SVOA Neurology

e-ISSN 2753-9180

ScienceVolks Open Access

Review Article

Endogenous Nasal Nitric Oxide Generation and Conscious Respiratory Modulation: A Neurophysiological Perspective

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DOI: https://doi.org/10.58624/SVOANE.2026.07.008

Received: February 13, 2026

Published: March 07, 2026

Citation: Krishna D. Endogenous Nasal Nitric Oxide Generation and Conscious Respiratory Modulation: A Neurophysiological Perspective. *SVOA Neurology* 2026, 7:2, 38-50. doi. 10.58624/SVOANE.2026.07.008

Abstract

Introduction: Nitric oxide (NO) is a critical gaseous signaling molecule involved in vascular regulation, autonomic integration, and neural function. While systemic and endothelial NO pathways have been extensively characterized, endogenous NO generated within the nasal cavity and paranasal sinuses represents a distinct and physiologically significant source that has received comparatively limited neurophysiological attention. Continuous production of NO within the paranasal sinuses and its delivery during nasal breathing position nasal NO as a potential intermediary linking respiratory behavior with cardiopulmonary, autonomic, and neurovascular regulation.

Methods: This perspective review synthesizes current evidence supporting a mechanistic framework in which nasal NO enhances pulmonary vasodilation, optimizes ventilation–perfusion matching, and improves arterial oxygenation, thereby contributing to hemodynamic stability and cerebral perfusion support. NO-dependent endothelial signaling further supports cerebrovascular reactivity and neurovascular coupling, while modulation of brainstem autonomic nuclei may facilitate vagal predominance and autonomic flexibility. Through these converging pulmonary, vascular, and vagal pathways, nasal NO modulation may influence higher-order processes including attention, executive regulation, perceptual integration, and sustained awareness.

Results: Specific structured nasal breathing techniques may differentially amplify endogenous NO dynamics. Humming-based breathing *(Bhramari)* has been shown to increase nasal NO output by approximately fifteen-fold compared with quiet exhalation, likely through oscillatory airflow-mediated enhancement of sinus ventilation. Breath retention practices *(kumbhaka)* introduce transient hypercapnic-hypoxic stimuli that may augment endothelial NO synthase activation and shear stress-dependent NO signaling, while slow rhythmic nasal breathing promotes sustained NO delivery and autonomic stabilization.

Conclusion: Although direct causal validation remains limited, integrating respiratory physiology, neurovascular science, and autonomic neuroscience provides a biologically coherent framework for investigating nasal NO as a mediator of breathing-induced neurophysiological effects. Standardized nasal NO quantification combined with multimodal cardiovascular and neuroimaging assessments may be essential to determine translational relevance. Elucidating these pathways may inform the development of safe, non-pharmacological strategies targeting cardiopulmonary health, stress resilience, and preventive neurovascular care.

Keywords: *Nasal nitric oxide; Conscious breathing; Neurovascular coupling; Autonomic nervous system; Cerebral blood flow; Respiratory physiology; Nitric oxide signaling*

1. Introduction

Nitric oxide (NO) is a gaseous signaling molecule that plays a fundamental role in the regulation of vascular tone, neural communication, immune defense, and respiratory physiology. Since its identification as an endothelium-derived relaxing factor, NO has been recognized as a critical mediator of cardiovascular and neurophysiological homeostasis[1]. Within the nervous system, NO functions as a non-classical neurotransmitter and neuromodulator, influencing synaptic plasticity, neuronal excitability, and cerebral blood flow regulation[2]. Increasing evidence further highlights its role in neurovascular coupling and autonomic integration, positioning NO as a key molecular interface linking respiration, circulation, and neural function [3]. Among endogenous sources of NO, the nasal cavity and paranasal sinuses represent a distinctive and physiologically significant site of continuous NO generation. High concentrations of NO are produced by the epithelial lining of the paranasal sinuses through constitutive NO synthase activity and released into the nasal airflow during respiration[4]. Unlike endothelial NO, which acts locally within the vasculature, nasal NO is inhaled into the lower respiratory tract during nasal breathing, allowing it to exert distal pulmonary effects [5]. This unique mode of delivery underscores the importance of airflow patterns in modulating endogenous NO availability. Physiologically, nasal NO contributes to airway defense through antimicrobial activity and facilitation of mucociliary clearance, while also acting as a selective pulmonary vasodilator that improves ventilation–perfusion matching and arterial oxygenation [5]. These pulmonary effects are closely linked to cerebral perfusion and metabolic demand, as alterations in pulmonary hemodynamics and arterial oxygen content can influence neurovascular coupling and brain oxygenation [6]. Beyond respiratory actions, NO is an important modulator of autonomic pathways, influencing baroreflex sensitivity, chemoreflex control of breathing, and vagal–sympathetic balance [3]. Breathing behavior is a major determinant of nasal NO delivery. Nasal breathing results in greater NO transfer to the lungs compared with oral breathing due to direct sinus ventilation [5]. Airflow characteristics such as velocity, turbulence, and oscillatory patterns influence sinus gas exchange and NO release. These physiological principles are particularly relevant in conscious breathing practices (*pranayama*), which emphasize controlled nasal breathing, slow respiratory rhythms, and techniques involving humming or vibratory airflow. Experimental studies have shown that humming markedly increases nasal NO output by enhancing sinus ventilation, whereas slow breathing optimizes respiratory mechanics and autonomic balance [7]. From a neurophysiological perspective, voluntary slow breathing has been associated with enhanced parasympathetic activity, reduced sympathetic drive, and improved heart rate variability, reflecting increased autonomic flexibility [8]. Neuroimaging and electrophysiological studies further suggest that regulated breathing influences cortical activity, emotional regulation, and attentional processes [9]. Despite these observations, the biological mediators linking breathing behavior to neurophysiological outcomes remain incompletely understood.

