Clinical Study

Hyperoxia Reversibly Alters Oxygen Consumption and Metabolism

Patrick Lauscher,1 Sabine Lauscher,2 Harry Kertscho,3 Oliver Habler,2 and Jens Meier1

1 Department of Anesthesiology and Intensive Care Medicine, Tübingen University Hospital, Eberhard-Karls University, 72076 Tübingen, Germany
2 Clinic of Anesthesiology, Intensive Care Medicine, and Pain Control, Nord-West Hospital, 60488 Frankfurt, Germany
3 Clinic of Anesthesiology, Intensive Care Medicine and Pain, Therapy Goethe-University Hospital Center, 60590 Frankfurt, Germany

Correspondence should be addressed to Patrick Lauscher, patrick.lauscher@gmx.de

Received 14 November 2011; Accepted 22 December 2011

Aim. Ventilation with pure oxygen (hyperoxic ventilation: HV) is thought to decrease whole body oxygen consumption (VO2). However, the validity and impact of this phenomenon remain ambiguous; until now, under hyperoxic conditions, VO2 has only been determined by the reverse Fick principle, a method with inherent methodological problems. The goal of this study was to determine changes of VO2, carbon dioxide production (VCO2), and the respiratory quotient (RQ) during normoxic and hyperoxic ventilation, using a metabolic monitor.

Methods. After providing signed informed consent and institutional acceptance, 14 healthy volunteers were asked to sequentially breathe room air, pure oxygen, and room air again. VO2, VCO2, RQ, and energy expenditure (EE) were determined by indirect calorimetry using a modified metabolic monitor during HV.

Results. HV reduced VO2 from 3.4 (3.0/4.0) mL/kg/min to 2.8 (2.5/3.6) mL/kg/min (P<0.05), whereas VCO2 remained constant (3.0 [2.6/3.6] mL/kg/min versus 3.0 [2.6/3.5] mL/kg/min, n.s.). After onset of HV, RQ increased from 0.9 (0.8/0.9) to 1.1 (1.0/1.1). Most changes during HV were immediately reversed during subsequent normoxic ventilation.

Conclusion. HV not only reduces VO2, but also increases the respiratory quotient. This might be interpreted as an indicator of the substantial metabolic changes induced by HV. However, the impact of this phenomenon requires further study.

1. Introduction

Oxygen (O2) is widely used in emergency medicine as an acute measure for many different pathologies. Most of the emergency guidelines, such as for acute myocardial infarction or hemorrhagic shock, include usage of supplemental oxygen with the aim to improve macrohemodynamics, oxygen transport, and tissue oxygenation [1–4]. However, the application of pure oxygen is associated with side effects, including hyperoxic arteriolar constriction and reduced functional capillary density, which reduces nutritive organ blood flow and increases peripheral oxygen shunting [5–8].

Despite these negative side effects, hyperoxic ventilation is thought to prevent tissue hypoxia by other means: Chapler et al. were among the first to recognize that breathing 100% O2 significantly decreases oxygen consumption and optimizes oxygen delivery—oxygen consumption balance [9], a phenomenon that has been confirmed [10–14]. However, it is not known whether this repeatedly observed VO2 decrease after onset of hyperoxic ventilation is not merely the result of erroneous measurement, since all data collected thus far have been obtained by the reverse Fick method from data obtained by a pulmonary artery catheter (cardiac output [CO], arterial oxygen content [CaO2], and venous oxygen content [CvO2]).

There are several methodological weaknesses inherent to this indirect calculation of VO2 that make results interpretation difficult [15–17]. Of note, however, VO2 can not only be calculated but also directly measured using a metabolic monitor for low inspiratory oxygen fractions (FiO2 < 0.6). Although theoretically possible, VO2 measurement up to an inspiratory oxygen fraction of 100% has not been implemented to a metabolic
monitor so far. As a consequence, no study exists, where VO₂ has actually been directly measured during HV. In contrast to the Fick method, a metabolic monitor makes it possible to measure concomitant changes of carbon dioxide production (VCO₂) and the respiratory quotient (RQ) during HV. Changes in these 2 important indicators of oxygen balance may facilitate interpretation of the observed changes in VO₂.

