

REVIEW ARTICLE

Autonomic dysfunction in pulmonary arterial hypertension: Neurocardiological mechanisms and clinical implications

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Abstract

Pulmonary arterial hypertension (PAH) is a progressive cardiopulmonary disease characterized by pulmonary vascular remodeling, increased pulmonary vascular resistance, and right ventricular dysfunction. Although PAH is primarily defined by hemodynamic and vascular abnormalities, growing evidence suggests that autonomic nervous system dysregulation may contribute to its broader clinical phenotype. This narrative review examines the available evidence on autonomic dysfunction in PAH from a neurocardiological perspective, with emphasis on sympathetic and parasympathetic imbalance, cardiovascular reflexes, central autonomic regulation, neuropsychiatric manifestations, and potential clinical implications. Current evidence suggests that autonomic dysfunction may represent a relevant but still exploratory component of PAH pathophysiology. Heart rate variability and baroreflex sensitivity may provide complementary information beyond conventional hemodynamic assessment, but methodological heterogeneity and limited prospective data preclude routine clinical use. Similarly, autonomic-targeted interventions remain investigational. A more integrated brain–heart–lung framework may help clarify the relationship between pulmonary vascular disease, right ventricular adaptation, autonomic regulation, and patient-centered outcomes in PAH.

Keywords: Pulmonary arterial hypertension; Autonomic nervous system; Heart rate variability; Sympathetic overactivity; Neuropsychiatric manifestations; Brain–heart–lung axis

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1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive cardiopulmonary disease characterized by increased pulmonary vascular resistance, pulmonary vascular remodeling, and right ventricular pressure overload.¹ Although this vascular and hemodynamic framework remains central to diagnosis, risk stratification, and treatment, it does not fully explain the heterogeneity observed among patients with PAH. Patients

with similar hemodynamic profiles may differ substantially in symptom burden, exercise tolerance, neuropsychiatric manifestations, and disease trajectory. These differences suggest that additional mechanisms beyond pulmonary vascular obstruction may influence clinical expression and disease progression.^{1,2}

The central hemodynamic consequence of PAH is chronic right ventricular pressure overload. In early stages, right ventricular adaptation may preserve cardiac output through compensatory hypertrophy and maintained ventriculoarterial coupling. With sustained afterload, however, this response may become maladaptive, leading to right ventricular dilatation, impaired contractility, reduced cardiac output, and right-sided heart failure. Clinically, this transition is associated with worsening dyspnea, fatigue, reduced exercise capacity, edema, and functional decline, with important consequences for quality of life and survival.¹⁻³

Autonomic dysfunction has emerged as a potentially relevant, but still incompletely defined, component of PAH pathophysiology. Small physiological and observational studies have reported sympathetic overactivity, reduced parasympathetic modulation, impaired heart rate variability (HRV), and altered cardiovascular reflex control in patients with PAH.⁴⁻¹⁰ These abnormalities have been associated with disease severity, right ventricular dysfunction, functional limitation, and symptom burden, although their causal role in disease progression remains uncertain.^{4,5,7,11}

From a clinical perspective, autonomic dysfunction may help explain aspects of PAH that are not fully captured by resting hemodynamics, functional class, biomarkers, or imaging. In particular, altered autonomic regulation may provide an integrative framework linking pulmonary vascular disease, right ventricular adaptation, cardiovascular reflex impairment, exercise intolerance, and patient-reported symptoms. However, available evidence remains fragmented across physiological studies, imaging-based assessments, observational cohorts, and experimental models, limiting its integration into routine clinical assessment or therapeutic decision-making.

This narrative review examines the neurocardiological mechanisms potentially linking autonomic dysfunction to PAH, with emphasis on sympathetic and parasympathetic imbalance, cardiovascular reflexes, central autonomic regulation, neuropsychiatric manifestations, and clinical implications. We propose that autonomic imbalance in PAH may represent more than a secondary marker of advanced disease, but current evidence is insufficient to establish its causal role, prognostic value, or therapeutic relevance. Therefore, this review aims to distinguish established

findings from emerging hypotheses and to discuss how autonomic dysfunction may inform future research and more integrated approaches to PAH assessment. The proposed conceptual framework is illustrated in [Figure 1](#).

2. Review methodology

This narrative review was supported by targeted literature searches in PubMed/MEDLINE, Scopus, and Google Scholar, conducted between April 1 and April 30, 2026. These databases were selected to provide broad coverage of biomedical, cardiovascular, respiratory, and translational literature relevant to PAH and autonomic regulation.

The main search combined terms related to PAH and autonomic function, including “pulmonary arterial hypertension,” “pulmonary hypertension,” “autonomic dysfunction,” “autonomic nervous system,” “sympathetic nervous system,” “parasympathetic nervous system,” “heart rate variability,” “baroreflex,” “chemoreflex,” “neurocardiology,” and “neuromodulation.” This search retrieved 76 records from PubMed/MEDLINE, 161 records from Scopus, and approximately 7,250 records from Google Scholar. Because Google Scholar retrieves a large number of results with lower reproducibility, only the first 200 results sorted by relevance were screened.

Additional targeted searches were performed when needed for specific topics, including neuroinflammation, neuropsychiatric manifestations, cognitive dysfunction, quality of life, exercise training, and autonomic neuromodulation. Publications were selected based on their relevance to the scope of the review, with priority given to empirical studies published from 2022 onward. Older studies were retained when they provided foundational physiological, mechanistic, or clinical evidence not superseded by more recent publications. Selected review articles and guidelines were used for contextualization, but specific empirical claims were supported preferentially by original studies whenever available.

Reference selection was based on author judgment and scope relevance, with input from all five co-authors. The final reference list comprises 37 publications. Because this was a narrative review, no formal systematic protocol, risk-of-bias assessment, or meta-analysis was performed.

3. Results

3.1. Autonomic nervous system dysfunction in PAH

Patients with PAH have been reported to exhibit autonomic nervous system imbalance, most consistently characterized by sympathetic predominance and reduced parasympathetic modulation.^{4-7,12,13} This pattern has been described using direct and indirect measures of autonomic

