Pharmacological effects of nitric oxide in extracorporeal membrane oxygenation

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Abstract

Nitric oxide (NO) is a gas that has potent vasodilator properties. It can be administered via inhalation in situations where NO production is impaired, and results in vasodilatation of the pulmonary capillaries. Extracorporeal membrane oxygenation (ECMO), a technique for providing life support to patients with cardiac and/or respiratory dysfunction, allows the heart and lungs to rest. Inhaled NO (INO) therapy reduces the need for ECMO in hypoxemic respiratory failure and persistent pulmonary hypertension (PPHN) in neonates; it is now the standard of care for this population. Our review will focus on the role of INO as an anti-inflammatory agent and vasodilator in various respiratory and cardiac diseases as well as its effect on the use of ECMO in term and premature infants.

Key words: nitric oxide, extracorporeal membrane oxygenation, pulmonary hypertension.

Streszczenie

Tlenek azotu (NO) jest gazem o silnych właściwościach wazodylatacyjnych. Gdy produkcja NO jest upośledzona, można go podawać wziewnie, co powoduje rozszerzenie kapilar płucnych. Natlenianie pozaustrojowe (ECMO) jest metodą leczenia stosowaną u chorych z niewydolnością serca i/lub układu oddechowego, pozwalającą na odciążenie serca i płuc. Terapia inhalacją NO (INO) zmniejsza u noworodków potrzebę stosowania ECMO w wypadku niewydolności oddechowej i utrwalonego nadciśnienia płucnego (PPHN) i jest obecnie standardem opieki dla tej populacji chorych. Nasza praca koncentruje się na roli INO jako czynnika antyzapalnego i wazodylatacyjnego w chorobach układu krążenia i oddechowego, a także jego wpływu na stosowanie ECMO u wcześniaków.

Słowa kluczowe: tlenek azotu, natlenienie pozaustrojowe, nadciśnienie płucne.

Introduction

ECMO is an important treatment for infants and children with cardio-respiratory failure [1]. ECMO is the use of an artificial lung located outside the body that puts oxygen into the blood and then carries it to body tissues. It is employed in patients who have reversible cardiopulmonary failure attributed to pulmonary, cardiac or other disease [2]. Physiologically, blood is drained from the patient to the external pump which pushes it through a membrane gas exchanger and warmer then returns it to the patient circulation. The goal of ECMO is to support tissue oxygenation in infants with severe respiratory failure due to reversible pulmonary disease [3, 4]. More recently it has also been demonstrated that ECMO plays a significant role in the neurodevelopment of infants after cardiac surgery [5]. ECMO can be either:

1. Veno-arterial (VA), in which blood is drained from the right atrium (via a right internal jugular venous catheter) and returned to the thoracic aorta (via a right carotid arterial catheter). VA ECMO supports the heart and lungs; or
2. Veno-venous (VV), in which blood is drained from the right atrium (via the side holes of a double lumen catheter) and returned to the right atrium through the end hole of the catheter which is directed towards the tricuspid valve. VV ECMO is used for lung support only. This type of ECMO requires only one catheter to be surgically placed through the right side of the neck.

ECMO selection criteria vary among ECMO centres. These criteria should determine whether the risk of severe morbidity or mortality without ECMO treatment is greater than the risk of ECMO. Typically, this involves examining arterial oxygenation in relation to the degree of respiratory support. Because of the potential risks of ECMO, criteria have been designed to select patients with high predicted mortality under conventional therapy.

ECMO indications are:

- Hypoxemic respiratory failure [6].
- PPHN [7].
- Pulmonary hypoplasia.

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- Congenital diaphragmatic hernia [8, 9].
- Meconium aspiration syndrome (MAS) [10].
- Respiratory distress syndrome (RDS) [11].
- Severe surfactant deficiency disease.
- Severe air leak syndrome [9].
- Sepsis (B hemolytic streptococcus group B pneumonitis).
- Congenital heart lesion.

ECMO contraindications are:

- The presence of significant intracranial hemorrhage.
- Uncontrolled bleeding in other locations.
- Significant central nervous system of the congenital anomalies.
- Pulmonary disease that is not likely to be reversible. This criterion is applied as the risk of hemorrhagic and other complications increases with longer ECMO runs.