Therefore, the present perspective review synthesizes current evidence on endogenous nasal NO generation and examines NO-dependent pathways linking voluntary breathing modulation with pulmonary, cerebral, and autonomic regulation.

2. Biology of Nitric Oxide: Synthesis, Signaling, and Regulation

NO is a diffusible gaseous molecule that serves as a critical signaling mediator in neural, vascular, and autonomic systems. Over the past decade, advances in molecular physiology and neurovascular research have further clarified the role of NO as an integrative modulator of cerebral blood flow, synaptic activity, and autonomic regulation [10].

2.1 Nitric Oxide Synthase Isoforms

Endogenous NO is generated from L-arginine by the enzyme nitric oxide synthase (NOS), which exists in three major isoforms: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). Although these isoforms share common catalytic mechanisms, they differ in cellular localization, regulatory control, and physiological function.

2.1.1 Neuronal nitric oxide synthase (nNOS) is constitutively expressed in neurons of the central and peripheral nervous systems. High nNOS expression is observed in cortical interneurons, hippocampal circuits, brainstem autonomic nuclei, and sensory pathways. nNOS-derived NO functions primarily as a neuromodulator, influencing synaptic transmission, neuronal excitability, and plasticity. In recent studies, nNOS activity has been implicated in central autonomic integration, particularly within brainstem regions governing cardiorespiratory control [11]

2.1.2 Endothelial nitric oxide synthase (eNOS) is predominantly localized in vascular endothelial cells and plays a central role in maintaining vascular homeostasis. eNOS-derived NO regulates basal vascular tone, flow-mediated dilation, platelet aggregation, and endothelial integrity. In cerebral circulation, eNOS contributes to neurovascular coupling by linking neuronal metabolic demand to adaptive changes in cerebral blood flow [12]. Impaired eNOS signaling has been associated with endothelial dysfunction and cerebrovascular disease.

2.1.3 Inducible nitric oxide synthase (iNOS) is expressed in immune cells, glia, and vascular tissues under inflammatory conditions. Unlike nNOS and eNOS, iNOS activity is calcium-independent and capable of generating large amounts of NO over prolonged periods. While iNOS-derived NO plays a role in immune defense and inflammatory signaling, excessive or sustained iNOS activation may contribute to oxidative stress and neurovascular injury. Under normal physiological conditions, iNOS expression in neural tissue remains minimal [13].

Thus, physiological NO signaling in the nervous and vascular systems is primarily mediated by nNOS and eNOS, with spatial and temporal specificity.

2.2 Physiological Roles of Nitric Oxide in Neural and Vascular Systems

In the nervous system, NO acts as a non-synaptic neuromodulator capable of influencing neuronal populations beyond classical synaptic boundaries. nNOS-derived NO plays a role in synaptic plasticity, learning, memory, and sensory integration. It also contributes to central autonomic regulation by modulating neuronal networks involved in respiratory and cardiovascular control [14].

