The Role of Nitric Oxide Insufficiency In Aging & Disease

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Over the past ten years despite a slight increase in life expectancy and a decrease in all causes of deaths, the percent of the US population with heart disease, cancer, diabetes, hypertension and obesity have all increased. According to the 2010 National Center for Health Statistics Report life expectancy has increased 1.1 years over the past decade going from 76.8 to 77.9 [1]. All causes of death adjusted for age have decreased by 12.5% from 2000 to 2008. However, the percent of the population 18 years and over with heart disease has risen from 10.9% to 11.8% and the population 65 and over has risen from 29.6% to 31.7% over the same 8 years. Diabetes has gone from 8.5% of the population 20 years and older to 11.9% in just 8 years. The percent of people with hypertension has risen from 28.9% to 32.6%. Cancer has followed a similar trend going from 4.9% to 6.1% in patients 18 years old and over [1]. These data suggests that although people are living longer, they are not living better or they are living with a chronic disease that requires care and treatment. It is the care and treatment of these chronic patients that causes the enormous economic burden on the health care system and on the patients. In fact from 2000 to 2008, total healthcare expenditures increased from $1.1 to $2.0 trillion dollars or from $4,032 to $6,411 per capita [1].

This trend is also reflective of the global population where 17.3 million people died from cardiovascular disease in 2008 and an estimated 23.6 million expect to die in 2030. Whereas access to medical care and better management of certain diseases have improved, it is clear that the incidence and treatment of chronic disease is not improving. The discovery of nitric oxide (NO) production in the human body is a relatively new advancement of modern medicine. Unfortunately is still not at the forefront of modern medicine. There are no standard laboratory measurements of NO in the clinical setting and no prescription therapies to safely and effectively restore NO homeostasis despite being recognized as the earliest indicator of a number of different chronic diseases. We also now know that modern medical practices and western lifestyles actually

lead to a decrease in NO homeostasis in the patients from pediatrics to geriatrics.

The discovery of nitric oxide (NO) in the 1980s as a vasodilator and signaling molecule in the cardiovascular system [2,3], immune system [4] and nervous system [5] marked a point of inflexion in medicine. The discovery that a simple molecule produced as a gas could perform so many essential and critical biological and physiological functions established a new paradigm in cell signaling. Now almost 30 years later, endothelial dysfunction or insufficient NO production is recognized as the earliest event in the onset and progression of a number of chronic diseases. Loss of endothelial NO function is associated with several cardiovascular disorders, including atherosclerosis, which is due either to decreased production or to increased degradation of NO [6]. A number of studies provide evidence that endothelial NO dysfunction is not only associated with all major cardiovascular risk factors, such as hyperlipidemia, diabetes, hypertension, smoking and severity of atherosclerosis, but also has a profound predictive value for the future atherosclerotic disease progression [7-10]. There is becoming a clear and convincing association with Alzheimers disease (AD) and NO. Decreased levels of nitrite and nitrate (NOx) has been detected in patients with different forms of dementia especially AD [11]. The exact etiology of sporadic AD is unclear, but it is interesting that cardiovascular risk factors including hypertension, hypercholesterolemia, diabetes mellitus, aging, and sedentary lifestyle are associated with higher incidence of AD [12] (all conditions associated with NO insufficiency). The link between cardiovascular risk factors and AD has yet to be identified; however, a common feature is endothelial dysfunction, specifically, decreased bioavailability of NO [13]. Insulin has vasodilator actions that depend on endothelium-derived NO [14]. Type 2 diabetes mellitus accounts for 80-90% of diabetes cases in the US and is associated with an increased risk for a number of life-threatening complications. These include heart disease and stroke, high blood pressure, blindness, kidney disease, nervous system disease, amputation, and complications of pregnancy and surgery. Probably not coincidental, all of the above complications are associated with insufficient NO production [15]. Endothelial dysfunction with reduced NO generation and bioavailability plays a key role in the pathogenesis of diabetic vascular disease and complications and likely serves as the key link between metabolic disorders and cardiovascular disease (CVD) [16].

