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Mini Review

Therapeutic Role of Nitroglycerin: Treatment and Preservation Endothelial Dysfunction in the Perioperative and ICU Settings in High Risk Patients

Duraiyah Thangathurai[1]* and Elizabeth Hong[2]

[1]Professor of Clinical Anesthesiology, Surgery and Urology, Director of Department Development, Department of Anesthesiology, University of Southern California, LA, CA, USA

[2]Assistant Professor Clinical Anesthesiology, LAC/USC Medical Center, LA, CA, USA

***Corresponding Author:** Duraiyah Thangathurai, Professor of Clinical Anesthesiology, Surgery and Urology, Director of Department Development, Department of Anesthesiology, University of Southern California, LA, CA, USA.

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Abstract

Nitroglycerine (NTG) and other nitric oxide donors (NO) play a key role in maintaining endothelial function thereby improving microcirculation of the tissues, including vital organs. There are several mechanisms of actions including improvement of the integrity the of endothelial system, and expansion of intravascular volume, resulting increased perfusion, and minimizing the release and the effect of inflammatory mediators including cytokines. Historically nitroglycerine, has been used to improve coronary circulation in patients with angina. Recent studies show it is useful in protecting all the vital organs. In addition to the benefit in angina, it is also useful in heart failure. It improves diastolic dysfunction, lowers pulmonary artery pressures, and improves right heart failure. It is helpful to maintain integrity of the pulmonary endothelium and prevent ARDS related complications. Additionally, nitroglycerin also improves rheology of red cells and decrease viscosity (improving deformability) and improve the microcirculatory flow. This is beneficial in hyper viscosity conditions, hemoglobinopathies such as sickle cell anemia, and similar disorders. Storage of blood is associated with increased deformity of red cells, decreased flexibility increased viscosity, changes in rheology, causing resistance to capillary blood flow. Deformed red cells are more susceptible to hemolysis. Nitroglycerine improves cerebral oxygenation, and increase mixed venous oxygen values, probably from increasing the capacity of whole microcirculatory system.

Keywords: *Nitroglycerin; Endothelium; eNOS; Mitochondria; Nitric Oxide (NO)*

Introduction

Nitroglycerin is a commonly used drug that has been in use for more than a century. It was initially used as a sublingual medication as a coronary dilator to treat angina and congestive heart failure. Many new vasodilator medications have become available which include direct acting arterial vasodilators such as hydralazine, nitroprusside, minoxidil, papaverine, phosphodiesterase inhibitors, autonomic ganglion blockers, pentolinium, trimetaphan, calcium channel blockers, diltiazem, verapamil, ARBs, and ACE-inhibitors. These drugs are useful for hypertensive situations, both acute and chronic. Most of the above medications act primarily on arterioles by directly causing

vasodilation of vascular smooth muscles. In the last two decades more research has been done on the endothelium of the circulatory system. It is considered a vast organ that helps oxygenate and nourish each and every cell of human body. This paper will review the effects of nitroglycerin as a vasodilator, a nitric oxide (NO) donor, and an also an upholder of endothelial integrity [1].

History of nitroglycerin

Chemist Ascanio Sobrero first prepared nitroglycerin in 1846 at the University of Turin. Alfred Nobel then popularized the use as an explosive, namely dynamite, used in mining, demolition, and construction industries [2]. William Murrel later introduced it in 1876 for medical use for anginal attacks [2]. More than a century later, three American scientists, Robert F. Furchgott, Louis J Ignarro, and Ferid Murad, were awarded the Nobel Prize in 1998 for their discoveries, "the nitric oxide as a signaling molecule in the cardiovascular system" [3,22].

Endothelium

The endothelium is made up of a single layer of cells, highly dynamic, involved actively numerous vital cardiovascular physiologic functions, that form a barrier between blood and tissues. It regulates exchanges between the blood stream and surrounding tissues. It is also an important source of vasoactive substances that modulate the blood pressure, vascular tone and organ perfusion. An adult human is composed approximate 10^{12} endothelial cells that weighs 100 -120 grams and covers a surface area about 1000^{2} meter [2]. The endothelium is also heavily involved in coagulation, fibrinolysis and immunologic processes [4]. Any insult/injury to the endothelium leads to endothelial dysfunction and interferes with the production of these vasoactive substances leading to acute inflammation, increasing the permeability and third spacing. Eventually, this leads to chronic inflammation and ischemic injury to the vascular system and vital organs. This review focuses on the risk of endothelial dysfunction and the role of nitric oxide donors, namely nitroglycerin, and their effects on preventing and improving endothelial dysfunction.

