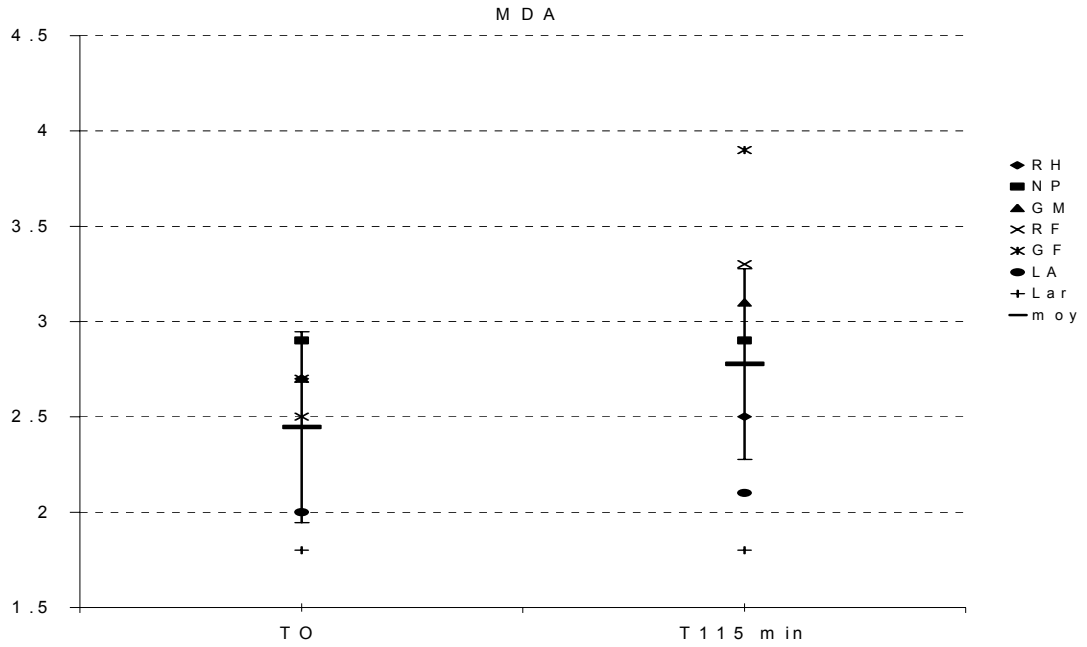


**Figure 4 :** Individual malondialdehyde (MDA) concentrations (μM) 115 min after breathing oxygen (60%$O_2$) during 30 minutes

## DISCUSSION

The principal finding of this study is the increase of NO concentrations in healthy subjects after breathing hydrocarbon-free air and oxygen (60% $O_2$ for 30 min). In contrast, exhaled pentane levels and MDA concentrations did not change after hyperoxia.

In this study, NO concentrations were significantly higher ($p<0.05$) than NO values observed in basal condition (TO) after breathing a dry gas (HFA). Moreover, the NO concentrations increase slightly after breathing HFA in all subjects. NO readings could be underestimated in the presence of water vapour, which affect the chemoluminescence process (23). Van Der Mark et al. (23), have found a significant decrease in NO readings in the water saturated samples compared to the dry gas ($p<0.001$), strongly dependent on the partial pressure of water. However, in the present study, a water absorber was used in the tubing leading to the NO analyser, unlike Van De Mark study. Thus, the NO values reported in the present study could not be explained by underestimation of NO readings. In animals, the inhalation of a dry air during 30 min may result in airway epithelial damage and inflammation (14). To our knowledge, no studies have investigated in humans the effect of dry air on exhaled NO. However, during nasal air inhalation, it has been shown that a dry gas can reduce NO release in humans (15). In recreational diving, the reserve gas under pressure is dried before compression in a cylinder and chilled by the relief valve on leaving the reservoir. It is widely accepted that inhalation of dry and cold air associated with hyperventilation during the dive can induce acute airflow limitation