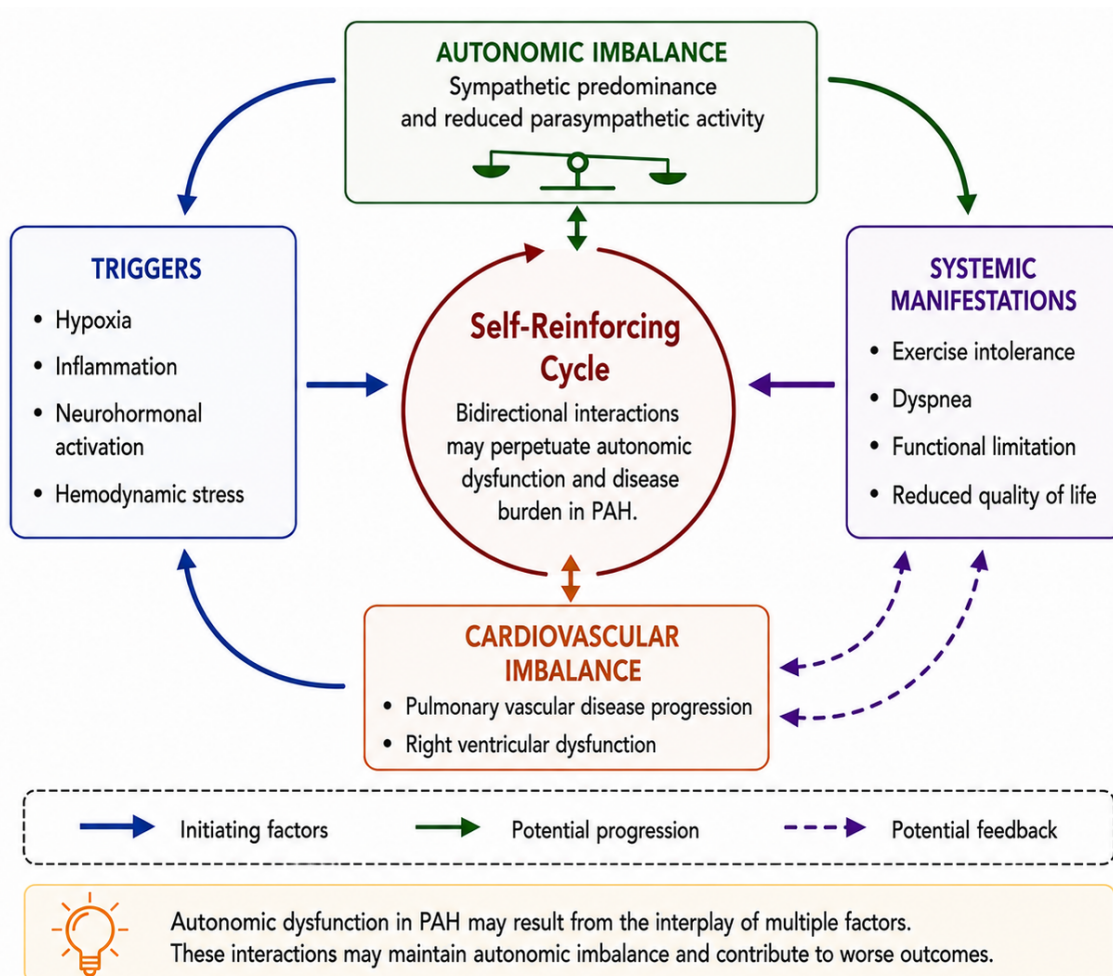


Figure 1. Conceptual model of autonomic dysfunction in pulmonary arterial hypertension. Multiple factors—including hypoxia, inflammation, neurohormonal activation, and hemodynamic stress—may interact to promote autonomic imbalance, characterized by sympathetic predominance and reduced parasympathetic activity. This imbalance may sustain a self-reinforcing cycle linking cardiovascular consequences and systemic manifestations, potentially contributing to disease progression. Image adapted with Adobe Illustrator and Canva from material provided by Smart Servier (<https://smart.servier.com/>).

Abbreviation: PAH: Pulmonary arterial hypertension.

function, including muscle sympathetic nerve activity, HRV, heart rate recovery, and imaging-based assessments of cardiac sympathetic innervation.^{4-7,11-14}

The mechanisms underlying autonomic dysfunction in PAH are likely multifactorial. Chronic right ventricular pressure overload, reduced cardiac output, hypoxemia, neurohormonal activation, systemic inflammation, and impaired cardiovascular reflex control may all contribute to altered autonomic regulation.^{3-5,7,13} However, the relative contribution of each mechanism remains uncertain, and current evidence does not establish whether autonomic dysfunction is primarily a consequence of disease severity, a contributor to disease progression, or both.

In this context, autonomic imbalance should be interpreted as a biologically plausible and clinically relevant feature of PAH, but not yet as a validated causal mechanism or therapeutic target.¹⁵ Its main current value lies in its potential to provide additional insight into symptom burden, exercise limitation, cardiovascular adaptability, and the heterogeneity observed among patients with similar hemodynamic profiles. Further longitudinal studies integrating autonomic, hemodynamic, imaging, and clinical outcomes are needed to clarify its prognostic and mechanistic significance.^{9,10}

3.1.1. Sympathetic overactivity

Sympathetic overactivity is one of the most consistently

described autonomic findings in PAH. Direct evidence comes from small microneurography studies showing higher muscle sympathetic nerve activity in patients with PAH compared with healthy controls.⁴ Increased sympathetic activity has also been associated with clinical and hemodynamic markers of disease severity, including functional class, oxygen desaturation, pericardial effusion, and adverse outcomes.^{4,11}

Importantly, circulating catecholamine levels may not fully reflect sympathetic neural activation in PAH.^{4,13} This observation suggests that conventional biochemical markers may underestimate autonomic activation and that direct or functional autonomic measures may capture different aspects of sympathetic regulation.

Additional evidence has been obtained from imaging-based studies of cardiac sympathetic innervation. Altered cardiac sympathetic integrity has been reported in PAH using ¹²³I-metaiodobenzylguanidine scintigraphy, with abnormalities associated with markers of disease severity.^{6,14} Although these findings support the presence of sympathetic dysregulation, available studies remain small and do not establish whether sympathetic activation is a driver of disease progression or a marker of more advanced cardiopulmonary impairment.

3.1.2. Reduced parasympathetic tone

Reduced parasympathetic modulation has also been described in PAH, mainly through indirect functional measures such as HRV and heart rate recovery after exercise.^{5,7,9,10} These parameters suggest impaired vagal modulation and reduced autonomic flexibility, particularly among patients with more severe functional limitation or right ventricular dysfunction.^{5,9,10}

Under physiological conditions, parasympathetic activity contributes to beat-to-beat heart rate modulation and cardiovascular adaptability. In PAH, reduced vagal modulation may contribute to a persistent shift toward sympathetic predominance and impaired heart rate regulation during physical stress. However, the clinical meaning of reduced parasympathetic tone remains incompletely defined, because most available data come from small observational cohorts with heterogeneous methods of autonomic assessment.

Therefore, reduced parasympathetic modulation should currently be interpreted as an associated feature of PAH rather than an established independent determinant of disease progression. Its potential prognostic and therapeutic relevance requires confirmation in larger prospective studies.

3.1.3. Hemodynamic and functional associations

Autonomic imbalance in PAH has been associated with hemodynamic severity, right ventricular dysfunction, and impaired exercise capacity.^{4,5,9,10,11} Sympathetic predominance may be linked to higher heart rate, reduced cardiovascular adaptability, and increased myocardial workload, whereas reduced parasympathetic modulation may limit dynamic heart rate control during exercise and recovery.^{4,5,11}

Reduced HRV and impaired autonomic control have been associated with lower functional capacity and worse disease severity in observational studies.^{5,9,10} These findings suggest that autonomic markers may capture aspects of disease burden not fully represented by resting hemodynamic measurements alone. Nevertheless, the directionality of these associations remains uncertain. Autonomic dysfunction may reflect the physiological consequences of right ventricular overload and reduced cardiac output, but it may also participate in maladaptive responses to chronic cardiopulmonary stress.