Physiology/pathophysiology

Nitric oxide is synthesized from an amino acid, L-arginine, by Nitric oxide synthase (NOS) [5]. There are three different isoforms of NOS but the two more commonly seen are endothelial NOS (eNOS) and inducible NOS (iNOS). eNOS is expressed in the endothelium and iNOS can be expressed during various conditions such as inflammation and sepsis due to the expression of mediators such as cytokines and endotoxins [5]. Neuronal nitric oxide nNOS produced in the nervous system. It is expressed in the central nervous system and plays a key role in maintaining synaptic plasticity and neural protection and excess nNOS may be harmful [4,6]. The production of NOS plays a critical role in the integrity of the endothelial border.

Endothelial dysfunction and inflammation

There are many causes of endothelial dysfunction but a state of reduced NO synthesis and function is often observed in many cardiovascular diseases [12]. Reduced NO bioavailability can be due to decreased L-arginine availability, the phosphorylation of eNOS, and increased NO scavenging by reactive oxygen species (ROS) made by NADPH and xanthine oxidases [6]. In response to injury or insult, endothelial cells also produce pro-inflammatory and immune mediators. These inflammatory mediators increase endothelial permeability, promote the aggregation and adhesion of leukocytes, and facilitate interactions between chemokine receptors and the transendothelial migration of leukocytes to inflamed tissues [7]. Inflammation often times leads to reduce NO bioavailability.

In large blood vessels, viscosity of blood plays a minor role in total resistance, but rather vascular resistance is the main determinant. In smaller blood vessels viscosity can increase to 6 - 7 fold at the capillary level [5]. The effects of vascular resistance and viscosity can be compounded, that even small changes in viscosity can make large differences in total resistance. *In vitro* studies have proven that NO can directly affect erythrocyte distensibility and deformability [20]. NO donors, specifically nitroglycerin, have been shown in hepatic studies to increase oxygen release from the endothelium without increasing flow. Erythrocytes are also now thought to have a more integral role

in the metabolism of NO. They are thought to facilitate NO-related signaling through the activity of S-nitrosothiols (SNOs), which produce NO synthase products with bioactivity far from the site of synthesis. NO leads to vascular smooth muscle relaxation by binding to guanylate cyclase and converting guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP) [5]. Chronic inhibition of NOS has been shown to profoundly reduce RBC deformability in rats leading to diminished flow at the capillary level [8,18]. This suggests that NO plays a significant role in microcirculatory flow of RBCs [19,20].

Endothelial dysfunction can further the progression of several disease states including but not limited to insulin resistance and diabetes mellitus, hypertension, pulmonary hypertension, chronic kidney disease (CKD), and sepsis. Duplain., *et al*. demonstrated that mice without the eNOS gene had increased rates of insulin resistance, hypertension, and hyperlipidemia [9]. Hyperglycemia is known to increase the production or ROS through activated kinase-C mediated NADPH oxidases, which subsequently leads to a reduction in NO availability [10]. In patients with essential hypertension, endothelium-dependent vasodilation to acetylcholine and bradykinin are impaired at least in part to reduce NO activity which can also be linked to a L-arginine deficiency, and eNOS uncoupling due to oxidation [11,12]. Reduced NO availability may not necessarily be the inciting event to endothelial dysfunction in these states; however, it plays a crucial role in the progression of these diseases. Moreover, endothelial dysfunction has been long linked to CKD. The early mechanisms involve a reduction in NO synthesis and availability due to oxidative stress and inhibition of eNOS [12]. Evidence demonstrates that these changes become less reversible in the later stages of CKD likely due to a massive reduction in uptake of L-arginine, and reduced production of NO [14,25]. Lastly, it is widely known that sepsis is associated with severe endothelial cell dysfunction, which leads to widespread dysregulation of vascular reactivity, in addition to tissue edema [8]. Endothelial dysfunction is fundamental to the progression of sepsis leading to organ failure. Nitric oxide also stimulates mitochondrial biogenesis and enhance formation of ATP [26]. Gao., *et al*. describe the docking of endothelial nitric oxide synthase (eNOS) to the mitochondrial outer membrane [27]. Reduced endothelial NOS activity and NO bioavailability, as the main factors underlying the endothelial dysfunction that occurs in metabolic syndrome [28].