The role of INO administration in ECMO applications

NO

NO, produced by most cells of the body, is an unstable radical which reacts rapidly with other molecules, particularly superoxide. It is endogenously produced by NO synthases which transform arginine into NO and L-citrulline. NO can modulate the action of several molecules by nitrosylation or nitration of residues [12].

The effect of NO in the cardiovascular system has been the most studied, as it controls vascular tone and myocardial contractility, flow distribution and blood pressure [13]. In the central and peripheral nervous system, NO is considered a neuromodulator or neurotransmitter which is released after synaptic transmission. NO can interact with pre- and postsynaptic processes, altering neurotransmitter release and receptor action. It binds with very high affinity to haemoglobin, which is both a scavenger and a carrier of the NO molecule [14].

Since it is a gas, NO can be administered through the lungs. INO has been considered for a long time as a selective pulmonary vasodilator which improves oxygenation and decreases pulmonary pressure independently of endothelial cell function. Therefore, it has been employed in the preoperative, perioperative, and postoperative assessment of pulmonary hypertension. INO improves oxygenation without clinically significant effects on cardiac output and systemic pressure, making it an ideal treatment for patients suffering from respiratory failure and RDS [15-19].

ECMO and inflammation

ECMO and cardiopulmonary bypass (CPB) induce a systemic inflammatory response that may result in numerous changes, ranging from mild pulmonary dysfunction to multisystem organ failure (fig. 1). This leads to acute lung injury (ALI), and neurological and cognitive dysfunction in the brain. INO might be one of the strategies that can counteract the deleterious effect of surgery by attenuating the inflammatory response.

Modulation of inflammation by INO or NO added to the gas mixture ventilating ECMO or CPB machines can prevent or decrease inflammation that affects many organs in the body. A systemic inflammatory response associated with CPB results in the release of inflammatory mediators, such as interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α). We have demonstrated that INO can prevent the systemic and pulmonary inflammation induced by CPB with cardioplegic cardiac arrest in a pig model [20, 21]. These studies have shown that INO delivered early and at a low dose of 20 parts per million (ppm) decreases inflammation by reducing cytokine synthesis such as IL-8 and inhibiting both neutrophil activation and migration into the alveolar spaces. INO also exhibited a pro-apoptotic role in our pig model. Indeed, INO promotes apoptosis in inflammatory conditions. Increasing apoptosis could be one of the mechanisms by which INO removes inflammatory cells and avoids damage to surrounding tissues. Attenuation of the inflammatory response observed after INO administration indicates its beneficial role after CPB in animal models [22].

The importance of metalloproteinases (MMP-2 and -9) in an animal model of CPB-induced ALI was demonstrated when all pathological changes typical of ALI after CPB were prevented by using chemically modified tetracycline, a potent MMP and elastase inhibitor [23]. We have found that after CPB in pig, the pre-emptive, continuous administration of INO suppresses the rise of plasma MMP-2 and MMP-9 activity and IL-8 related to the inflammatory

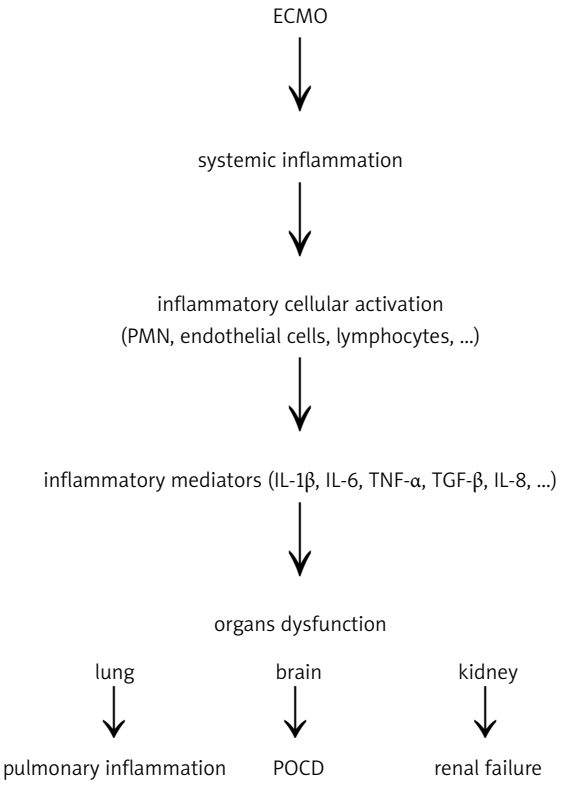

Fig. 1.

reaction [24]. Our data have confirmed the previous result reported by Cheung et al. that INO inhibits the release of MMP-2 during ECMO in adult rabbits [25].