At present, the available evidence supports an association between autonomic dysregulation and clinical severity in PAH, but not a definitive causal relationship. This distinction is important when considering autonomic markers as potential tools for disease monitoring or future therapeutic targeting.^{9,10}

3.1.4. Clinical evidence

Heart rate variability (HRV) is the most frequently studied non-invasive marker of autonomic function in PAH. Reductions in time-domain and frequency-domain HRV parameters have been reported, suggesting reduced overall autonomic modulation and impaired vagal activity.^{5,7,9,10} In small cohorts, HRV abnormalities have been associated with disease severity, exercise limitation, and right ventricular function.^{5,9,10}

Baroreflex sensitivity has also been reported to be reduced in PAH, supporting the presence of impaired cardiovascular reflex control.^{16,17} These findings are clinically relevant because baroreflex dysfunction may reflect reduced capacity to buffer short-term changes in blood pressure and heart rate. However, baroreflex assessment remains technically demanding and is not standardized for routine use in PAH.

Overall, clinical evidence supports the presence of autonomic dysregulation in PAH, but several limitations remain. Available studies are generally small, use different autonomic assessment methods, and vary in acquisition protocols, analytical approaches, and clinical populations.

For this reason, autonomic markers should currently be considered exploratory and complementary rather than established tools for risk stratification or treatment guidance.^{9,10}

3.1.5. Integrated pathophysiological view

The available evidence suggests that autonomic dysfunction may be part of the broader systemic expression of PAH. Sympathetic activation, reduced parasympathetic modulation, impaired HRV, and altered cardiovascular reflex control may interact with right ventricular dysfunction, hypoxemia, inflammation, and neurohormonal activation.^{4-6,9-11,16} However, these interactions remain incompletely defined and should be interpreted as a conceptual framework rather than a proven mechanistic pathway. The integrated pathophysiological pathways are summarized in Figure 2.

This integrated view may help explain why patients with similar resting hemodynamic profiles can have different levels of functional limitation, symptom burden, and clinical trajectory. Autonomic assessment may eventually provide additional information about cardiovascular adaptability and patient-centered outcomes. However,

before autonomic markers can be incorporated into clinical practice, their reproducibility, prognostic value, and incremental contribution beyond established PAH risk models must be demonstrated.

3.1.6. Conceptual considerations and unresolved questions

Several questions remain unresolved. First, it is unclear whether autonomic dysfunction is mainly a marker of disease severity, a contributor to progression, or a compensatory response to chronic cardiopulmonary stress. Second, the temporal evolution of autonomic abnormalities in PAH has not been well characterized. Third, different autonomic assessment tools measure distinct physiological domains and should not be considered interchangeable.

Future studies should prioritize longitudinal designs integrating autonomic markers with hemodynamic data, right ventricular imaging, exercise testing, biomarkers, and patient-reported outcomes. Such studies are needed to determine whether autonomic dysfunction has independent prognostic value and whether it can identify clinically meaningful phenotypes within PAH. Key

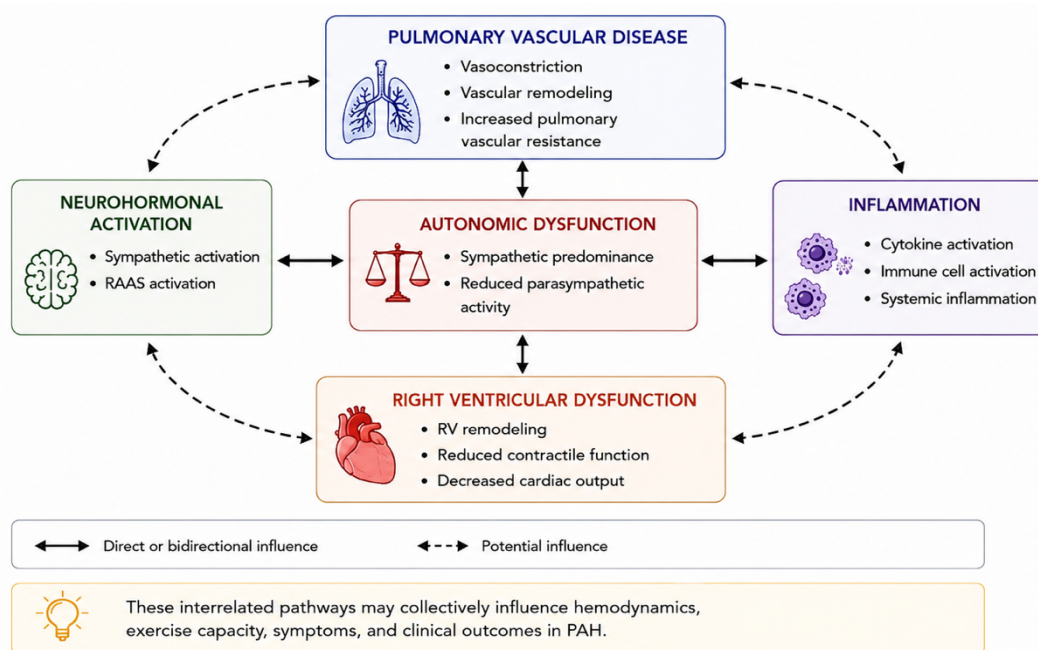


Figure 2. Conceptual model of integrated pathophysiological pathways of autonomic dysfunction in PAH. Pulmonary vascular disease, right ventricular dysfunction, neurohormonal activation, autonomic dysfunction, and systemic inflammation may interact through direct, bidirectional, and interrelated pathways. These interrelated mechanisms may collectively influence hemodynamics, exercise capacity, symptoms, and clinical outcomes in PAH. Image adapted with Adobe Illustrator and Canva from material provided by Smart Servier (<https://smart.servier.com/>).

Abbreviations: PAH: Pulmonary arterial hypertension; RAAS: Renin–angiotensin–aldosterone system; RV: Right ventricle.

unresolved questions and research priorities are illustrated in Figure 3.

Until these gaps are addressed, autonomic dysfunction should be regarded as a relevant but exploratory dimension of PAH pathophysiology. Its main contribution at present is conceptual and investigative: it provides a framework for studying the interaction between pulmonary vascular disease, right ventricular adaptation, cardiovascular reflex control, and symptom burden.

3.2. Cardiovascular reflexes and neural control

Cardiovascular homeostasis depends on the integration of peripheral sensory inputs and central autonomic networks that regulate heart rate, vascular tone, and blood pressure.¹⁸⁻²⁰ In PAH, this regulatory system appears altered, with studies reporting sympathetic activation, reduced parasympathetic modulation, impaired HRV, and reduced baroreflex sensitivity.^{4,5,7,9,10,16}

Dysfunction of cardiovascular reflexes may represent one pathway through which autonomic imbalance is associated with hemodynamic instability, reduced physiological adaptability, and symptom burden in PAH.

Among these pathways, baroreflex impairment has the most direct clinical evidence in PAH, whereas chemoreflex activation and central autonomic integration remain more inferential and require further study.^{16,17,19,21,22} The main cardiovascular reflex pathways and their central integration in PAH are depicted in Figure 4.

