

COPD-Asthma-Heart Failure Overlap: Optimizing Bronchodilators and ICS in a High-Risk Triad

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Abstract: Chronic obstructive pulmonary disease (COPD), asthma, and heart failure (HF) frequently coexist, forming a high-risk clinical triad characterized by overlapping symptoms and pathophysiological mechanisms. This COPD-asthma-HF overlap complicates diagnosis and treatment due to shared clinical features such as dyspnea, wheezing, and exercise intolerance. Epidemiologically, up to 30% of COPD patients have concomitant HF, while 15–20% of obstructive airway disease patients exhibit asthma-COPD overlap, many of whom also develop HF due to chronic hypoxia, systemic inflammation, or shared risk factors like smoking. The interplay between these conditions is driven by chronic inflammation, airway obstruction, and cardiac dysfunction, creating a self-perpetuating cycle of disease progression. Inflammation in COPD and asthma contributes to endothelial dysfunction and atherosclerosis, exacerbating HF, while HF-induced hypoxia and congestion worsen pulmonary inflammation. Diagnostic challenges arise from overlapping symptoms and limitations of traditional tools such as spirometry and biomarkers, necessitating a multimodal approach. Therapeutic management is complex, as treatments for one condition may worsen another (eg, beta-agonists exacerbating HF or diuretics increasing mucus viscosity in COPD). Precision medicine approaches targeting treatable traits such as eosinophilic inflammation, fluid overload, and bronchospasm offer a strategic framework for personalized care. Pharmacological strategies must balance bronchodilation, anti-inflammatory effects, and cardiac support, with careful consideration of drug safety profiles. This review highlights the need for integrated diagnostic and therapeutic strategies to optimize outcomes in this high-risk population, emphasizing the importance of recognizing shared pathophysiology and individualized management.

Keywords: COPD, asthma, heart failure, overlap symptoms, pharmacological intervention

Introduction

COPD, asthma, and HF frequently coexist, creating a high-risk clinical triad with overlapping symptoms and pathophysiological mechanisms.^{1,2} COPD-asthma-HF overlap refers to the concurrent presence of these conditions in a single patient, complicating diagnosis and treatment due to shared features such as dyspnea, wheezing, and exercise intolerance.³ While COPD and asthma are both obstructive airway diseases, HF contributes to respiratory symptoms through pulmonary congestion and reduced cardiac output, further exacerbating airflow limitation.^{4–6} Epidemiologically, this overlap is increasingly recognized, particularly in older adults with long-standing respiratory disease and cardiovascular risk factors. Studies suggest that up to 30% of COPD patients have concomitant HF, while 20–25% of HF patients exhibit undiagnosed COPD or asthma.^{7–9} Asthma-COPD overlap affects 15–20% of obstructive airway disease patients, many of whom also develop HF due to chronic hypoxia, systemic inflammation, or shared risk factors like smoking and hypertension.¹⁰ In a study, it was stated that 14.5% was died who diagnosed COPD with right and left heart failure. The right heart failure is an individual and primary risk factor for mortality in COPD. In the patients, 86.3% had COPD alone, 8.1% had COPD and HF, 3.9%, Ischemic heart disease (IHD) 1.7%.¹¹ It was found that mortality was increased in the patient with higher cardiovascular risk. The interplay between COPD, asthma, and HF is driven by overlapping pathophysiological mechanisms, including chronic inflammation, airway obstruction, and cardiac dysfunction, which



collectively worsen disease progression and clinical outcomes.^{12,13} Persistent low-grade inflammation is a hallmark of all three conditions. In COPD and asthma, airway inflammation involves neutrophils, eosinophils, and pro-inflammatory cytokines (eg, IL-6, TNF- α), contributing to bronchoconstriction and remodeling.^{14,15} This inflammatory milieu extends beyond the lungs, promoting endothelial dysfunction and atherosclerosis, which exacerbate HF progression. Conversely, HF itself induces systemic inflammation due to reduced cardiac output and tissue hypoxia, further aggravating pulmonary inflammation and airway hyperresponsiveness.¹⁶ Both COPD (fixed obstruction) and asthma (reversible obstruction) impair airflow, increasing work of breathing and oxygen demand.^{17,18} In HF, pulmonary congestion from left ventricular dysfunction leads to interstitial edema and reduced lung compliance, mimicking or worsening obstructive symptoms.^{19,20} Additionally, chronic hypoxia in advanced COPD or asthma can induce pulmonary hypertension, increasing right ventricular afterload and accelerating HF development.^{21–23} HF exacerbates respiratory disease through fluid overload and reduced perfusion, while chronic lung disease strains the heart via hypoxia-induced vasoconstriction and hyperinflation-related impaired ventricular filling (eg, “cardiopulmonary coupling”).^{5,24,25} Beta-agonist overuse in obstructive lung disease may also precipitate arrhythmias or worsen myocardial demand in HF.^{26–28}