Within the vascular system, NO is a primary regulator of vascular tone and blood flow distribution. Endothelial NO maintains basal vasodilation, counterbalances vasoconstrictor influences, and facilitates adaptive vascular responses to metabolic demand. In the cerebral circulation, NO is a critical mediator of neurovascular coupling, ensuring adequate perfusion during neuronal activation [15].

NO also plays an important role in autonomic nervous system regulation. Both experimental and clinical studies demonstrate that NO modulates sympathetic and parasympathetic outflow, enhances baroreflex sensitivity, and attenuates excessive sympathetic activity. These effects contribute to cardiovascular stability and autonomic balance [16]. Such autonomic actions of NO are particularly relevant when considering breathing-related modulation of cardiovascular and neural function.

3. Nasal and Paranasal Sinus Nitric Oxide Generation

The nasal cavity and paranasal sinuses constitute a distinct and physiologically significant source of endogenous NO within the human respiratory system. Unlike systemic NO production, which primarily exerts local vascular effects, nasal NO is continuously generated and released into the respiratory airflow, allowing it to influence both pulmonary and downstream neurovascular physiology. Over the past decade, renewed interest in upper airway physiology has highlighted nasal NO as a functional mediator linking breathing behavior with respiratory, vascular, and neural regulation [17].

3.1 Anatomical Sources of Nasal Nitric Oxide

The principal source of nasal NO is the epithelium of the paranasal sinuses, including the maxillary, ethmoidal, frontal, and sphenoidal sinuses. These sinuses are lined by a highly specialized respiratory epithelium rich in constitutively active NO synthase, predominantly endothelial NOS (eNOS) and neuronal NOS (nNOS). This epithelium produces NO at concentrations several orders of magnitude higher than those found in the lower respiratory tract [18].

The anatomical configuration of the paranasal sinuses allows NO to accumulate within relatively closed cavities. NO enters the nasal cavity primarily through small sinus ostia during airflow-driven gas exchange. The efficiency of this exchange is influenced by nasal airflow patterns, turbulence, and oscillatory pressure changes during breathing. Consequently, the anatomical relationship between the sinuses and the nasal airway plays a critical role in determining nasal NO availability [19].

3.2 Mechanisms of Endogenous Nasal Nitric Oxide Generation

Endogenous nasal NO generation is largely constitutive and enzymatic, arising from NOS-mediated conversion of L-arginine to NO and L-citrulline. Unlike inducible NO production associated with inflammation, sinus-derived NO is continuously generated under physiological conditions and is relatively independent of inflammatory signaling [20].

Several factors regulate the effective release of NO from the sinuses into the nasal airflow. Nasal airflow velocity and pattern are key determinants; slow, nasal breathing promotes sustained contact between airflow and sinus ostia, facilitating NO diffusion. Oscillatory airflow, such as that produced during humming, markedly enhances sinus ventilation and NO release by generating pressure fluctuations that promote gas exchange [21].

In addition, nasal resistance and unilateral nasal dominance influence NO distribution between the nostrils. These physiological variations may contribute to asymmetric NO delivery and differential autonomic effects, although this aspect remains underexplored in experimental studies [22].

3.3 Physiological Significance of Nasal Nitric Oxide

Nasal NO serves multiple physiological functions, extending beyond local airway defense. At the upper airway level, NO exhibits antimicrobial properties and enhances mucociliary clearance, contributing to innate immune defense of the respiratory tract. When inhaled into the lower respiratory tract, nasal NO exerts significant pulmonary effects. NO acts as a selective pulmonary vasodilator, improving ventilation-perfusion matching and reducing pulmonary vascular resistance without causing systemic hypotension. These effects enhance arterial oxygenation and pulmonary efficiency, particularly during nasal breathing [23].

Improved pulmonary hemodynamics and oxygenation have downstream implications for cerebral circulation. Pulmonary-cerebral coupling plays an important role in maintaining cerebral perfusion and oxygen delivery, especially during conditions of altered respiratory patterns. Emerging evidence suggests that inhaled NO, even at low endogenous concentrations, may indirectly influence cerebral blood flow regulation through its effects on pulmonary circulation, arterial oxygen content, and autonomic reflexes [24].

Furthermore, nasal NO may contribute to the modulation of autonomic nervous system activity. NO influences vagal afferent signaling and baroreflex sensitivity, thereby affecting sympathovagal balance. Given the strong coupling between respiration and autonomic control, nasal NO may act as a biochemical intermediary linking nasal breathing with autonomic and neurophysiological regulation [25].