(16). Therefore, increase in exhaled NO may be the result of an airflow limitation or an airway inflammation. Airway inflammation could cause the increase in exhaled NO (24). However, nitric oxide can exert both protective and proinflammatory actions. NO formed physiologically by constitutive NO synthases, modulates adhesion of inflammatory cells. In contrast, expression of an inducible isoform of NO synthase, capable of producing excessive NO levels, is implicated in tissue injury (25). Such proinflammatory effets of NO, may depend of environment, and involve further cytotoxic moties such as peroxynitrite. Further, the mechanisms by which dry air may modulate NO levels are unclear. In fact, the water loss and the subsequent changes in the osmolarity may be as important as heat loss in inducing bronchoconstriction. Thorsen et al. (17) have demonstrated that dry air challenges induce a bronchoconstrictive response at increased ambient pressure. By warming and humidifying the gas breathed in deep saturation diving, bronchoconstriction may be prevented (26). Moreover, chronic exposure to dry compressed air may also enhance airway reactivity to non-specific bronchoconstrictor stimuli in divers (27).
In our study, we observed an increase in NO production after hyperoxia. Several studies have demonstrated that NO production depends on oxygen tension (20, 28, 29). In rat lungs, hyperoxic exposure caused 5-fold increase in inducible nitric oxide synthase (iNOS) levels (29). Similar results for iNOS have been shown after hyperoxia in rat liver (28). However, hyperoxia can create inducible NO synthase expression in rat lungs without an increase in exhaled NO concentration (30). A dose – dependent change in exhaled NO during graded oxygen breathing was observed (20), and 60% $O_2$ breathing resulted in an approximately 23% increase in exhaled NO levels compared with the baseline. In our study, after the same hyperoxia, NO mean values increased (10.6%) significantly (T30 vs. T60, $p<0.05$). However, Dweik et al. (31) have found no increase in exhaled NO in going from air breathing to 50% oxygen. They also found a reduction in exhaled NO during exposure to hypoxia. Thus, it is possible that our exhaled NO elevation represents a physiological rather than a inflammatory response to hyperoxia. Moreover, NO determination in exhaled air, can vary with test procedures between different laboratories (32) and can explain in part these differences.

Expiratory flows and $FEV_1$ of the present study were not lower 165 min after the oxygen exposure, corresponding to a depth of 20m, indicating no acute changes of pulmonary function induced by hyperoxia. This result is in agreement with previous reports indicating that exposure to hyperoxia with an inspired oxygen tension of 50 kPa could be breathed for infinite time without pulmonary problems (2). Although few studies have investigated the effects of low oxygen concentration corresponding to shallow air dives, airway obstruction in air divers has also been found (7) but not in all cases (8). Oxygen is considered by several authors to be the principal cause of pulmonary function changes, such as expiratory flow rate reductions (5, 13). However, the higher NO concentrations observed in our subjects after a dry and brief hyperoxia raises fundamental questions about whether these alterations can induce chronic pulmonary effects.

Several studies (18, 19, 33) have investigated markers of lipoperoxidation (MDA or pentane) and have shown that these biomarkers are increased in blood or in the alveolar expirate of animals and humans exposed to high oxygen concentration. However, to our knowledge, no data have been reported in humans exposed to brief, low oxygen concentrations. In our study, pentane concentrations increase by 27% 145 min after 60%$O_2$ breathing (at T175 versus T30), but the changes did not reach significant levels. The same results were obtained with MDA concentrations. Several studies (18, 19) have reported similar results with a significant increase of pentane production, from 30 to 145 min after breathing 100%$O_2$. However, measurements of

pentane could underestimate lipid peroxidation due perhaps to a rapid metabolism in contrast to MDA, which was metabolised slowly. Thus our measurement techniques are not sensitive enough to detect an oxidative stress after breathing 60%$O_2$. Moreover, in our study, the small number of subjects does not allow us to conclude definitively. Therefore, we are not able to detect with these two biomarkers (MDA and pentane) the occurrence of oxidative stress.

## CONCLUSION

In conclusion, our measurements of lipoperoxidation assessed by MDA and pentane exhalation did not allow us to detect an oxidative stress while breathing a 60% $O_2$ gas. However, both oxygen and hydrocarbon-free dry air breathing induce an increase of NO concentrations, indicating airway inflammation. A possible long-term effect on pulmonary function may be expected. Because oxygen and dry gas were breathed simultaneously, it is however, difficult to distinguish which gas is responsible for the NO increases. Moreover, the observed increases in NO could represents a physiological rather than an inflammatory response to hyperoxia. Thus, we proposed in a further study, to examined the effect of 60 minutes breathing dry air to sorting out the effect of dry air alone on NO increases.

## ACKNOWLEDGEMENTS

This study was supported in part by a grant from the "French society of physiology and subaquatic and hyperbaric medicine" (MEDSUBHYP). Special acknowledgements are given to the laboratory technicians for excellent support and the subjects of this study. We moreover thank Mr Forrest Patterson for his translation assistance in the preparation of the manuscript.

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