The aim of this study was to determine VO₂, VCO₂, and RQ during normoxic and hyperoxic ventilation in healthy volunteers by means of a modified metabolic monitor, especially designed for VO₂ measurement during HV (Oxycon Pro, VIASYS Healthcare, Hoechberg, Germany). We hypothesized that HV not only decreases VO₂ but also alters VCO₂ and RQ, probably indicating substantial changes in oxygen metabolism during HV versus normoxic ventilation.

2. Materials and Methods

2.1. Study Design. Following approval by the local ethics committee and informed consent, the experiments were performed in 14 volunteers (7 men and 7 women) as a single blinded, nonrandomized cross-over study.

2.2. Measurement of VO₂ and VCO₂. Volunteers were connected to a modified metabolic monitor (Oxycon Pro, VIASYS Healthcare, Hoechberg, Germany) that is designed to measure VO₂, VCO₂, and RQ during hyperoxic ventilation. The basic version of this metabolic monitor has been thoroughly described and validated elsewhere [18]. Experimental measurements of VO₂ and VCO₂ were obtained by calibrating the metabolic monitor with the inspiratory oxygen concentration of every time point (room air, pure oxygen, and room air) and applying a modified, validated Haldane equation. Expired gas was passed through a flow meter, oxygen analyzer, and carbon dioxide analyzer. The flow meter and gas analyzers were connected to a computer, which calculated minute ventilation, oxygen uptake (VO₂), carbon dioxide production (VCO₂), the respiratory quotient (RQ), and energy expenditure (EE) each minute, from adapted equations for hyperoxic ventilation. Values obtained over 20 min were averaged and are given as the median value for each time point.

2.2.1. Participants. Fourteen healthy nonsmoking volunteers (7 men and 7 women) agreed to participate in this study. Health histories and physical examinations were completed, and written informed consent was obtained according to protocols approved by the University of Frankfurt ethics committee. Prior to the experiments, the subjects were interviewed and examined for the following exclusion criteria: neurological, cardiovascular, pulmonary, hepatic, renal, hematopoietic, gastrointestinal, metabolic, or psychiatric dysfunction; receiving medication on a regular basis. Subjects’ physical characteristics were as follows: age 29.3 (range: 24–37) yrs; height 176 cm (range: 162–198 cm); weight 74.5 kg (range: 53–105 kg).

2.3. Experimental Protocol. Measurements were made as subjects watched television while seated in a beach-chair position in a temperature-controlled room (21°C). Measurements were made using the metabolic monitor connected to an intensive care respirator (Vela, VIASYS Healthcare, Hoechberg, Germany). The gas mixture was administered through a nonrebreathing system with a tightly fitted facemask. The resistance of the breathing system was not compensated for by pressure support throughout the protocol. No continuous positive airway pressure was applied, since volunteers had no artificial airway. The inspiratory oxygen fraction was controlled by oxygen sensors in the circuit. After 30 min of adaptation, the volunteers sequentially breathed room air (FiO₂ 0.21; time point NOX 1), pure oxygen (FiO₂ 1.0; time point NOX 2), and room air (FiO₂ 0.21; time point NOX 2) again for 20 min each. Before each measurement, the metabolic monitor was recalibrated according to the manufacturer’s instructions. After each change in FiO₂, an equilibration period of 8 min was allowed to elapse, to achieve steady state conditions. We demonstrated in 3 pilot experiments that after a wash-in phase of 5 min, a steady state oxygen uptake is reached, and any changes in VO₂ cannot be attributed to wash-in kinetics after this time period. All the volunteers were blinded to the FiO₂ used; however, the different FiO₂ were not applied in a randomized order.