4. Neurophysiological and Neurovascular Integration of Nasal Nitric Oxide

NO functions as an important integrative mediator linking respiratory dynamics, vascular regulation, and neural activity. Although its pulmonary and systemic vascular roles are well established, the neurophysiological relevance of endogenous nasal NO is best understood through its contribution to neurovascular coupling, the process by which regional cerebral blood flow is dynamically matched to neuronal metabolic demand. During nasal breathing, NO generated in the paranasal sinuses enters the lower respiratory tract and acts as a selective pulmonary vasodilator through activation of soluble guanylyl cyclase and cyclic guanosine monophosphate signaling [26]. This mechanism improves ventilation-perfusion matching, reduces pulmonary vascular resistance, and enhances arterial oxygenation without systemic hypotension. Even modest increases in arterial oxygen content may stabilize cerebral oxygen delivery and support efficient neurovascular responses, particularly in individuals with compromised vascular reserve or impaired autoregulation [27].

Pulmonary and cerebral circulatory systems are tightly coupled through shared sensitivity to arterial oxygen and carbon dioxide levels. Optimization of pulmonary gas exchange through nasal NO delivery may attenuate hypoxia-driven sympathetic activation and reduce variability in cerebral perfusion pressure. In parallel, endothelial-derived NO plays a central role in cerebrovascular reactivity by promoting smooth muscle relaxation and rapid vasodilation of cerebral resistance vessels during neuronal activation [28]. Although nasal NO may not directly penetrate the brain in physiologically meaningful concentrations, its indirect effects on systemic oxygenation, endothelial shear stress, and autonomic regulation may enhance overall NO signaling capacity and preserve endothelial function.

Autonomic integration provides a critical pathway linking respiratory behavior with cerebral perfusion. Excess sympathetic activity increases cerebrovascular resistance and promotes oxidative stress–mediated endothelial dysfunction, whereas parasympathetic predominance supports vascular flexibility and baroreflex stability [29]. Slow, regulated nasal breathing enhances respiratory sinus arrhythmia and vagal dominance, reducing sympathetic vasoconstrictor drive. NO signaling within brainstem cardiorespiratory centers modulates reflex gain and neuronal excitability, contributing to coordinated regulation of respiratory rhythm and cardiovascular control [30]. Through this autonomic recalibration, breathing-induced changes in endogenous NO availability may stabilize cerebral autoregulation and reduce fluctuations in cerebral blood flow.

NO also interacts with vagal pathways involved in cardiorespiratory integration. Within brainstem nuclei such as the nucleus tractus solitarius and dorsal motor nucleus of the vagus, NO influences synaptic transmission and parasympathetic output through cyclic guanosine monophosphate-dependent mechanisms. Enhanced vagal activity is associated with improved autonomic flexibility, increased heart rate variability, and greater baroreflex sensitivity [31]. Conversely, reduced NO bioavailability is linked to sympathetic dominance and impaired vagal tone, conditions frequently observed in chronic stress and cardiovascular disease. Breathing patterns emphasizing slow nasal respiration and prolonged exhalation may facilitate vagal recalibration through combined mechanical and reflex pathways.

Efficient neurovascular coupling is essential for cognitive performance, as attention, executive function, and sensory processing rely on rapid and localized adjustments in cerebral perfusion. Endothelial NO signaling enables these adaptive responses by maintaining vascular responsiveness within cortical networks [32]. By enhancing pulmonary oxygenation, supporting endothelial function, and stabilizing autonomic balance, nasal NO-modulating breathing patterns may indirectly reinforce neurovascular coupling efficiency. Although direct causal evidence remains limited, converging pulmonary, autonomic, and vascular mechanisms provide a biologically plausible framework linking respiratory modulation with cognitive regulation and cerebrovascular stability.