In COPD and asthma, persistent airway inflammation driven by neutrophils, eosinophils, and cytokines like IL-6 and TNF- α triggers bronchoconstriction, remodeling, and oxidative stress.^{29,30} This inflammatory cascade extends beyond the lungs, promoting endothelial dysfunction and atherosclerosis, which exacerbate HF.^{31,32} Conversely, HF amplifies pulmonary inflammation through reduced cardiac output, tissue hypoxia, and venous congestion, further worsening airway obstruction.^{22,33} Additionally, mechanical interactions between the heart and lungs play a critical role: pulmonary hypertension from chronic hypoxia in COPD or asthma increases right ventricular afterload, while left ventricular dysfunction in HF induces pulmonary edema, impairing gas exchange and lung compliance.^{34,35} These intertwined processes blur the lines between cardiac and respiratory symptoms, complicating clinical management. Pollen-induced allergic asthma contributes to cardiovascular disease pathogenesis via dual inflammatory and hypoxic mechanisms. IgE-mediated mast cell/eosinophil activation releases pro-inflammatory cytokines (IL-4, IL-6, IFN- γ), driving persistent pulmonary inflammation and hypoxia in asthmatic lungs^{29,36} (Figure 1).

In COPD and asthma, fixed or reversible airflow limitation increases the work of breathing and oxygen demand, straining an already compromised cardiovascular system.³⁷ HF exacerbates this burden by reducing perfusion to respiratory muscles and promoting fluid retention, which narrows airways and mimics obstructive symptoms.^{20,38} Meanwhile, therapies for one condition may inadvertently harm another, for instance, beta-agonists for asthma/COPD can precipitate tachycardia or arrhythmias in HF, while diuretics for HF may exacerbate COPD-related mucus viscosity.^{39,40} The resulting therapeutic dilemma underscores the need for a nuanced approach that balances bronchodilation, anti-inflammatory effects, and cardiac support (Table 1).

Diagnostic Challenges and Phenotyping in Overlapping Presentations

The clinical diagnosis of COPD-asthma-HF overlap is notoriously challenging due to the significant symptom overlap between these conditions, particularly dyspnea, wheezing, and reduced exercise tolerance.⁵⁵ Dyspnea, the most common presenting symptom, occurs in all three disorders but arises from distinct mechanisms: airflow limitation in COPD and asthma versus pulmonary congestion and reduced cardiac output in HF.⁵⁵ This makes it difficult to attribute breathlessness to a single cause without comprehensive testing. Wheezing, traditionally associated with asthma and COPD, can also manifest in HF due to bronchial compression from pulmonary edema or increased airway resistance from interstitial fluid, leading to potential misdiagnosis.^{2,4} Similarly, reduced exercise tolerance may reflect skeletal muscle deconditioning in COPD, bronchoconstriction in asthma, or impaired cardiac function in HF, further complicating clinical assessment.^{56,57} Cigarette smoke induces a pathogenic cascade linking airway disease (asthma/COPD) to cardiovascular complications through synergistic inflammatory and hypoxic pathways. By triggering airway obstruction, inflammatory cell infiltration, and ROS generation, smoking establishes chronic hypoxia^{58–60} (Figure 2).

The diagnostic dilemma is compounded by the limitations of traditional diagnostic tools. Spirometry, while essential for identifying obstructive lung disease, cannot differentiate between COPD and asthma in the context of HF, where bronchodilator responsiveness may be blunted due to cardiac-related airflow limitation.^{61–63} Biomarkers such as B-type natriuretic peptide (BNP) may be elevated in HF but can also be influenced by acute exacerbations of lung disease.^{64,65}