2.4. Monitoring. Brachial blood pressure was recorded at 5 min intervals by a semiautomated noninvasive oscillometric sphygmomanometer (Datascope Passport, NJ, USA). Pulse oximeter saturation (SpO₂) was monitored noninvasively by a standard anesthesia monitor (Datascope Passport, NJ, USA). A digital 12-channel ECG recording was registered continuously throughout the protocol (Cardiax Mesa, Benediktbeuren, Germany). VO₂, VCO₂, RQ, and EE were determined as described above. No further invasive measurements have been established.

2.5. Statistical Analysis. Data are presented as medians (Q1-Q3). Calculations and statistical analysis were performed with the R software package (R-Project, 2.2.0, R-Foundation, Vienna, Austria). Distribution of data was tested by a Shapiro-Wilk test. Because not all data were normally distributed, differences between NOX 1, NOX 2, and NOX 2 were analyzed with a Wilcoxon-s signed-rank test. Post hoc analysis of differences detected with the Wilcoxon signed-rank test was performed by the Bonferroni-Holm method. Overall, statistical significance was accepted at P < 0.05.

3. Results

All the 14 volunteers completed the study, and none reported discomfort from the facemask or the administration of pure oxygen.

Figure 1 and Table 2 illustrate the changes of VO₂, VCO₂, RQ, and EE during the 3 time points. After onset of HV, VO₂ was reduced 18% at time point Hox (P < 0.05), whereas VCO₂ remained unaltered (n.s.). Simultaneously, RQ increased by 22% (P < 0.05) and EE decreased by 12% (P < 0.05). Table 1 depicts the hemodynamic changes during the study: HV slightly increased SaO₂ and decreased HR (both P < 0.05). Arterial blood pressures (AOP_sys, AOPDia)
were not affected by HV. At time point NOX 2, VO₂ returned to the value obtained before HV, whereas VCO₂ and RQ were significantly decreased, even below the threshold of NOX 1 (−13% and −27%, resp., both $P < 0.05$). EE returned to baseline at time point NOX 2.

4. Discussion

The main findings of this study were as follows. (1) Changes from normoxic to hyperoxic ventilation significantly reduced
VO₂. (2) After the onset of HV, the respiratory quotient (RQ) increased, whereas carbon dioxide production (VCO₂) remained unaltered. (3) Most variables immediately returned to baseline when FiO₂ was returned to 0.21 at time point NOX 2. Only VCO₂ and RQ recovered slower and did not reach NOX 1 levels within the measurement period of NOX 2.

Whole-body VO₂ can be measured by a pulmonary artery catheter or by a metabolic monitor. For resting patients breathing room air, both methods yielded satisfactory results for daily clinical practice. It is well known, however, that the accuracy of a standard metabolic monitor is rather low if FiO₂ increases [19]. This is even more true for ventilation with pure oxygen. As a consequence, it has been impossible to use standard metabolic monitors to accurately determine VO₂ above a maximum FiO₂ of 0.6 due to technical problems (mainly the Haldane transformation; for technical details see Appendix). Therefore, all studies of hyperoxic ventilation and oxygen consumption have been conducted with a pulmonary artery catheter. However, this approach has several weaknesses, which cast the results obtained by this method into doubt [15–17, 20, 21]. Apart from the inferior reproducibility of the reversed Fick method, the most important finding is a consistent negative bias of calculated VO₂ values versus calorimetric VO₂ data observed by the majority of authors during normoxic conditions [22]. We determined VO₂, VCO₂, and RQ during HV for the first time by using a modified metabolic monitor, which is not limited by these restrictions. We did not measure VO₂ simultaneously by means of a pulmonary artery catheter during our protocol to directly compare the results of both methods. Since the main goal of our study was to determine VO₂ during HV, placement of a pulmonary artery catheter might be judged an inappropriate risk for the subjects participating in the study. Furthermore, several studies already demonstrated a decline of VO₂ during HV by means of a pulmonary artery catheter [10–14, 23, 24]. Using a modified metabolic monitor, we were able to replicate the results of these authors by a completely different technique. Consequently, we can state that HV actually decreases VO₂, and that this phenomenon is unlikely to be judged a measurement artifact due to the method used. The fact that there are no studies validating the Delta Trac Pro for use with HV might be seen as a limitation to this study. Although the basic version of our metabolic monitor has been described and validated thoroughly elsewhere [18], there are no studies validating the Oxycon Pro during HV. This has to be stated as a limitation to our study.