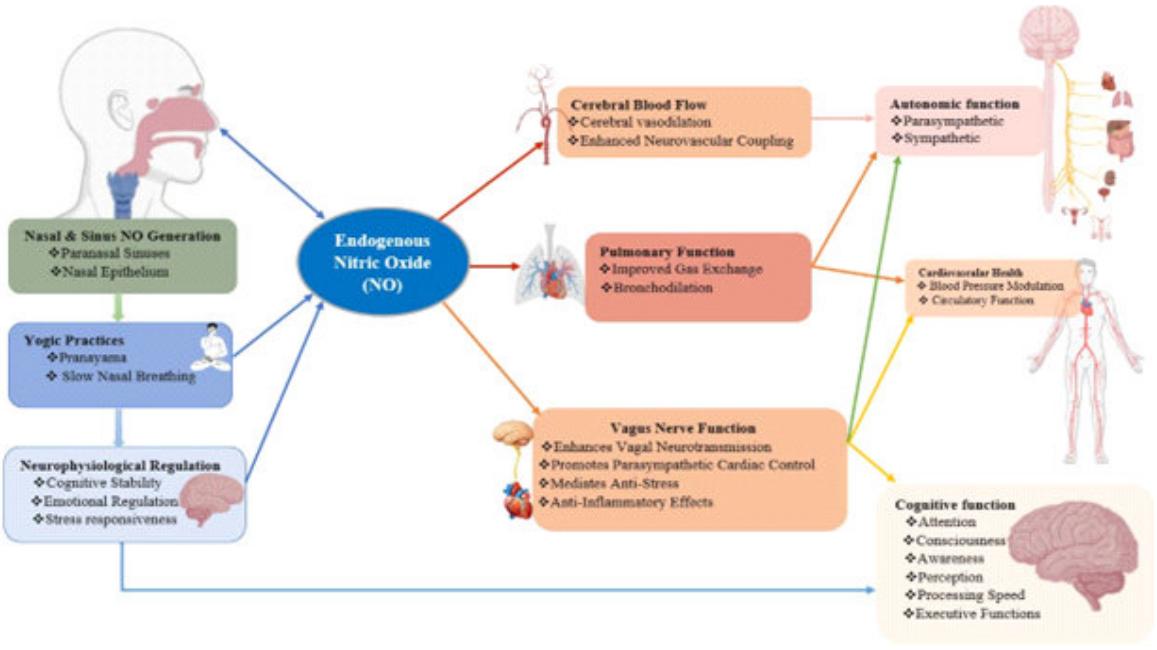

Figure 1. Integrated Physiological Pathways Linking Endogenous Nasal Nitric Oxide to Cardiopulmonary, Autonomic, and Cognitive Regulation.

Figure 1 schematically illustrates three interconnected physiological domains through which endogenous nasal NO, generated within the paranasal sinuses during nasal breathing, may exert systemic and neurophysiological effects.

First, NO influences cerebral blood flow and autonomic function through endothelial and central autonomic mechanisms. NO-mediated vasodilation supports cerebrovascular reactivity and dynamic regulation of cerebral perfusion, while modulation of brainstem autonomic nuclei contributes to parasympathetic predominance and stabilization of cardiovascular reflexes.

Second, NO enhances pulmonary function and cardiovascular health by acting as a selective pulmonary vasodilator. Improved ventilation-perfusion matching and reduced pulmonary vascular resistance enhance arterial oxygenation and decrease right ventricular afterload. These effects support systemic hemodynamic stability and may contribute to improved vascular resilience.

Third, NO modulates vagal nerve activity and cognitive function. Through its influence on autonomic integration within the nucleus tractus solitarius and related brainstem structures, NO supports vagal tone and autonomic flexibility. Vagal afferent pathways project to limbic and prefrontal cortical networks implicated in attention, awareness, emotional regulation, and executive function. Through this pathway, respiratory modulation of endogenous NO may indirectly influence higher-order cognitive processes.

Together, these parallel but interacting pathways suggest that nasal nitric oxide serves as a physiological intermediary linking respiratory behavior with cardiopulmonary efficiency, autonomic regulation, cerebrovascular dynamics, and cognitive function. This integrative framework remains mechanistically plausible and warrants validation through multimodal experimental investigation.

5. Structured Nasal Breathing Practices and Endogenous Nitric Oxide Modulation

Conscious breathing practices (*pranayama*) involve voluntary regulation of respiratory rhythm, depth, airflow pattern, and breath retention, with a strong emphasis on nasal breathing. From a physiological perspective, these practices introduce controlled alterations in airflow dynamics, intrathoracic pressure, gas exchange, and autonomic activity, all of which are known modulators of NO signaling. Increasing evidence suggests that specific features of Conscious breathing may enhance endogenous nasal NO availability and amplify its downstream pulmonary, autonomic, and neurovascular effects.

5.1 Physiological Characteristics of Nasal Breathing

A defining feature of Conscious breathing practices is the predominance of nasal airflow, often combined with slow respiratory rates (typically 4-6 breaths per minute), prolonged expiratory phases, and intermittent breath retention (*kumbhaka*). These characteristics contrast with spontaneous breathing, which is often faster, irregular, and includes oral airflow during stress or exertion.

