The ‘normobaric oxygen paradox’: a simple way to induce endogenous erythropoietin production and concomitantly raise hemoglobin levels in anemic patients

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LETTER TO THE EDITOR

Dear Sir,

There is increasing concern regarding the inherent hazard of blood transfusions, host–graft reactions and transfusion-related acute lung injury. Considering the increasing population age, the increased need for blood products when reaching older age, and an already chronic shortage of blood products today, the need for alternative techniques to blood transfusion, and for new blood substitutes or blood salvage techniques is becoming more and more pressing.1,2

The use of blood cell progenitor enhancers like exogenous erythropoietin (EPO) is extensively recognized, and in patients with appropriate medical follow-up, a relatively low rate of adverse effects has been reported.3 However, the price of such medications is very high and in some countries, their availability is limited.

A recently described phenomenon called the ‘normobaric oxygen paradox’ (NOP)4 may have clinical applications. The technique consists in a simple administration of high oxygen concentration to spontaneously breathing subjects. This has been shown to trigger a
significant increase in endogenous EPO production. A few clinical applications have already been described, using NOP to increase hemoglobin (Hb) concentration in humans.

THE NORMOBARIC OXYGEN PARADOX

The suggested mechanism to explain this phenomenon lays deep into the fundamental cellular mechanism of apoptosis. This mechanism depends on oxygen-free radical availability. In the presence of reactive oxygen species (ROS), the hypoxia-inducible factor alpha (HIF-1α) is continuously bound to von Hippel-Lindau protein (VHLp). This formed complex is subsequently ubiquitinized through the prolyl oxidase pathway and finally recycled in the proteasome. In case of limited availability or absence of ROS (such as in hypoxic situations), HIF-1α will not be linked to VHLp and thus can be bound to the HIF-1β dimer. This HIF complex will then induce a cascade of EPO gene expression and subsequently de novo EPO synthesis.

Raising the oxygen level inhaled by the patient (thereby increasing the presence of ROS in the cell) will increase the production of protective agents against ROS. This will be reflected by upregulation of glutathione synthetase activity (γ-glutamylcysteine synthetase). Production of reduced glutathione (GSH) and subsequently the rate of ROS ‘scavenging’ will increase. When hyperoxic ventilation stops, the increased amount of GSH, together with an ongoing reconversion of oxidized glutathione (GSSG) to GSH, will produce a surplus of ROS scavenging. This phenomenon will persist a certain time after the oxygen concentration in the breathing mixture has been reduced, and will therefore mimic a ‘hypoxic’ situation with a reduced amount of ROS.5,6 This situation will, just as in a ‘true’ hypoxic situation, allow the binding of the HIF dimers and start EPO gene expression.

In a recent experiment (2008, Abyss Project) aimed at understanding human adaptation during a prolonged stay under mild hyperbaric conditions, six healthy humans lived for 14 days at a depth of 9 m breathing air. They were thus breathing a gas with an oxygen partial pressure equivalent to 40% O₂ (pO₂ 0.4 ATA).

The EPO levels in these volunteers decreased during the hyperbaric stay, but increased markedly and rose above control values 24 hours after the end of their hyperbaric stay. These observations indicate that NOP is still present even if the oxygen tension variation is less than what was previously reported.4 Indeed in 2006, Balestra et al. showed that a drop from 100% to 20% of oxygen in the breathing gas induced NOP in healthy volunteers. The present observation indicates that a drop from 40% to 20% appears to be sufficient to induce a significant increase in EPO levels 24 hours after the change in oxygen concentration.

NOP appears thus to be an efficient way to increase EPO. Clinical applications may lie not only in the field of cardioprotection or neuroprotection,7–9 where a single session would be sufficient, but also, by repeated sessions, to increase Hb levels without the need for exogenous EPO administration.

CASE REPORTS

Only two case reports about the application of NOP in clinical situations are available. The first one, published by Burk,10 describes the application of normobaric oxygen breathing sessions for several days in a 42-year-old woman receiving chemotherapy after breast cancer [doxorubicin (Adriamycin) + cyclophosphamide (Cytoxan) and paclitaxel (Taxol)]. She developed progressive anemia. No erythropoiesis-stimulating agents (ESAs) were given, but at a nadir Hb of 8.8 g/dL, the patient was given oxygen 3 times a week by means of a nasal cannula for about 90 minutes. With a usual flow of 6–8 L/min, this is equivalent to approximately 40% of oxygen. After a few days, the Hb level started to rise. As the increase in Hb concentration after the nadir level might have been due to the natural course observed after chemotherapy, the author, after having reached a comfortable level of Hb (12 g/dL) stopped the oxygen administrations. After a few days, the Hb level dropped, and when the oxygen administrations were resumed, the Hb concentration increased again (Figure 1).

A 71-year-old woman suffering from myelofibrosis had to undergo an aortic valve repair. Due to religious concerns, she wanted to avoid the use of blood products during and after the procedure. She was therefore given darbepoetin alpha (Aranesp 300 μg) twice a month and intravenous iron therapy in order to increase the Hb level prior to surgery. In addition to that classical approach, 30 minutes of pure oxygen every other day was given by means of a demand valve mask. The Hb level increased in 60 days to a comfortable level of 13.5 g/dL. The patient was feeling very well and decided
to take a two-week vacation to rest before surgery. The whole treatment was maintained except for the oxygen administration. Upon her return, the level of Hb had dropped to 12.5 g/dL; after resuming oxygen breathing, it increased again (Figure 1).

A higher speed of Hb response is seen for the patient with both strategies (adjuvant drugs and O2 breathing). Nevertheless, the speed of Hb increase in both patients is compatible with the usual rise observed in patients under ESAs (erythroid-stimulating agents) without reduced bone marrow activity.11–13 In the two cases reported by us and by Burk, the efficiency of NOP on Hb increase was unexpected.

Plotting the two patients’ data on a single regression line graph (with Hb increase on the y-axis and days of treatment on the x-axis) shows that the absolute Hb increase (0.05 g/dL per day of treatment) is similar for both treatment strategies ($y = 0.05x + 9.4$; $r^2 = 0.79$; $P < 0.0001$). Other treatment strategies may be evaluated for efficacy using a similar approach.

CONCLUSIONS

These two cases showed a marked and steady increase of Hb levels using different approaches. It seems that a negative delta PO2, i.e. a ‘relative hypoxia’ from 40% to 20%, is as effective as a delta PO2 of 100% to 20% to induce NOP. Likewise, a pattern of oxygen breathing every other day or three times per week showed to be a similarly potent erythropoietic stimulus.

We propose new clinical applications of NOP that can take two different directions. A low number of O2 breathing sessions, even one, seems to be sufficient4 to increase the circulating endogenous EPO level for neuroprotective and cardioprotective effect prior to surgery. Increasing the number of sessions to 2–3 times per week for 30–90 minutes of O2 breathing at a concentration varying from 40% to 100% for several weeks seems to increase the Hb level of some patients. We would encourage more clinical investigations to determine the optimal use of the normobaric oxygen paradox.

REFERENCES

9 Hare GM, Tsui AK, McLaren AT, et al. Anemia and cerebral outcomes: many