Several mechanisms might be responsible for the observed decrease of VO₂ during hyperoxic ventilation. It is well known that HV reduces heart rate and myocardial oxygen consumption [11, 25]. It might therefore be speculated that the HV-induced decline of whole-body VO₂ might originate from a decrease of myocardial O₂ consumption. However, because we observed only a negligible reduction of heart rate during HV, it seems unlikely that a concomitant decline of myocardial oxygen consumption is solely responsible for the observed decline of whole-body oxygen consumption.

Furthermore, it is known that breathing O₂-enriched air transiently decreases minute ventilation by 10–20%, a phenomenon which might reduce respiratory work load and O₂ consumption [26]. However, this effect, which has been attributed to a decrease in carotid body activity, lasts for less than 5 min [10]. Thereafter, minute ventilation returns to the baseline value and after another 5 min breathing of O₂-enriched air increases minute ventilation up to 15% [27]. We therefore assume that this effect played a minor role in our setting.

Using a modified metabolic monitor for the determination of VO₂ and VCO₂ during HV yielded an additional result, which has not been observed previously: hyperoxic ventilation does not alter carbon dioxide production, despite a significant decline in oxygen consumption. This phenomenon might be explained by 2 different mechanisms: (1) During anaerobiosis, the VCO₂/VO₂ ratio (RQ) increases above 1.0, because alternative metabolic pathways (mainly anaerobic glycolysis) are engaged, using less-molecular oxygen for the production of the same amount of carbon dioxide. For example, the respiratory quotient increases during hypovolemia as soon as the anaerobic threshold is reached [28]. However, it seems very unlikely that HV resulted in severe anaerobic conditions in our setting, and this explanation might only play a minor role. (2) A second possible explanation for the decline of VO₂ despite constant VCO₂ during HV might be the fact that exposure to hyperoxia causes a substantial change in the metabolism of cells and tissues [29]. In Chinese hamster ovary cells exposed to hyperoxia for 24 h or more, Schoonen et al. found that the rate of oxygen consumption was substantially lower than that of cells maintained at normoxia [30]. The reduction in ATP generation from oxidative phosphorylation was partially offset by increased glycolysis; however, steady-state ATP levels were significantly reduced. One possible mechanism for this phenomenon is that aconitate, a mitochondrial matrix enzyme responsible for the hydration of citrate and isocitrate at the beginning of the citric acid cycle, is inactivated by exposure to hyperoxia [31]. These substantial changes in the oxidative pathway might at least partially explain the changes of VO₂ despite constant VCO₂ during HV. However, little is known about the different effects of HV on cellular oxygen metabolism in different organs in vivo, and therefore the relevance of this mechanism remains unclear. However, HV resulted in substantial changes of RQ in our model, and we speculate that changes of cellular O₂ metabolism might, at least in part, be responsible for the changes of VO₂ during HV.

The clinical impact of these HV-induced effects is ambiguous. HV is frequently used to treat hypoxemia and to preserve tissue oxygenation by increasing CaO₂ during various pathological conditions where a critical restriction of oxygen transport is assumed (myocardial infarction, normovolemic anemia, hemorrhagic shock, etc.) [32–34]. However, it has been shown by many different investigators that HV regularly increases CaO₂ but usually fails to increase local and systemic oxygen delivery (DO₂) [11, 34–36]. This phenomenon is mainly attributed to the fact that HV induces generalized arteriolar constriction, which is accompanied
by reduced functional capillary density [5–8] and nutritive organ blood flow, and increased peripheral oxygen shunting [8, 35]. As a consequence, HV-induced oxygen shunting might result in higher venous oxygen partial pressures and lower tissue oxygen partial pressures [7]. This should result in a reduction of VO₂ at the expense of peripheral O₂ delivery. However, we did not assess for signs of peripheral acidosis in our setting.