Slow nasal breathing increases airflow residence time within the nasal cavity and promotes sustained interaction between inspired air and sinus ostia, facilitating diffusion of sinus-derived NO into the nasal stream. Reduced respiratory frequency also stabilizes intrathoracic pressure fluctuations, optimizing pulmonary perfusion and gas exchange. Recent physiological studies indicate that slow breathing enhances respiratory efficiency while simultaneously promoting parasympathetic dominance and autonomic stability [33].

5.2 Mechanisms Enhancing Nasal Nitric Oxide During Conscious Breathing Practices

5.2.1 Bhramarin Pranayama (Humming)

Bhramari Pranayama is a regulated yogic breathing technique characterized by controlled nasal inhalation followed by prolonged nasal exhalation accompanied by sustained humming vocalization. From a physiological perspective, *Bhramari pranayama* may be operationally defined as a structured form of voluntary nasal humming performed within a controlled respiratory framework. It represents a coordinated neuromuscular respiratory maneuver that integrates somatic motor control, cranial nerve-mediated laryngeal and velopharyngeal function, and autonomic modulation to generate sustained oscillatory nasal airflow [34].

Several physiological mechanisms may underlie the observed enhancement of nasal NO bioavailability during conscious breathing practices. Oscillatory airflow generated during humming produces low-frequency acoustic vibrations and cyclical intranasal pressure fluctuations [35]. These pressure oscillations facilitate augmented paranasal sinus ventilation by intermittently reducing ostial resistance and enhancing convective gas exchange between the sinus cavities and the nasal lumen. Consequently, NO-enriched air accumulated within the sinuses is more efficiently mobilized and released into the nasal passages, resulting in a measurable increase in nasal NO concentration.

Experimental studies have demonstrated that humming produces a marked elevation in nasal NO output, reaching approximately a 15-fold increase compared with quiet, non-phonatory exhalation [21]. This effect is attributed to the generation of oscillatory airflow and acoustic resonance within the nasal cavity, which induces periodic pressure fluctuations. These pressure oscillations mechanically vibrate the nasal and paranasal sinus walls, leading to micromechanical stimulation of the respiratory epithelium and transient deformation of the sinus ostia. Such vibratory forces enhance sinus ventilation by intermittently widening the ostial openings, thereby reducing diffusional resistance and promoting convective gas exchange [36]. Consequently, NO-rich air is rapidly mobilized and washed out from the paranasal sinuses into the nasal passages, substantially augmenting measurable nasal NO levels. Slow nasal breathing, commonly employed in Conscious practices, has also been shown to optimize respiratory mechanics, improve gas exchange efficiency, and modulate autonomic balance [9]. Breath retention practices may further influence NO bioavailability by altering intrathoracic pressure, pulmonary circulation, and shear stress-dependent NO signaling.

The marked augmentation of nasal NO during Bhramari pranayama has important physiological and potential clinical implications. NO derived from the paranasal sinuses exerts antimicrobial, antiviral, and antifungal properties within the upper airway, contributing to innate mucosal defense and regulation of ciliary motility. Enhanced sinus ventilation during humming may therefore support mucociliary clearance and reduce stagnation of secretions within the ostiomeatal complex. Systemically, increased inhalation of NO-enriched air into the lower respiratory tract may promote pulmonary vasodilation, improve ventilation-perfusion matching, and reduce pulmonary vascular resistance. These effects are mechanistically relevant in conditions characterized by impaired endothelial function or dysregulated vascular tone. Furthermore, NO-mediated vasodilation and reduced oxidative stress may contribute to improved microvascular perfusion and endothelial homeostasis. The slow, prolonged expiratory phase characteristic of *Bhramari* also enhances vagal afferent activity via laryngeal mechanoreceptors and baroreflex pathways, promoting parasympathetic predominance and attenuation of sympathetic outflow. Such autonomic modulation may reduce heart rate, improve heart rate variability, and support cardiovascular resilience.

Bhramari pranayama represents a non-pharmacological intervention capable of simultaneously modulating upper airway NO dynamics, endothelial signaling, and autonomic regulation. While preliminary physiological evidence is compelling, controlled clinical trials are required to quantify its effects on endothelial function, inflammatory biomarkers, pulmonary hemodynamics, and cardiometabolic outcomes.