3.2.1. Baroreflex impairment

The arterial baroreflex contributes to short-term blood pressure regulation through mechanosensitive receptors located in the carotid sinus and aortic arch. These receptors transmit afferent signals to brainstem autonomic centers, which modulate sympathetic and parasympathetic outflow to maintain cardiovascular stability.^{18,19}

In PAH, baroreflex sensitivity has been reported to be reduced, supporting impaired cardiovascular reflex control in this population.^{16,17} In a study using spontaneous sequence analysis and repeated sit-to-stand maneuvers, patients with PAH showed reduced cardiac baroreflex sensitivity and baroreflex effectiveness compared with healthy controls, including among non-hypoxemic patients with less advanced disease.^{16,17}

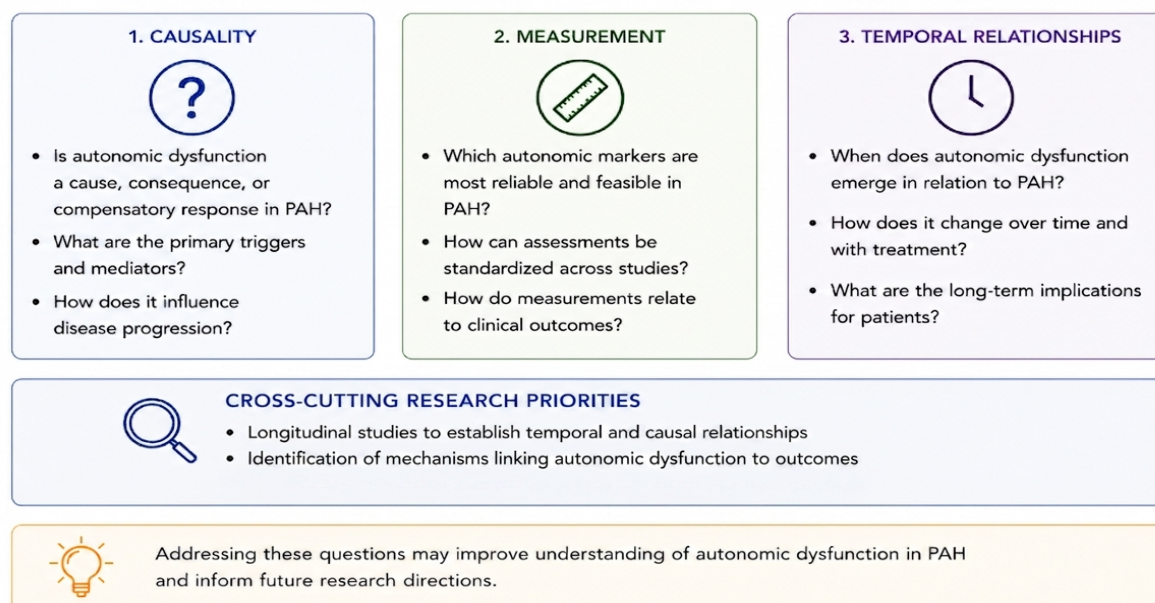


Figure 3. Conceptual model of unresolved questions and research priorities in autonomic dysfunction in PAH. Three key domains require further investigation: causality, whether autonomic dysfunction is a driver, consequence, or compensatory response in PAH; measurement, identifying the most reliable and feasible autonomic markers and addressing standardization across studies; and temporal relationships, clarifying when autonomic dysfunction emerges and how it evolves with treatment. Cross-cutting research priorities include longitudinal studies to establish causal relationships and identification of mechanisms linking autonomic dysfunction to clinical outcomes. Images adapted with Adobe Illustrator and Canva from material provided by Smart Servier (<https://smart.servier.com/>).

Abbreviation: PAH: Pulmonary arterial hypertension.

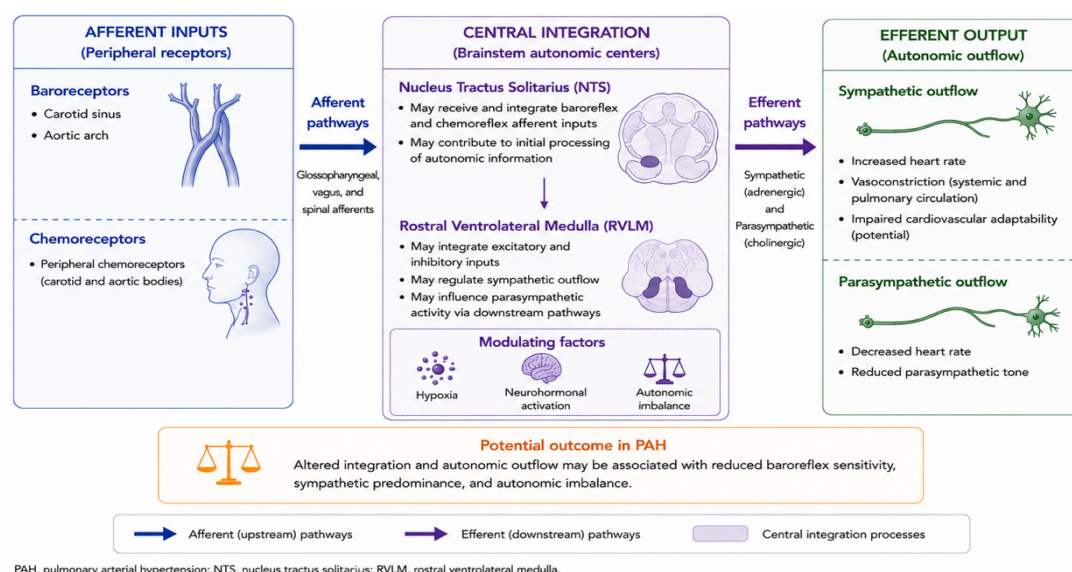


Figure 4. Conceptual model of cardiovascular reflex pathways and central autonomic integration in pulmonary arterial hypertension. Peripheral receptors, including arterial baroreceptors, chemoreceptors, and pulmonary receptors, may convey afferent signals via glossopharyngeal, vagal, and spinal pathways to brainstem autonomic centers. The nucleus tractus solitarius may receive and integrate baroreflex and chemoreflex inputs, while the rostral ventrolateral medulla may regulate sympathetic outflow. Modulating factors including hypoxia, neurohormonal activation, and autonomic imbalance may further influence central integration. Altered integration and autonomic outflow may be associated with reduced baroreflex sensitivity, sympathetic predominance, and autonomic imbalance in PAH. Images adapted with Adobe Illustrator and Canva from material provided by Smart Servier (<https://smart.servier.com/>). Abbreviations: PAH: Pulmonary arterial hypertension.

The mechanisms underlying reduced baroreflex sensitivity in PAH remain incompletely defined and may involve altered vascular compliance, reduced cardiac output, and sustained autonomic activation.^{16,17} Functionally, impaired baroreflex control may reduce the ability to buffer short-term fluctuations in blood pressure and heart rate during postural change or exercise. However, current evidence remains limited, and the clinical and prognostic implications of baroreflex impairment in PAH require further prospective validation.