In summary, we speculate that the additional amount of O₂ actually transported to the cells after initiation of HV might be negligible, since HV increases CaO₂ but the accompanying decrease in nutritive organ blood flow prevents an increase of regional and whole-body DO₂. Furthermore, this mechanism is in contrast to the beneficial effects of HV on oxygen transport and tissue oxygenation described above. One might speculate that the beneficial effects of HV during many different pathologies may to some extent be contributed to the fact that oxygen consumption of tissues is decreased by HV, and to the fact that HV increases CaO₂. However, no clear proof of this concept is provided by the current data.

5. Conclusion

The change from normoxic to hyperoxic ventilation reduces whole-body oxygen consumption, regardless of the detection method, whereas carbon dioxide production (VCO₂) remains unaltered. This phenomenon might be caused by substantial metabolic changes during HV; however, clarification of this phenomenon and its impact on oxygen transport and tissue oxygenation require further study.

Appendix

The Haldane Transformation

Standard metabolic monitors quantify VO₂, VCO₂, and RQ by continuous measurement of the in- and expiratory oxygen fractions (F_iO₂ and F_eO₂). The difference F_dO₂ of F_iO₂ and F_eO₂ can be calculated as

\[ F_dO₂ = F_iO₂ - F_eO₂ \]  \tag{A.1}

Using these values and the in- and expiratory CO₂ concentrations (F_iCO₂ and F_eCO₂) and the Haldane transformation, the respiratory quotient can be calculated as follows:

\[ RQ = \frac{1 - F_iO₂}{(F_dO₂/(F_iCO₂ - F_eCO₂)) - F_iO₂}. \] \tag{A.2}

Because the respiratory quotient RQ is defined as

\[ RQ = \frac{VCO₂}{VO₂}, \] \tag{A.3}

VO₂ can be calculated as

\[ VO₂ = \frac{VCO₂}{RQ}. \] \tag{A.4}

However, using the Haldane transformation, an FiO₂ of 1.0 will regularly result in a respiratory quotient of 0. Therefore, VO₂ cannot be calculated this way for FiO₂ = 1.0.

Calibration of the metabolic monitor and application of an adapted Haldane algorithm enables measurement of VO₂ and VCO₂ during hyperoxic conditions. However, the underlying algorithm has not been published by the manufacturer of the metabolic monitor.

Acknowledgment

Support was provided solely from institutional and departmental sources.

References

[1] E. M. Antman, D. T. Anbe, P. W. Armstrong et al., “ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of cardiology/American heart association task force on practice guidelines (writing committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction),” Canadian Journal of Cardiology, vol. 20, no. 10, pp. 977–1025, 2004.

[2] H. Bitterman, V. Brod, G. Weisz, D. Kushnir, and N. Bitterman, “Effects of oxygen on regional hemodynamics in hemorrhagic shock,” American Journal of Physiology, vol. 271, no. 1, pp. H203–H211, 1996.

[3] C. Nicholson, “A systematic review of the effectiveness of oxygen in reducing acute myocardial ischaemia,” Journal of Clinical Nursing, vol. 13, no. 8, pp. 996–1007, 2004.

[4] M. Wijesinghe, K. Perrin, A. Ranchord, M. Simmonds, M. Weatherall, and R. Beasley, “Routine use of oxygen in the treatment of myocardial infarction: systematic review,” Heart, vol. 95, no. 3, pp. 198–202, 2009.

[5] J. F. Baron, E. Vicaut, X. Hou, and M. Duvelleroy, “Independent role of arterial O₂ tension in local control of coronary blood flow,” American Journal of Physiology, vol. 258, no. 5, pp. H1388–H1394, 1990.

