Oxygen kinetics, oxidative stress, and cardiac autonomic function in type 2 diabetes mellitus: Is nitric oxide the connecting link?

Shalini Verma, Email:shaliniverma3001@gmail.com

Jamia Millia Islamia, India

Abstract

Type 2 diabetes mellitus (T2DM) is a multi-faceted metabolic disorder associated with a spectrum of complications, such as the commonly overlooked- cardiac autonomic neuropathy. Additionally, oxidative stress is increased in diabetes and may be linked to the development of chronic complications. T2DM is also shown to blunt the oxygen uptake kinetics, implying impairment of the control of oxygen delivery to and/or utilization of oxygen by contracting muscles. Nitric oxide (NO) has been proposed as a common denominator in the molecular mechanisms underlying these manifestations; however its behavior in diabetics is still controversial. Purpose: The purpose of this study was to examine the correlation between levels of nitric oxide and oxygen uptake kinetics, antioxidant defense, and autonomic function in patients with type 2 diabetes. Methods: Sixty T2DM patients were assessed for plasma levels of nitric oxide, oxygen uptake kinetics (time constant of steady state), antioxidant enzymes (catalase, superoxide dismutase), and cardiac autonomic function (heart rate variability). Results: Our results revealed that NO levels were correlated positively with τVO2 (r = 0.503), LFnu (r = 0.334), and LF: HF ratio (r = 0.270), and negatively with CAT (r = -0.456), AvgNN (r = -0.384), RMSSD (r = -0.323), and pRR50 (r = -0.353). Conclusion: Nitric oxide levels showed a negative correlation with antioxidant enzymes, oxygen uptake kinetics, and vagal indices of heart rate variability. These results are contradictory to the previously proposed protective effects of nitric oxide.

Nitric oxide (NO) may be a small radical with critical signaling roles in physiology and pathophysiology. The generation of sufficient NO levels to manage the resistance of the blood vessels and hence the upkeep of adequate blood flow is critical to the healthy performance of the vasculature. A novel paradigm indicates that classical NO synthesis by dedicated NO synthases is supplemented by nitrite reduction pathways under hypoxia. At an equivalent time, reactive oxygen species (ROS), which include superoxide and peroxide , are produced within the system for signaling purposes, as effectors of the immune reaction , or as byproducts of cellular metabolism. NO and ROS are often generated by distinct enzymes or by an equivalent enzyme through alternate reduction and oxidation processes. The latter oxidoreductase systems include NO synthases, molybdopterin enzymes, and hemoglobins, which may form superoxide by reduction of molecular oxygen or NO by reduction of inorganic nitrite. Enzymatic uncoupling, changes in oxygen tension, and therefore the concentration of coenzymes and reductants can modulate the NO/ROS production from these oxidoreductases and determine the redox balance in health and disease. The dysregulation of the mechanisms involved within the generation of NO and ROS is a crucial explanation for disorder and target for therapy. In this review we will present the biology of NO and ROS in the cardiovascular system, with special emphasis on their routes of formation and regulation, as well as the therapeutic challenges and opportunities for the management of NO and ROS in disorder.

Nitric oxide (NO) may be a small radical molecule with critical signaling roles. The discovery of the function of NO within the vascular endothelium as endothelium-derived relaxing factor led to the awarding of the 1998 Nobel prize to Drs. Furchgott, Ignarro and Murad (36, 324, 449, 491, 716). The functions of NO in mammalian systems extend beyond vascular signaling and are relevant altogether organ systems, including but not limited to neuronal signaling, and host defense (448, 659, 738). A number of oxygen-related species of high chemical reactivity are mentioned as reactive oxygen species (ROS). These include oxygen radicals and peroxides, like superoxide (O2•−) and peroxide (H2O2), nitrogen radical species, like NO and dioxide (NO2•), and other species, such as peroxynitrite (ONOO−) and hypochlorite (ClO−). The species containing nitrogen are often treated separately as reactive nitrogen species (RNS). It is worth indicating that despite being long considered toxic species, most of those molecules are shown to exert important signaling functions (249, 778, 937, 960). Therefore, the role of the many of those molecules in health and disease is said to their production rates, steady-state concentrations, and therefore the ability of the cellular antioxidant systems to modulate their

activity.

In general, dysregulated production of ROS/RNS, as is the case for NO, leads to oxidative stress and deleterious consequences for living systems. However, as acknowledged above, these molecules often have important signaling roles at low concentrations. For instance, the differences in response to NO at varying concentrations have attracted considerable attention. It has been shown that low levels (pM/nM) are physiological and associated with the activation of high affinity primary binding targets like soluble guanylyl cyclase (sGC) and cytochrome c oxidase (433, 863). An emerging paradigm proposes that intermediate levels (50–300 nM) can activate a variety of positive and negative responses from wound healing to oncogenic pathways (938). Higher concentrations of NO (>1 μM) can lead not only to oxidative stress but also nitrative and nitrosative stress via the generation of peroxynitrite and nitrosating species (411, 412, 938, 939), and together with oxygen, can trigger posttranslational modification of proteins, lipids, and DNA (277, 433, 938)..

Biography :

Shalini Verma is currently a PhD Research Scholar (Exercise Physiology). Her Doctoral work is focused on the compromised oxygen uptake kinetics, elevated oxidative stress, and autonomic dysfunction in patients with type 2 diabetes and the effect of exercise on the same. She has been a part of the Diabetes Research Group exploring the role of physical activity in prevention and management of diabetic complications. With previous research work in exercise-induced muscle damage, and cardiovascular and neuromuscular physiology, she has over 15 papers in reputed journals. Her research interests include metabolic syndrome and physical activity, cardiovascular and pulmonary complications in type 2 diabetes, autonomic dysfunction, and oxygen uptake kinetics in healthy vs. diseased.

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