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Room air resuscitation—two decades of neonatal research

Ola Didrik Saugstad*

Department of Pediatric, Research Rikshospitalet, University of Oslo, 0027 Oslo, Norway

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Abstract Experimental as well as clinical studies have demonstrated that room air is as efficient as pure oxygen for newborn resuscitation. Recent data even indicate that outcome is improved if pure oxygen is avoided. Thus, in a meta-analysis, neonatal mortality was significantly lower in those newly born infants resuscitated with 21% than with 100% oxygen. Short-term recovery is also improved in the room air group since time to first breath is shorter, heart rate at 90 s and 5 min Apgar score are higher.

Animal data indicate that injury in a number of organs, including the brain, is aggravated by giving pure oxygen to newly born depressed infants even for a brief period. Although the optimal oxygen concentration probably is not known for newborn infants in need of resuscitation, pure oxygen should be avoided. These data should be reflected in new guidelines that are under way.

1. Background

In 1973, I started as a Research Fellow at the Perinatal Research Lab, Department of Pediatrics, The University Hospital of Uppsala, Sweden and was given the task from my supervisor, Gosta Rooth, to investigate whether purine metabolites could be used as indicators of birth asphyxia. Since these are breakdown products from ATP, they also could reflect the intracellular energy status. At that time, we believed that, more or less, all children developing cerebral palsy also had suffered birth asphyxia. Accordingly, we also believed a biochemical "Apgar Score" in the umbilical cord blood could be used as means to pick out immediately after birth those who eventually developed CP. Today, we know this is not the case, a biochemical method alone probably never can fully identify those who develop brain injury or not.

After having studied my textbooks of biochemistry, I decided to concentrate on the metabolite hypoxanthine. This seemed to be the perfect choice since its normal level is very low and more importantly, it is the end product of ATP catabolism in most tissues of man. Furthermore, it needs oxygen to be converted to uric acid via xanthine. However, this metabolite was not possible to measure in blood at that time in reasonable blood

* Tel.: +47 23072790; fax: +47 23072780.
E-mail address: o.d.saugstad@medisin.uio.no.

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volumes. I was therefore strongly warned by some chemists to use time and effort on this metabolite. Hypoxanthine was according to them not possible to measure in newborns. But by the help of Rooth, I developed a new simple, cheap and inexpensive method to determine hypoxanthine by measuring the oxygen consumption when hypoxanthine was converted to uric acid in the presence of xanthine oxidase [1]. I was able, for the first time, to measure hypoxantine in newborn blood and demonstrated that hypoxanthine indeed is augmented not only after intrauterine hypoxia but hypoxia from other reasons as well.

It was known from the 1960s by studies in isolated organs, as the kidney and myocardium, that all purine metabolites are elevated during ischemia and I soon came across this literature [2,3]. But thanks to the new and easy method that required low volumes of blood, I was the first that measured hypoxanthine in a whole organism and consecutively followed the development of hypoxanthine during different pathophysiological conditions. Although not yet being used in the routine, together with several other investigators in this field, I still believe it is the superior biochemical indicator of hypoxia—since it reflects the intracellular energy status closely [4,5].

2. Hypoxanthine as a free radical generator

Fridovich and McCord [6,7] had described hypoxanthine and xanthine in relation to generation of free radicals. We knew from our own studies that the hypoxanthine concentration is high in blood and other body fluids during hypoxia [8,9] and further increases exponentially in blood during resuscitation, due to release from the periphery into the bloodstream [9]. We also knew from Fridovich's studies that superoxide radical production is proportional with the oxygen concentration present, at least in vitro conditions [7]. Therefore, at the end of the 1970s, we assumed that the rate of oxygen radical generation when hypoxanthine is converted to uric acid in the presence of xanthine oxidase could explode during the reoxygenation period and especially if high oxygen concentrations were given. Could we have found the solution of the so-called "oxygen paradox"? This phenomenon had been known for decades and described the paradoxical finding that cell and tissue injury are enhanced if hypoxic tissue is supplemented with high oxygen concentrations. We submitted our concept; however, no important American journals had been interested in our work, so in 1980, it was published in a European journal [10]. Here, we suggested that oxygen free radicals produced by the hypoxanthine—xanthine oxidase system might trigger injury in the reoxygenation period. In this same article, we, for the first time, also suggested that resuscitation perhaps should not be carried out with 100% oxygen since this might be toxic.

A year later, McCord's group published a similar hypothesis without giving a single reference to our work [11]. In 1985, I wrote a review article in Pediatric Pulmonology [12] in which these mechanisms of hypoxia reoxygenation injury were described in more detail. That same year, McCord [13] wrote a similar review article in New England Journal of Medicine in which the mechanism we had described 5 years earlier was attributed as the mechanism for so-called ischemia reperfusion injury. Still, no references to our work and ideas were given. Some years later, I introduced a hypothesis that free radicals inflict injury of several organs of the newborn [14].

3. Experimental studies

At the end of the 1980, we started experiments resuscitating young and subsequently newborn hypoxic piglets with room air or pure oxygen.

We found that regarding basic biochemical and physiological variables, restoration after hypoxia was just as quick with reoxygenation with room air as with pure oxygen. The brain injury assessed by histology did not reveal any difference either [15,16]. However, the production of H_2O_2 in leukocytes from the brain circulation was higher in those resuscitated with 100% than 21% oxygen. In fact, no increase at all could be found in those given ambient air [17]. This finding was in accordance with a study by Kondo et al. [18]. Temesvari's group could then demonstrate that piglets with pneumothorax-induced asphyxia had a better short term neurological outcome than animals resuscitated with 100% oxygen [19]. This was in accordance with a study in adult dogs resuscitated after cardiac arrest [20].

It has been argued that pure oxygen is needed for resuscitation of newborn infants to reduce the pulmonary blood pressure adequately. However, to my knowledge, no studies have checked whether pure oxygen reduces the pulmonary pressure faster than ambient air. In experimental series in hypoxic newborn piglets, we have been able to show that pulmonary pressure decreases at exactly the same rate whether 21% or 100% O_2 is used for reoxygenation [21].