While the medical literature is rich with clear association and almost causal relationships between NO and the onset and progression of chronic disease, it is not commonly considered in the treatment or

management of patients. In fact, some prescription medications will reduce NO availability, many lifestyle and dietary habits that lead to chronic disease are linked to insufficient NO production or availability and the standard of care for patients in intensive care units or hemodialysis patients leads to a complete removal of NO functionality in the patients.

Despite NO being recognized by the scientific and medical community as one of the most important molecules produced within the body and being named "Molecule of the Year" by *Science* in 1992 [17] and a Nobel Prize in Physiology or Medicine awarded for its discovery, there are currently only 3 FDA approved products on the market directly related to NO: 1) organic nitrates, such as nitroglycerin for the treatment of acute angina (these have been used for centuries long before the discovery of NO); 2) inhaled NO therapy for neonates for treatment of pulmonary hypertension due to underdeveloped lungs; and 3) phosphodiesterase inhibitors, such as sildenafil, which do not directly affect NO production but act through affecting the downstream second messenger of NO, cyclic guanosine monophosphate (cGMP). With the knowledge gained in the physiology and pharmacology of NO, better and new drugs are being designed not only for cardiovascular diseases but for neurological and several other disorders as well.

One of the most predictive indicators for insufficient NO production is age. As we age we lose our ability to produce NO through the L-arginine pathway. Aging and hypertension are well-documented cardiovascular risk factors [18,19]. Most of the functional and structural vascular alterations that lead to cardiovascular complications are similar in aging and hypertension [20]. Moreover, these vascular changes associated with essential hypertension are generally considered to be an accelerated form of the changes seen with aging [21]. When we are young and healthy, the endothelial production of NO through L-arginine is efficient and sufficient to produce NO; however, as we age we lose our ability to synthesize endothelial derived NO. Most of the works on the activity of NO in cells and tissues agree that the bioavailability or the generation of NO decreases with aging. It has been proposed that superoxide can scavenge NO to form peroxynitrite and thereby reduce its effective concentrations in cells [22]. It has also been reported that there is decreased nitric oxide synthase (NOS) expression with aging both in constitutive and inducible isoforms [23,24]. Berkowitz *et al.* [25] observed the upregulation of arginase (an enzyme that degrades the natural substrate for NOS, L-arginine) in aged blood vessels and the corresponding modulation of NOS activity. Taddei *et al.* [26] have shown that there is a gradual decline in endothelial function due to aging with

greater than 50% loss in endothelial function in the oldest age group tested as measured by forearm blood flow assays. Egashira *et al.* [27] reported more dramatic findings in the coronary circulation of aging adults whereby there was a loss of 75% of endothelium-derived nitric oxide in 70-80 year old patients compared to young, healthy 20 year olds. Vita and colleagues [28] demonstrated that increasing age was one predictor of abnormal endothelium-dependent vasodilation in atherosclerotic human epicardial coronary arteries. Gerhard *et al*. [29], concluded from their 1996 study that age was the most significant predictor of endothelium-dependent vasodilator responses by multiple stepwise regression analysis. Collectively, these important findings illustrate that endothelium-dependent vasodilation in resistance vessels declines progressively with increasing age. This abnormality is present in healthy adults who have no other cardiovascular risk factors, such as diabetes, hypertension, or hypercholesterolemia. Most of these studies found that impairment of endothelium-dependent vasodilation was clearly evident by the fourth decade. In contrast, endothelium-independent vasodilation does not change significantly with aging, demonstrating that the responsiveness to NO does not change only the ability to generate it. These observations enable us to conclude that reduced availability of endothelium-derived NO occurs as we age. Being able to diagnose and intervene early on is the key to optimal health and disease prevention.

Summary

The largest demographic in the history of America is turning 65 in record numbers every day. Boomers and their physicians must understand the importance of nitric oxide restoration to insure quality of life and curb the cardiovascular disease epidemic. Taking steps to recognized and restore NO insufficiency is paramount for preventing age related diseases.

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