[6] B. R. Duling, “Microvascular responses to alterations in oxygen tension,” Circulation Research, vol. 31, no. 4, pp. 481–489, 1972.

[7] N. Lund, L. Jorfeldt, D. H. Lewis, and S. Odman, “Skeletal muscle oxygen pressure fields in artificially ventilated, critically ill patients,” Acta Anaesthesiologica Scandinavica, vol. 24, no. 5, pp. 347–353, 1980.

[8] A. G. Tsai, P. Cabrales, R. M. Winslow, and M. Intaglietta, “Microvascular oxygen distribution in awake hamster window chamber model during hyperoxia,” American Journal of Physiology, vol. 285, no. 4, pp. H1537–H1545, 2003.

[9] C. K. Chapler, S. M. Cain, and W. N. Stainsby, “The effects of hyperoxia on oxygen uptake during acute anemia,” Canadian Journal of Physiology and Pharmacology, vol. 62, no. 7, pp. 809–814, 1984.

[10] L. Becker, P. Schumacker, and D. P. Nelson, “Influence of FiO₂ on the relationship between oxygen delivery and uptake (VO₂) in the dog,” Federation Proceedings, vol. 44, no. 3, p. 2325, 1985.

[11] R. F. Lodato, “Decreased O₂ consumption and cardiac output during normobaric hyperoxia in conscious dogs,” Journal of Applied Physiology, vol. 67, no. 4, pp. 1551–1559, 1989.
[12] K. Reinhart, F. Bloos, F. König, B. Bredel, and L. Hannemann, “Reversible decrease of oxygen consumption by hyperoxia,” Chest, vol. 99, no. 3, pp. 690–694, 1991.

[13] K. Reinhart, C. D. Spies, A. Meier-Hellmann et al., “N-acetylcysteine preserves oxygen consumption and gastric mucosal pH during hyperoxic ventilation,” American Journal of Respiratory and Critical Care Medicine, vol. 151, no. 3 I, pp. 773–779, 1995.

[14] K. Reinhart, M. Specht, U. Fohring, O. Mayr, and K. Eyrich, “Preoxygenation decreases whole-body oxygen consumption,” Anaesthesia, vol. 38, no. 5, pp. 233–237, 1989.

[15] G. I. Kemming, F. G. Meisner, M. Kleen, and O. P. Habler, “Calculation is unsuitable for determination of O2-consumption (VO2) in case of O2-supply-dependency,” European Journal of Medical Research, vol. 7, no. 4, pp. 139–148, 2002.

[16] P. J. Peyton and G. J. B. Robinson, “Measured pulmonary oxygen consumption: difference between systemic oxygen uptake measured by the reverse Fick method and indirect calorimetry in cardiac surgery,” Anaesthesia, vol. 60, no. 2, pp. 146–150, 2005.

[17] T. S. Walsh, P. Hopton, and A. Lee, “A comparison between the Fick method and indirect calorimetry for determining oxygen consumption in patients with fulminant hepatic failure,” Critical Care Medicine, vol. 26, no. 7, pp. 1200–1207, 1998.

[18] J. Carter and A. E. Jeukendrup, “Validity and reliability of three commercially available breath-by-breath respiratory systems,” European Journal of Applied Physiology, vol. 86, no. 5, pp. 435–441, 2002.

[19] J. S. Ultman and S. Bursztein, “Analysis of error in the determination of respiratory gas exchange at varying FI(O2);” Journal of Applied Physiology Respiratory Environmental and Exercise Physiology, vol. 50, no. 1, pp. 210–216, 1981.

[20] J. P. Archie, “Mathematic coupling of data. A common source of error,” Annals of Surgery, vol. 193, no. 3, pp. 296–303, 1981.

[21] C. G. Vermeij, B. W. A. Feenstra, and H. A. Bruining, “Oxygen delivery and oxygen uptake in postoperative and septic patients,” Chest, vol. 98, no. 2, pp. 415–420, 1990.