3.2.2. Chemoreflex activation

The arterial chemoreflex is initiated by peripheral chemoreceptors, particularly in the carotid bodies, which respond to changes in arterial oxygen tension, carbon dioxide, and pH. Afferent signals are transmitted to brainstem autonomic centers and may influence sympathetic outflow, ventilation, and cardiovascular regulation.^{18,19, 21}

In PAH, chemoreflex activation is biologically plausible because hypoxemia, impaired pulmonary vascular function, and altered cardiopulmonary signaling may provide persistent afferent stimuli to autonomic networks. However, direct evidence specifically demonstrating enhanced chemoreflex sensitivity in PAH remains limited. Therefore, chemoreflex activation should be interpreted

as a potential contributor to autonomic imbalance rather than an established mechanism of disease progression.¹⁹

The interaction between chemoreflex activity and baroreflex impairment may be relevant to exercise intolerance, cardiovascular instability, and symptom burden, but this relationship has not been adequately characterized in PAH. Future studies integrating chemoreflex testing, baroreflex assessment, exercise physiology, and hemodynamic measurements are needed to clarify the role of chemoreflex pathways in this population.^{17,19}

3.2.3. Central neural integration

Central autonomic regulation is mediated by brainstem and higher neural structures that integrate afferent cardiovascular and respiratory signals and coordinate efferent sympathetic and parasympathetic responses.^{18,20} In PAH, central autonomic regulation may be influenced by chronic cardiopulmonary stress, hypoxemia, neurohormonal activation, and systemic inflammation, but direct evidence remains limited.^{20,23}

At present, central autonomic dysfunction in PAH should be regarded as a plausible conceptual mechanism rather than a proven disease pathway. Its potential relevance lies in its ability to integrate peripheral signals from the pulmonary circulation, right ventricle, and systemic

inflammatory milieu into autonomic responses that may influence symptoms and functional limitation. Further translational and clinical studies are required to determine whether central autonomic changes are independently associated with disease severity, progression, or treatment response in PAH.²⁰

3.3. Brain–heart–lung axis

The concept of a brain–heart–lung axis provides a useful framework for discussing how pulmonary vascular disease, right ventricular dysfunction, autonomic regulation, and systemic manifestations may interact in PAH. This framework should be interpreted as conceptual and hypothesis-generating rather than as an established mechanistic model. Current evidence supports the presence of autonomic dysregulation in PAH, but the directionality and causal significance of interactions among the pulmonary circulation, right ventricle, and central nervous system remain incompletely defined.^{4–6,9,10,16} The conceptual model of the brain–heart–lung axis is illustrated in Figure 5.²⁴

Pulmonary vascular disease imposes chronic pressure overload on the right ventricle, leading to adaptive and

eventually maladaptive changes in ventricular structure and function.^{1,3} As right ventricular function declines, reduced cardiac output, impaired oxygen delivery, neurohormonal activation, and systemic inflammation may influence peripheral and central regulatory pathways.^{1,3,25,26} Conversely, altered autonomic regulation may be associated with higher sympathetic tone, reduced cardiovascular adaptability, and impaired reflex control, which may contribute to symptom burden and functional limitation.^{4,5,9–11,16,17} However, whether autonomic dysfunction directly contributes to right ventricular deterioration or primarily reflects disease severity remains uncertain.

3.3.1. Hypoxia and neural activation

Hypoxemia and altered gas exchange may provide afferent stimuli to peripheral chemoreceptors and central autonomic networks.^{18,19,21,27} In cardiopulmonary diseases, chemoreflex activation is a biologically plausible contributor to sympathetic excitation and altered cardiorespiratory regulation.^{19,21,22} In PAH, however, direct evidence linking chemoreflex activation to disease progression is limited. Therefore, hypoxia-related neural activation should be

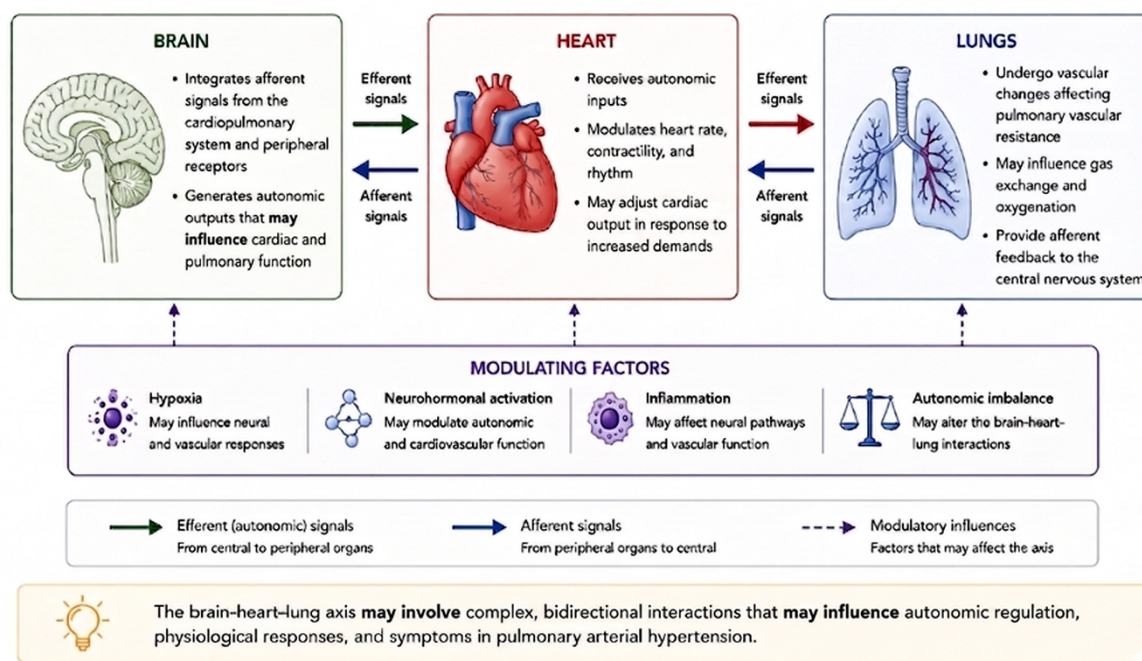


Figure 5. Conceptual model of the brain–heart–lung axis in pulmonary arterial hypertension. Integrated bidirectional communications among the brain, heart, and lungs may influence autonomic regulation and clinical manifestations in PAH. The brain may integrate afferent signals from the cardiopulmonary system and generate autonomic outputs that may influence cardiac and pulmonary function. Modulating factors, including hypoxia, neurohormonal activation, inflammation, and autonomic imbalance, may further affect neural pathways, vascular function, and brain–heart–lung interactions. Images adapted with Adobe Illustrator and Canva from material provided by Smart Servier (<https://smart.servier.com/>).

Abbreviation: PAH: Pulmonary arterial hypertension.

considered a potential pathway that requires further investigation rather than a proven mechanism.

3.3.2. Neuroinflammation and central nervous system involvement

Inflammation is recognized as an important component of PAH pathobiology and may interact with vascular remodeling, right ventricular adaptation, and systemic manifestations.^{25,26,28} More recently, experimental evidence has suggested that PAH may be associated with neuroinflammation, blood–brain barrier dysfunction, and cognitive impairment, supporting the hypothesis that disease-related changes may extend beyond the cardiopulmonary system.²³ These findings are relevant but remain exploratory, and their translation to clinical PAH populations requires further validation.²³

At present, it is not possible to determine whether neuroinflammatory changes are a cause, consequence, or parallel feature of PAH-related systemic dysfunction. Claims linking neuroinflammation directly to pulmonary vascular remodeling, autonomic dysregulation, or clinical outcomes should therefore be interpreted with caution. The proposed interactions between neuroinflammation and vascular remodeling are depicted in Figure 6.²³

3.3.3. Neurohormonal activation

Neurohormonal activation is involved in cardiovascular adaptation and maladaptation in PAH, particularly in the setting of right ventricular pressure overload and heart failure physiology.^{1,3} Endothelin signaling, nitric oxide–cyclic guanosine monophosphate signaling, prostacyclin pathways, and activin signaling are established therapeutic targets in PAH.^{1,24}

Within a neurocardiological framework, neurohormonal activation may be viewed as one of several systemic processes that could interact with autonomic regulation, inflammation, and right ventricular adaptation. This interpretation remains hypothesis-generating and should not be considered evidence that neurohormonal modulation directly corrects autonomic dysfunction in PAH.