5.2.2 Kumabhaka

Breath retention practices, traditionally termed *kumbhaka* in traditional yogic physiology, induce a controlled state of intermittent hypoxia and hypercapnia. It is characterized by a transient decline in arterial oxygen tension (PaO_2), accompanied by progressive elevation of arterial and tissue carbon dioxide ($PaCO_2$). From a physiological standpoint, this reversible perturbation of blood gas homeostasis initiates integrated respiratory, hemodynamic, and molecular adaptive responses that may modulate oxygen delivery, NO bioavailability, and cellular stress resilience[37]. During voluntary apnea, cessation of alveolar ventilation leads to CO_2 retention and a mild respiratory acidosis. Elevated $PaCO_2$ and decreased pH reduce hemoglobin-oxygen affinity via the Bohr effect, thereby facilitating oxygen unloading to peripheral tissues [38]. Consequently, tissue oxygen extraction may increase despite relatively preserved arterial oxygen saturation, underscoring the distinction between arterial oxygen content and effective microvascular oxygen delivery. When applied intermittently and within physiological tolerance, such brief hypoxic exposures may enhance tissue oxygen utilization rather than precipitate hypoxic injury [39]. Concomitantly, hypoxia and hypercapnia exert direct and indirect effects on the vascular endothelium. Fluctuations in intrathoracic pressure during breath retention alter venous return, pulmonary vascular resistance, and cardiac preload, thereby modifying endothelial shear stress patterns within both the pulmonary and systemic circulations. These mechanical and biochemical stimuli promote activation of eNOS and, under certain conditions, iNOS, potentially augmenting NO production [40]. Increased NO bioavailability contributes to vasodilation, improved microvascular perfusion, inhibition of platelet aggregation, attenuation of oxidative stress, and modulation of mitochondrial respiration.

Emerging evidence further suggests that intermittent hypoxia may influence central nervous system plasticity. HIF-1-dependent signaling, coupled with NO-mediated synaptic modulation and improved cerebral perfusion, may facilitate structural and functional remodeling of neuronal networks [41]. These mechanisms may underlie observed associations between controlled hypoxic exposure and enhanced neuroplasticity, stress resilience, and cognitive adaptation [42]. Additionally, hypoxia-induced activation of genomic maintenance pathways, including upregulation of the tumor suppressor protein p53, supports a role for transient hypoxic signaling in DNA repair and cellular homeostasis.

These physiological mechanisms suggest that *kumbhaka* represents a controlled hormetic stimulus capable of engaging adaptive cardiopulmonary and neurovascular pathways. Through enhancement of oxygen unloading, augmentation of endothelial NO signaling, and modulation of autonomic balance, intermittent breath retention may improve vascular reactivity, microcirculatory efficiency, and baroreflex sensitivity [43]. Increased NO bioavailability and reduced sympathetic overactivity are particularly relevant in the context of endothelial dysfunction, hypertension, and cardiometabolic risk states [44].

However, the clinical translation of *kumbhaka* requires careful consideration of dose, duration, and patient-specific risk factors. While brief, controlled breath retention may exert beneficial adaptive effects, prolonged or excessive hypoxia may provoke sympathetic surges, arrhythmogenesis, or oxidative stress, particularly in individuals with underlying cardiopulmonary disease. Therefore, future randomized controlled studies with direct assessment of endothelial function, NO metabolites, autonomic indices, and long-term cardiovascular outcomes are warranted to establish safety parameters and therapeutic efficacy.

5.2.3 Nadishodhana Pranayama (Alternate Nostril Breathing)

Nadi Shodhana Pranayama (alternate nostril breathing) is a structured yogic breathing technique characterized by slow, rhythmic inhalation and exhalation through alternating nasal passages in a cyclical pattern. Physiologically, it can be defined as a controlled respiratory maneuver that deliberately modulates nasal airflow resistance, respiratory rate, and expiratory duration to influence autonomic balance, cardiovascular dynamics, and endothelial function. Typically, it is performed at a reduced breathing frequency of approximately 4-8 breaths per minute [45]. This slow respiratory rhythm engages both somatic respiratory control and autonomic regulatory pathways.

Alternate nostril breathing interacts with the physiological nasal cycle, which involves reciprocal congestion and decongestion of the nasal turbinates under autonomic control. Directing airflow through one nostril at a time alters intranasal pressure gradients and airflow velocity, potentially enhancing mobilization of NO from the paranasal sinuses, where it is produced in high concentrations by iNOS in the sinus epithelium. Slow nasal inhalation facilitates entrainment of NO-enriched air into the lower respiratory tract, contributing to improved pulmonary vasodilation and ventilation-perfusion matching [46].