[22] M. N. Smithies, B. Royston, K. Makita, K. Konieczko, and J. F. Nunn, “Comparison of oxygen consumption measurements: indirect calorimetry versus the reversed Fick method,” Critical Care Medicine, vol. 19, no. 11, pp. 1401–1406, 1991.

[23] Z. Bak, F. Sjöberg, A. Rousseau, I. Steinwall, and B. Janerot-Sjöberg, “Human cardiovascular dose-response to supplemental oxygen,” Acta Physiologica, vol. 191, no. 1, pp. 15–24, 2007.

[24] A. Rousseau, Z. Bak, B. Janerot-Sjöberg, and F. Sjöberg, “Acute hyperoxaemia-induced effects on regional blood flow, oxygen consumption and central circulation in man,” Acta Physiologica Scandinavica, vol. 183, no. 3, pp. 231–240, 2005.

[25] W. Ganz, R. Donoso, H. Marcus, and H. J. Swan, “Coronary hemodynamics and myocardial oxygen metabolism during oxygen breathing in patients with and without coronary artery disease,” Circulation, vol. 45, no. 4, pp. 763–768, 1972.

[26] P. May, “Immediate action of oxygen on ventilation in normal man,” Helvetica Physiologica et Pharmacologica Acta, vol. 15, no. 2, pp. 230–240, 1957.

[27] N. Shock and M. Soley, “Effect of breathing pure oxygen on respiratory volume in humans,” Proceedings of the Society for Experimental Biology and Medicine, no. 44, pp. 418–420, 1940.

[28] I. L. Cohen, F. M. Sheikh, R. J. Perkins, P. J. Feustel, and E. D. Foster, “Effect of hemorrhagic shock and reperfusion on the respiratory quotient in swine,” Critical Care Medicine, vol. 23, no. 3, pp. 545–552, 1995.

[29] N. S. Chandel and G. R. S. Budinger, “The cellular basis for diverse responses to oxygen,” Free Radical Biology and Medicine, vol. 42, no. 2, pp. 165–174, 2007.

[30] W. G. Schoonen, A. H. Wanamarta, J. M. van der Klei-van Moorsel, C. Jakobs, and H. Joenje, “Respiratory failure and stimulation of glycolysis in Chinese hamster ovary cells exposed to normobaric hyperoxia,” Journal of Biological Chemistry, vol. 265, no. 19, pp. 1118–1124, 1990.

[31] P. R. Gardner, D. D. H. Nguyen, and C. W. White, “Aconitase is a sensitive and critical target of oxygen poisoning in cultured mammalian cells and in rat lungs,” Proceedings of the National Academy of Sciences of the United States of America, vol. 91, no. 25, pp. 12248–12252, 1994.

[32] S. K. Koerner, “Oxygen in ischemic heart disease,” American Heart Journal, vol. 82, no. 2, pp. 269–274, 1971.

[33] J. Meier, G. I. Kemming, H. Kisch-Wedel, J. Blum, A. Pape, and O. P. Habler, “Hyperoxic ventilation reduces six-hour mortality after partial fluid resuscitation from hemorrhagic shock,” Shock, vol. 22, no. 3, pp. 240–247, 2004.

[34] J. Meier, G. I. Kemming, H. Kisch-Wedel, S. Wölkkhammer, and O. P. Habler, “Hyperoxic ventilation reduces 6-hour mortality at the critical hemoglobin concentration,” Anesthesiology, vol. 100, no. 1, pp. 70–76, 2004.

[35] O. Habler and K. Meßmer, “Hyperoxaemia in extreme haemodilution,” British Journal of Anaesthesia, vol. 81, 1, pp. 79–82, 1998.

[36] C. Spies, C. Giese, A. Meier-Hellmann et al., “Influence of prophylactic administration of N-acetylcysteine on the clinical indicators of tissue oxygenation during hyperoxic ventilation in cardiac risk patients,” Anaesthesist, vol. 45, no. 4, pp. 343–350, 1996.