3.3.4. Bidirectional communication

Bidirectional communication among the lungs, right ventricle, autonomic nervous system, and central nervous system may contribute to the clinical heterogeneity of PAH. Signals related to hypoxemia, inflammation, hemodynamic stress, and reduced cardiac output may influence autonomic regulation, while altered autonomic output may

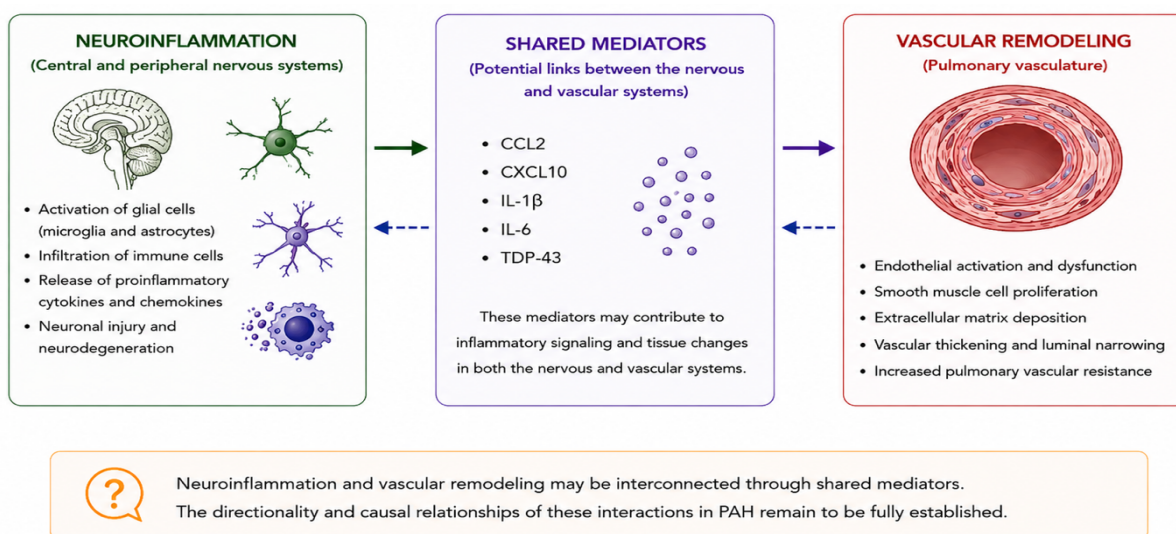


Figure 6. Conceptual model of neuroinflammation and vascular remodeling in PAH. Neuroinflammatory processes and vascular remodeling have been proposed to share mediators in PAH, based on experimental models. Central and peripheral neuroinflammation, involving activation of glial cells, release of proinflammatory mediators, and molecular alterations including CCL2, CXCL10, IL-1 β , IL-6, and TDP-43, may interact with vascular remodeling through endothelial activation, smooth muscle cell proliferation, and increased pulmonary vascular resistance. The directionality and causal relationships of these interactions remain uncertain, and their extrapolation to human PAH is not established. Images adapted with Adobe Illustrator and Canva from material provided by Smart Servier (<https://smart.servier.com/>).

Abbreviations: CCL2: C–C motif chemokine ligand 2; CXCL10: C–X–C motif chemokine ligand 10; IL-1 β : interleukin-1 beta; IL-6: interleukin-6; PAH: pulmonary arterial hypertension; TDP-43: TAR DNA-binding protein 43.

affect heart rate control, vascular tone, and cardiovascular adaptability.^{4,5,11,16,18,21} The bidirectional interactions within the brain–heart–lung axis are illustrated in Figure 7.

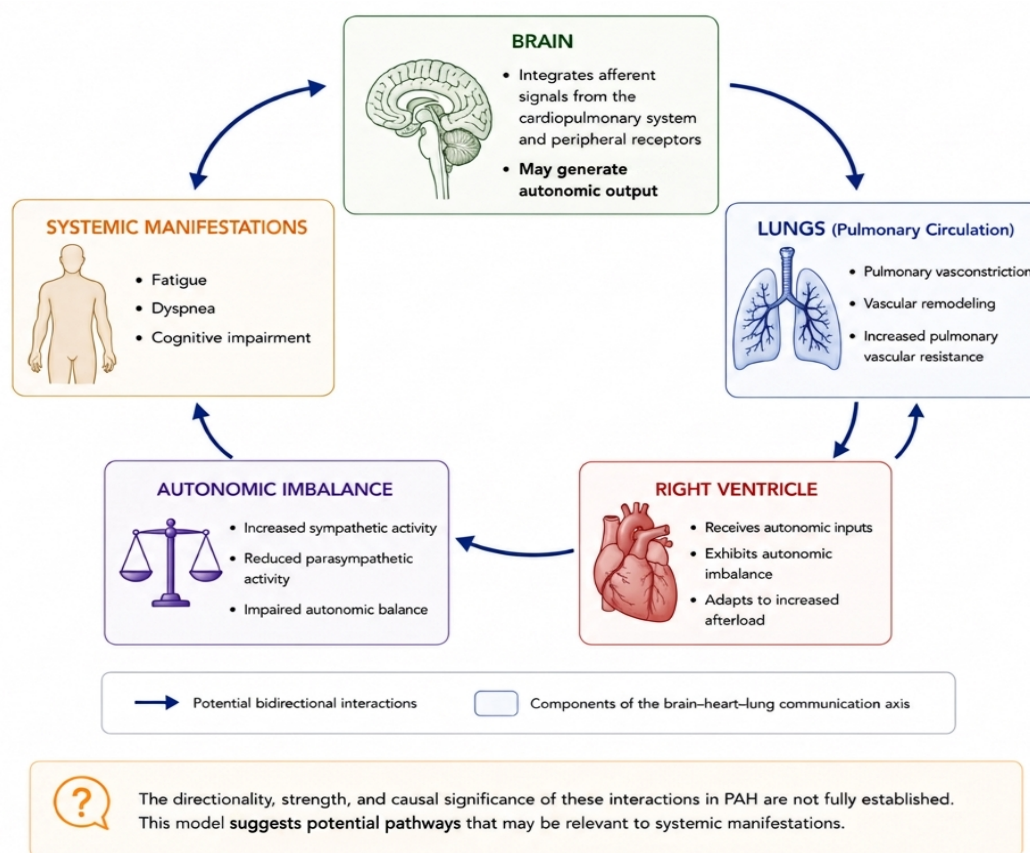
This model may help explain why symptom burden and functional limitation are not always fully explained by resting hemodynamic measurements. Nevertheless, the brain–heart–lung axis remains a conceptual framework. Further studies integrating autonomic testing, right ventricular imaging, hemodynamics, inflammatory biomarkers, cerebral perfusion, and patient-reported outcomes are needed to determine whether these interactions have independent clinical or prognostic relevance in PAH.