The endothelium is an expansive organ that plays a crucial role in maintaining the intravascular space and providing oxygenation at the microcirculatory level. Any endothelial disruption leads to intravascular fluid migration into tissues and poor organ perfusion. Nitroglycerin and other NO donors should be used in many of the above-mentioned clinical states to help protect and maintain the endothelial barrier.

Therapeutic benefits of nitroglycerin

It is widely accepted that a reduction in NO availability leads to endothelial dysfunction and ultimately organ damage. Nitroglycerin is a medication that can help prevent and protect the endothelial integrity particularly in disease states such as ARDS and septic shock [23,24]. Liu., *et al*. studied the effects of nitroglycerin infusions of 0.5 - 1 mg/hr in patients with ARDS being treated for sepsis and a control group receiving standard treatment [15]. They found that time of mechanical ventilation, ICU and hospital stays were respectively lower in the nitroglycerin group as opposed to the control group. They concluded that nitroglycerin infusions could reduce the resistance in pulmonary circulation, help mitigate systemic inflammatory reactions, and enhance immunity by improving the microcirculation [15]. The use and benefit of nitroglycerin and nitrates in cardiovascular disease is also well known. It is particularly useful in patients with diastolic heart failure as it increases the speed of isovolumic relaxation and improves left ventricular relaxation [16]. Low dose of nitroglycerin has been used to improve microcirculation in hospitalized patients with acute failure [31]. Lima., *et al*. found nitroglycerin was a useful agent to improve poor peripheral perfusion in patients with circulatory shock [32]. Nitroglycerin may be useful to minimize the negative effects of cytokines, chemokines and acidosis in patients receiving massive transfusions of blood products. In our study Mikhail., *et al*. observed increased blood flow of coronary arteries velocity, during controlled hypotensive anesthesia with intravenous nitroglycerin. Intravenous nitroglycerine increases cerebral oximetry values [29]. In our institution Van Noord., *et al*. had observed with use of nitroglycerin was associated will increase cerebral oximetry values [30]. Kawashima., *et al*. demonstrated the protective effect of nitroglycerin from ischemia from reperfusion lung injury [33].

Van Manen., *et al*. studied of effect of red blood cell transfusion on inflammation, endothelial cell activation and coagulation in the critically ill. He observed the antigen levels of vWF (one mg) antigen levels in critically ill patients who received red blood cell blood transfusion and in a control group who did not receive a transfusion [17]. The group that received blood transfusions was noted to have increased levels of vWF antigens. This antigen is a known endothelial activator and increases occurrences of adverse events such as third spacing [17].

Healthy red blood cells (RBCs) deform readily in response to shear stress in the circulation, facilitating their efficient passage. In diseases including sickle cell anemia and other hemoglobin conditions including blood banking storage, these adaptive functions may be compromised resulting in limited RBC deformability, resulting in impairment of blood flow to vital organs [34]. Primary or secondary defects in RBC impair the ability of the RBC to flow freely in the microcirculatory system. Nitroglycerin is a useful drug as nitric oxide donor to maintain RBC deformability, and helpful to improve microvascular perfusion [34].

Conclusion

In conclusion, the endothelium is an expansive organ that plays a crucial role in maintaining the intravascular volume and providing oxygenation at the microcirculatory. Nitroglycerine and other nitric oxide donors are useful to improve endothelial function thereby increasing the microcirculation in high-risk patients in the perioperative period and ICU settings.

Disclosure

We believe these findings will be of interest to the readers of your journal. We declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We have no conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome. As corresponding author, I confirm that the manuscript has been read and approved for submission by all the named authors.

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