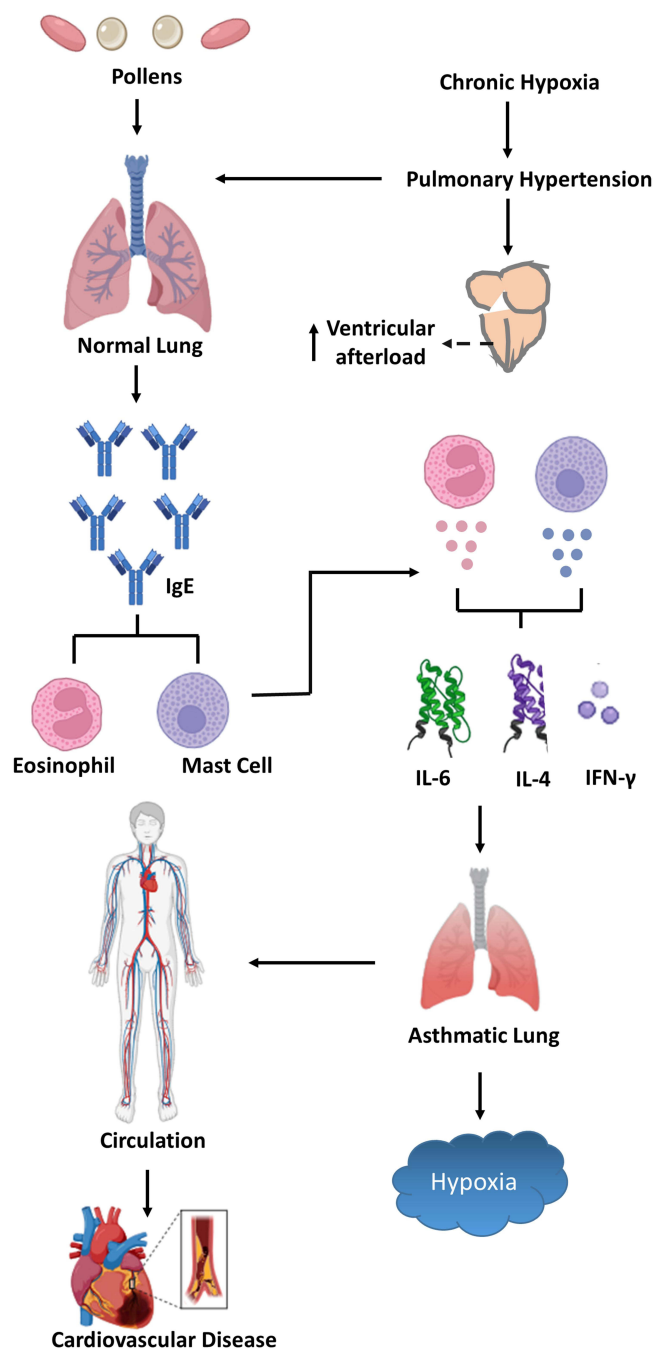


Figure 1 Pollen-induced allergic asthma promotes cardiovascular disease through inflammatory and hypoxic pathways. When exposed to pollen, IgE-mediated responses stimulate mast cells and eosinophils, leading to the release of cytokines like IL-4, IL-6, and IFN- γ . Unlike healthy lungs, asthmatic lungs experience persistent inflammation and hypoxia. This systemic inflammation, driven by circulating inflammatory factors, increases the risk of cardiovascular disease (CVD). Additionally, hypoxia worsens both asthma and CVD, establishing a connection between pollen-induced allergic asthma and cardiovascular disease through immune and vascular pathways.

Imaging studies like chest X-rays or echocardiograms may reveal cardiogenic pulmonary edema or structural heart disease but often fail to distinguish between chronic lung pathologies.⁶⁶ Consequently, clinicians must rely on a combination of detailed history-taking, multimodal testing, and therapeutic trials to disentangle these overlapping conditions, emphasizing the need for an integrated diagnostic approach in this high-risk population.

Phenotyping these patients requires a multimodal approach that integrates clinical history, biomarkers, and imaging. Eosinophilia may indicate an asthma-predominant phenotype but can also occur in COPD or even HF with eosinophilic inflammation.^{67,68} Provocative testing, such as cardiopulmonary exercise testing, may further clarify whether exercise

Table 1 Diagnostic Challenges in COPD-Asthma-HF Overlap

Feature	COPD	Asthma	Heart Failure	Overlap Considerations	References
Primary Symptom	Chronic dyspnea	Episodic dyspnea	Exertional dyspnea	All three cause dyspnea; assess pattern and triggers	[41–43]
Wheezing	Common (fixed)	Common (variable)	Possible (cardiac)	HF wheezing from bronchial edema may mimic asthma	[44–46]
Key Biomarkers	–	FeNO, eosinophils	BNP/NT-proBNP	BNP elevated in HF but also in RV strain from lung disease	[47,48]
Spirometry	Fixed obstruction	Reversible obstruction	May show restriction	HF can cause false obstruction pattern; bronchodilator response blunted in overlap	[49,50]
Imaging Findings	Emphysema, hyperinflation	Air trapping	Pulmonary edema	CT helps distinguish emphysema vs edema; echo essential for cardiac function	[51,52]
Treatment Paradoxes	Beta-agonists safe	Beta-agonists first-line	Beta-blockers preferred	Beta-agonist risks in HF; beta-blocker caution in asthma	[53,54]

limitation stems primarily from ventilatory impairment or cardiac insufficiency. Ultimately, accurate phenotyping is critical for guiding therapy, as misclassification risks inappropriate treatment such as excessive beta-agonist use in HF or underutilization of guideline-directed HF therapies in patients mistakenly attributed solely to pulmonary disease.