3.4. Neuropsychiatric manifestations in PAH

Neuropsychiatric manifestations are increasingly

recognized as part of the clinical burden of PAH. Depression and anxiety are frequently reported in patients with pulmonary hypertension and have been associated with impaired health-related quality of life.^{29–33} More recent observational and genetic studies in PAH and other forms of pulmonary hypertension suggest that these associations are clinically relevant, although the directionality and causal mechanisms remain uncertain.^{32,34,35}

The development of depressive and anxiety symptoms in PAH is likely multifactorial. Disease-related factors such as dyspnea, exercise limitation, uncertainty regarding prognosis, treatment burden, and reduced social participation may contribute to psychological distress. In addition, worse functional class, reduced exercise capacity, and hemodynamic impairment have been associated with higher depressive symptom burden in observational



PAH, pulmonary arterial hypertension; RV, right ventricle.

Figure 7. Conceptual model of bidirectional brain–heart–lung communication in PAH. Bidirectional interactions among the brain, lungs, right ventricle, and autonomic nervous system may influence systemic manifestations in PAH. The brain may integrate afferent signals from the cardiopulmonary system and peripheral receptors and generate autonomic output. The lungs may undergo pulmonary vasoconstriction and vascular remodeling, while the right ventricle may receive autonomic inputs, exhibit autonomic imbalance, and adapt to increased afterload. The directionality, strength, and causal significance of these interactions in PAH are not fully established. Images adapted with Adobe Illustrator and Canva from material provided by Smart Servier (<https://smart.servier.com/>).

Abbreviations: PAH: Pulmonary arterial hypertension; RV: Right ventricle.

studies.³⁵ However, current evidence does not support a simple causal pathway linking PAH directly to depression or anxiety, and these manifestations should be interpreted within a broader biopsychosocial framework.^{34,35}

Cognitive dysfunction has also been described in small exploratory cohorts of patients with PAH, with reported abnormalities involving memory, attention, executive function, and psychomotor speed.^{23,36} Structural neuroimaging findings, including changes in gray matter volume and microvascular lesions in regions involved in cognition and emotional processing, have also been reported, but available data remain limited and require validation in larger cohorts.^{23,36}

Autonomic dysfunction may provide a potential link between cardiopulmonary disease and neuropsychiatric manifestations, but this relationship remains insufficiently established. Sympathetic overactivity, impaired baroreflex control, reduced cardiac output, systemic inflammation, and altered cerebral perfusion are biologically plausible contributors to cognitive and emotional symptoms, although direct evidence in PAH remains limited.^{4,9,10,16,17,23,36} Therefore, neuropsychiatric manifestations should be considered clinically relevant components of PAH care, but mechanistic interpretations should remain cautious. The proposed pathophysiological links between neuropsychiatric manifestations and autonomic dysfunction are summarized in [Figure 8](#).

From a clinical perspective, screening for depression, anxiety, cognitive symptoms, and quality-of-life impairment may help identify unmet patient needs and support more comprehensive care. Future studies should clarify whether neuropsychiatric manifestations are independently associated with disease severity, treatment adherence, clinical outcomes, or autonomic markers in PAH.²⁴

3.5. Clinical implications and future perspectives

Autonomic dysfunction in PAH has potential clinical relevance because it has been associated with disease severity, right ventricular dysfunction, exercise limitation, and symptom burden.^{4,5,9-11} However, autonomic assessment is not currently part of routine PAH risk stratification, and available evidence remains insufficient to support its use for treatment decisions. Therefore, autonomic markers should be interpreted as exploratory tools that may complement, but not replace, established clinical, functional, imaging, biomarker, and hemodynamic parameters.^{1,9,10}

3.5.1. Autonomic markers in clinical assessment

Heart rate variability (HRV) is the most accessible non-invasive marker of autonomic function studied in

PAH. Reduced HRV has been associated with worse functional status, reduced exercise capacity, and right ventricular dysfunction in small observational and prospective cohorts.^{5,9,10} These findings suggest that HRV may capture aspects of cardiovascular adaptability that are not fully reflected by resting hemodynamics alone. Nevertheless, methodological heterogeneity, differences in recording conditions, variable analytical approaches, and limited sample sizes currently preclude routine clinical implementation.

Baroreflex sensitivity may also provide information on cardiovascular reflex control in PAH, but its assessment is less practical and less standardized than HRV.^{16,17} At present, both HRV and baroreflex sensitivity should be considered research tools. Future studies should determine whether these markers provide incremental prognostic value beyond established PAH risk models.

3.5.2. Therapeutic modulation of the autonomic system

Direct therapeutic modulation of the autonomic nervous system remains investigational in PAH. Current PAH therapies target established pulmonary vascular pathways, including the endothelin, nitric oxide–cyclic guanosine monophosphate, prostacyclin, and activin signaling pathways.¹ Although improvements in hemodynamics and right ventricular function may influence autonomic balance indirectly, current evidence does not support autonomic modulation as an established therapeutic mechanism of approved PAH treatments.

Device-based neuromodulation and vagal nerve stimulation have shown potential in experimental models of pulmonary hypertension, but clinical evidence in PAH remains limited.^{17,37} Similarly, the use of beta-blockers in PAH remains controversial because of concerns regarding negative inotropic effects in a pressure-overloaded right ventricle.³⁸⁻⁴⁰ Current guidelines do not recommend routine beta-blocker therapy in PAH unless there is another clear indication, such as arrhythmia, coronary disease, or systemic hypertension.¹

Exercise training and pulmonary rehabilitation may improve functional capacity and quality of life in patients with pulmonary hypertension, and recent reviews have discussed their potential effects on autonomic regulation.^{8,41} However, whether exercise-induced autonomic changes independently contribute to clinical improvement in PAH remains uncertain.

3.5.3. Approved pharmacological therapies in PAH

Approved PAH therapies are directed at pulmonary vascular remodeling, vasoconstriction, and abnormal