Briefly, the mechanism of NO inhalation attenuating the inflammatory process in the lungs is associated with decreased pulmonary neutrophil and platelet sequestration in animal models of ALI and reduced secretion of oxidative substances by neutrophils during ALI, suggesting that the deleterious effects induced by neutrophils could be diminished [26-31]. In addition, INO can also inhibit the inflammatory response by decreasing cytokine synthesis and inactivating nuclear factor kappa-B and by suppressing the expression of adhesion molecules, preventing neutrophil adhesion and migration [32-34]. Furthermore, in chronically-ventilated preterm lambs with chronic lung disease, INO preserves lung structure and function and enhances alveolar development [35].

INO therapy at a dose of 20 ppm reduces the need for ECMO in term newborns with hypoxemic respiratory failure, PPHN, and infants with severe experimental RDS. Human studies on term infants with respiratory failure have confirmed the beneficial effect of INO in improving oxygenation and reducing pulmonary vascular resistance without concomitant deleterious side effects, which may include pulmonary toxicity, methemoglobinemia and bleeding disorders. Jacobson J and others have indicated that it may be beneficial to add NO to the sweep gas to decrease platelet loss, platelet damage, postoperative bleeding, and the need for postoperative blood transfusions [36-41].

Neurocognitive dysfunction is a common complication of cardiac surgery with CPB. Cognitive changes involving memory, executive functions, and motor speed occur during the first few days to weeks after CPB, while late cognitive decline occurs between 1 and 5 years after surgery. A previous study has shown the presence of both neurological and neurocognitive impairment in a rodent recovery model of CPB similar to that commonly observed in humans subjected to the procedure [42]. Brain imaging with functional magnetic nuclear resonance or single photon-emitting computerized tomography has disclosed brain swelling with reduced regional blood flow and a decreased neuronal cell population after CPB [43]. In our lab we are conducting basic and clinical research in postoperative cognitive disorders (POCD) after CPB, and we suggest that INO may prevent POCD if INO is given during surgery [44]. The mechanism postulated is that CPB causes systemic inflammation that leads to brain inflammation and induces proinflammatory cytokine release (IL-1, IL-6, and TNF-α). INO might attenuate brain inflammation via the reduction of elevated proinflammatory cytokines level. A recent study by Mestan et al. found that premature infants treated with INO showed improved neurodevelopmental outcomes at two years of age [45].

All the anti-inflammatory effects of pre-emptive INO in our animal model of CPB have translated into beneficial effects on cardiopulmonary parameters. However, INO did not counteract CPB-induced alterations in lung mechanics (thoraco-pulmonary compliance and airway pressure), despite an interesting initial action on surfactant components [46]. If the above observations are confirmed by clinical trials, prophylactic INO at non-toxic concentrations could be an excellent medication reducing the excessive inflammatory response that follows CPB.

Conclusion

Wider application of INO therapy and improved ventilation strategies have led to a decrease in the need for invasive, life-sustaining therapies such as ECMO. Fewer patients with PPHN, MAS, RDS, or sepsis are requiring ECMO support than in the past. Many attribute this decline to the newer respiratory therapies, mainly surfactant, high-frequency oscillatory ventilation, and INO. It is clear that the mechanism by which INO leads to inflammation resolution remains to be clarified, and additional investigations are needed to discover if weaning from INO will cause rebound inflammation. Further research will help us to understand the mechanism of INO therapy in various cardiovascular and respiratory diseases.

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Komentarz

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This is a very interesting, well--balanced and up-to-date minireview describing the effects of inhaled nitric oxide (INO) in ECMO. Dr. Blaise's group has been championing for some time now the use of INO to limit thrombotic and inflammatory complications of ECMO, thus improving the clinical outcome of this procedure.

Although the beneficial effects of NO on circuit surface--induced platelet activation has been known for some time now, there is new evidence that the pharmacological profile of INO could also include some inflammation-regulating actions. Whether or not these effects of INO will translate into clear-cut clinical benefit for critically-ill patients remains to be demonstrated. As rightly pointed out by the Authors more basic and clinical research is needed to compile the portfolio of pharmacological and therapeutic indications and counter indications for INO in ECMO and other life-sustaining therapies.