The cardiovascular benefits of *Nadi Shodhana* are primarily mediated through autonomic modulation. Slow breathing near 0.1 Hz optimizes respiratory sinus arrhythmia and enhances baroreflex sensitivity, resulting in increased vagal tone and reduced sympathetic outflow [43]. Decreased sympathetic vasoconstrictor activity lowers peripheral vascular resistance and attenuates oxidative stress, both of which are critical determinants of eNOS function. Since endothelial dysfunction is characterized by reduced NO bioavailability due to oxidative degradation and impaired eNOS activity, shifting the autonomic balance toward parasympathetic predominance helps preserve endothelial integrity and NO signaling [47].

Additionally, slow breathing generates rhythmic fluctuations in intrathoracic pressure, influencing venous return, stroke volume, and pulsatile blood flow. These hemodynamic oscillations produce laminar shear stress along the vascular endothelium, a principal physiological stimulus for eNOS activation [33]. Shear stress-mediated phosphorylation of eNOS enhances NO production, promoting vasodilation, improving arterial compliance, and reducing vascular inflammation. Improved flow-mediated dilation observed in slow breathing interventions further supports enhanced endothelium-dependent vasodilatory capacity.

Mild elevations in carbon dioxide during prolonged exhalation may also contribute by facilitating oxygen unloading through the Bohr effect and inducing modest vasodilation [48]. Furthermore, increased vagal activity activates the cholinergic anti-inflammatory pathway, suppressing pro-inflammatory cytokines that otherwise impair endothelial function.

Nadi Shodhana Pranayama represents an integrative cardiopulmonary intervention that improves endothelial function through autonomic regulation, enhanced laminar shear stress, reduced oxidative stress, and augmented NO bioavailability. These mechanisms suggest potential therapeutic relevance for cardiovascular health, vascular resilience, and systemic autonomic balance, although further controlled studies with direct NO measurements are warranted to confirm these effects.

6. Clinical and Translational Perspectives

The clinical relevance of endogenous nasal NO extends beyond respiratory physiology to broader cardiopulmonary, vascular, and neuroregulatory health. Given the central role of NO in endothelial function, autonomic balance, and neurovascular coupling, breathing-based interventions that enhance nasal NO bioavailability may offer a physiologically grounded, non-pharmacological strategy for disease prevention and adjunctive therapy. Emerging evidence suggests potential applications in hypertension, pulmonary dysfunction, stress-related autonomic disorders, and early cerebrovascular impairment. However, translation into clinical practice requires rigorous investigation incorporating standardized nasal NO measurements, objective vascular and autonomic biomarkers, and well-controlled longitudinal trials. Establishing mechanistic clarity and dose-response relationships may be essential for integrating nasal breathing-based approaches into preventive and therapeutic frameworks.

7. Methodological Considerations and Research Gaps

Despite growing interest in endogenous nasal NO and structured breathing practices, methodological limitations constrain definitive interpretation of current evidence. Standardized protocols for measuring nasal NO during dynamic breathing remain limited, and variability in respiratory parameters complicates mechanistic comparisons across studies. Many investigations rely on indirect autonomic markers without concurrent nasal NO quantification, reducing causal inference. Future research should integrate multimodal physiological assessments, including respiratory flow analysis, endothelial function, cerebral hemodynamics, and autonomic indices. Attention to individual anatomical variability and rigorous randomized longitudinal designs will be essential to clarify dose-response relationships and strengthen the translational relevance of nasal NO-modulating respiratory interventions.

8. Conclusion and Perspectives

Endogenous nasal NO serves as a physiologically relevant mediator linking respiratory dynamics with vascular, autonomic, and neurophysiological regulation. Continuous NO generation within the paranasal sinuses and its delivery during nasal breathing contribute to pulmonary vasodilation, optimized ventilation-perfusion matching, and stabilization of arterial oxygenation, with downstream support of cerebrovascular reactivity and neurovascular coupling. Structured nasal breathing patterns, including humming and slow rhythmic respiration, enhance NO release primarily through oscillatory airflow-mediated sinus ventilation and autonomic modulation. Future investigations integrating standardized nasal NO quantification with multimodal cardiopulmonary and neuroimaging assessments may be essential to refine mechanistic understanding and advance translational applications in neurovascular health.

Funding

None

Competing Interests

The author declares no competing interests.

Data Availability

None

Ethical Approval

Not applicable

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