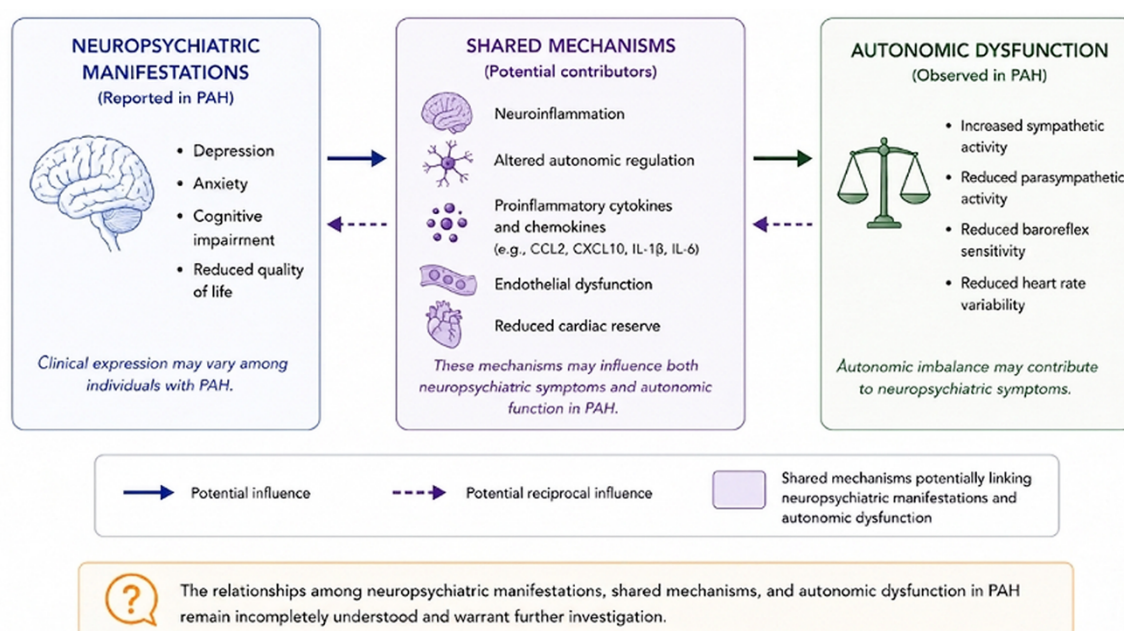


Figure 8. Conceptual model of neuropsychiatric manifestations and autonomic dysfunction in PAH. Neuropsychiatric symptoms, including depression, anxiety, cognitive impairment, and reduced quality of life, may be associated with autonomic dysfunction through shared pathophysiological mechanisms. Neuroinflammation, altered autonomic regulation, proinflammatory cytokines and chemokines (CCL2, CXCL10, IL-1 β , IL-6), endothelial dysfunction, and reduced cardiac reserve have been proposed as shared contributors to neuropsychiatric symptoms and autonomic function in PAH, based on indirect evidence. The relationships among neuropsychiatric manifestations, shared mechanisms, and autonomic dysfunction in PAH remain incompletely understood and warrant further investigation. Images adapted with Adobe Illustrator and Canva from material provided by Smart Servier (<https://smart.servier.com/>).

Abbreviations: CCL2: C-C motif chemokine ligand 2; CXCL10: C-X-C motif chemokine ligand 10; IL-1 β : interleukin-1 beta; IL-6: interleukin-6; PAH: pulmonary arterial hypertension.

signaling pathways rather than at the autonomic nervous system. Endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues, prostacyclin receptor agonists, and more recently activin signaling modulation with sotatercept form the basis of contemporary PAH treatment strategies.^{1,24} These therapies are used according to risk assessment, treatment response, and patient characteristics, frequently through multipathway combination approaches.^{1,24}

Supportive measures, including diuretics, oxygen therapy when indicated, supervised rehabilitation, and management of comorbidities, remain important components of comprehensive PAH care.¹ However, none of these approaches has yet established autonomic dysfunction as a direct treatment target in PAH.

3.5.4. Toward integrated and multidisciplinary care

The coexistence of cardiopulmonary limitation, autonomic abnormalities, psychological distress, cognitive symptoms, and impaired quality of life supports a broader approach to PAH care.^{29,32,35,42} Integration of cardiopulmonary

assessment with rehabilitation, psychological support, patient-reported outcomes, and symptom-directed care may help address dimensions of disease burden not fully captured by hemodynamic measurements alone.

This does not imply that autonomic assessment should currently guide routine management. Rather, autonomic dysfunction may serve as a useful research framework for understanding why patients with similar hemodynamic profiles may differ in symptoms, functional limitation, and quality-of-life impairment.²⁴

4. Discussion

4.1. Comparison with recent reviews and future research

Recent reviews have addressed autonomic dysfunction in pulmonary hypertension from complementary perspectives. Soares *et al.*⁸ discussed autonomic dysregulation in pulmonary hypertension with emphasis on physical exercise and rehabilitation. Plunkett *et al.*¹⁵ reviewed autonomic control of the pulmonary circulation and its implications for pulmonary hypertension. In contrast, the present review focuses on PAH from a

neurocardiological perspective, integrating autonomic imbalance, cardiovascular reflexes, central autonomic regulation, neuropsychiatric manifestations, and clinical implications within a cautious conceptual framework.

Future research should prioritize prospective studies that combine autonomic markers with right ventricular imaging, hemodynamics, exercise testing, biomarkers, and patient-reported outcomes. Standardized acquisition and analysis of HRV, baroreflex sensitivity, and other autonomic measures will be necessary before these tools can be evaluated for clinical use. Additional studies should also clarify whether autonomic dysfunction is a marker of disease severity, a contributor to disease progression, or a modifiable therapeutic target in selected PAH phenotypes.

4.2. Limitations of this review

This review has limitations. First, although the literature search was structured, this is a narrative review and was not conducted according to a systematic review protocol. Therefore, no formal risk-of-bias assessment or meta-analysis was performed.^{43,44} Second, available evidence on autonomic dysfunction in PAH remains limited and heterogeneous, with small sample sizes, different autonomic assessment methods, variable acquisition protocols, and differences in analytical approaches across studies.^{43,44}

Third, several associations discussed in this review are derived from observational or physiological studies and should not be interpreted as evidence of causality.^{9,45} In particular, the extent to which autonomic dysfunction is a marker of disease severity, a contributor to disease progression, or a compensatory response remains uncertain. Fourth, mechanistic links among autonomic dysfunction, neuroinflammation, cardiovascular reflex impairment, right ventricular adaptation, and neuropsychiatric manifestations remain incompletely established in PAH and are partly supported by indirect, translational, or exploratory evidence.

Finally, autonomic markers such as HRV and baroreflex sensitivity are not standardized for routine clinical use in PAH.^{10,46} The proposed neurocardiological and brain–heart–lung framework should therefore be interpreted as a conceptual and hypothesis-generating model rather than an established clinical paradigm.

5. Conclusion

Overall, the evidence reviewed partially supports the hypothesis that autonomic imbalance in PAH may represent more than a secondary marker of advanced disease, as sympathetic overactivity, reduced parasympathetic modulation, impaired HRV, and altered cardiovascular

reflex control have been associated with disease severity, right ventricular dysfunction, exercise limitation, and symptom burden. However, current evidence remains insufficient to establish autonomic dysfunction as an independent causal mechanism of disease progression, a validated prognostic biomarker, or a direct therapeutic target.

Autonomic dysfunction should therefore be interpreted as a relevant but still exploratory dimension of PAH pathophysiology. A neurocardiological perspective may help integrate pulmonary vascular disease, right ventricular adaptation, cardiovascular reflex control, neuropsychiatric manifestations, and patient-centered outcomes within a broader conceptual framework. At present, autonomic markers such as HRV and baroreflex sensitivity should be considered complementary research tools rather than components of routine clinical risk stratification.

Future studies should use standardized autonomic assessment methods and prospective designs integrating hemodynamic data, right ventricular imaging, exercise testing, biomarkers, and patient-reported outcomes. Such studies are needed to determine whether autonomic dysfunction provides incremental prognostic information, identifies clinically meaningful PAH phenotypes, or represents a modifiable pathway in selected patients. Until then, recognizing the autonomic and neurocardiological complexity of PAH may support more comprehensive research and, eventually, more individualized approaches to patient care.

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