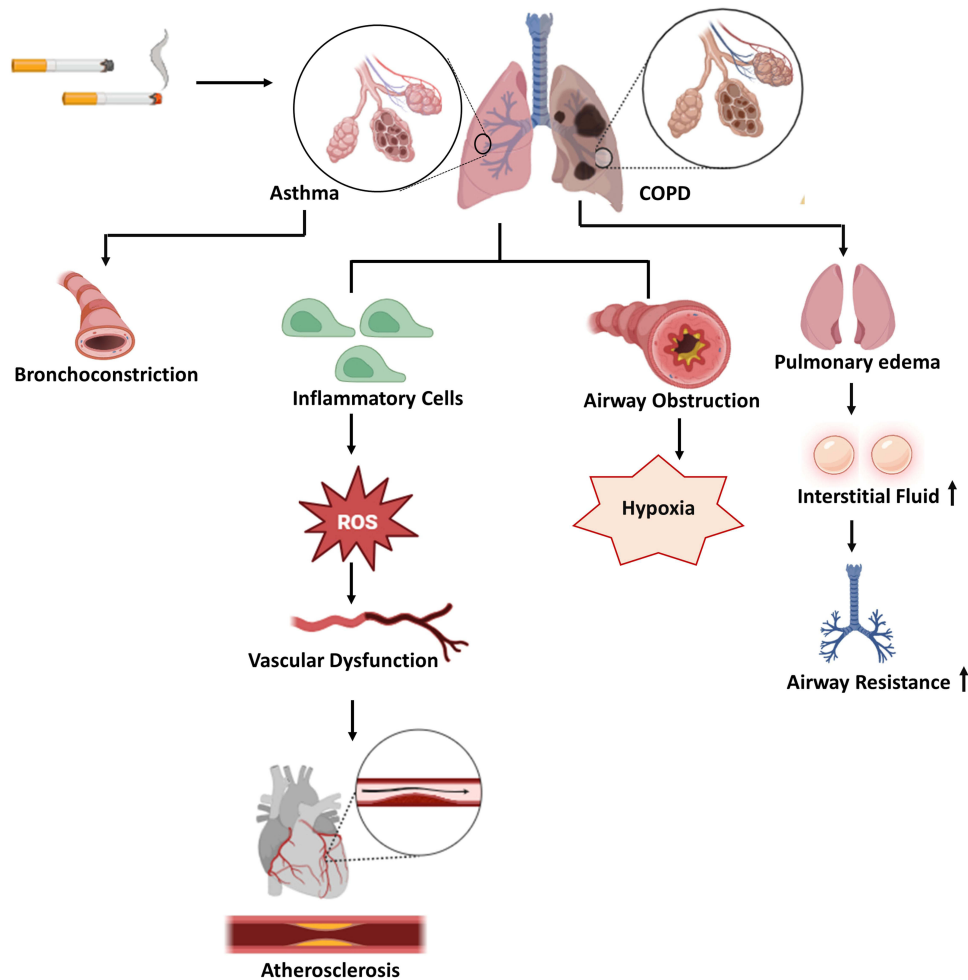


Figure 2 Mechanistic links between smoking-induced airway disease (asthma/COPD) and cardiovascular complications. Cigarette smoke causes airway blockage, attracts inflammatory cells, and generates reactive oxygen species (ROS), resulting in chronic hypoxia. In asthma and COPD, ongoing inflammation exacerbates impaired vascular function. Systemic oxidative stress and hypoxia further promote atherosclerosis, establishing a connection between smoking-induced lung disease and cardiovascular risk via common inflammatory and hypoxic pathways.

A structured diagnostic algorithm incorporating these elements is essential for optimizing care in this complex overlap population.

The Impact of Asthma and COPD Pathophysiology on Cardiac Function

The interplay between chronic airway inflammation and cardiac dysfunction forms a critical pathophysiological axis in the COPD-asthma-HF overlap syndrome. In both asthma and COPD, persistent pulmonary inflammation initiates a cascade of systemic effects that directly and indirectly impair cardiac function.⁶⁹ Asthma, typically characterized by eosinophilic airway inflammation driven by type 2 cytokines (IL-4, IL-5, IL-13), and COPD, dominated by neutrophilic inflammation with elevated IL-6, IL-8, and TNF- α , share the common feature of creating a pro-inflammatory milieu that extends beyond the lungs.^{70,71} These circulating inflammatory mediators promote endothelial dysfunction, accelerate atherosclerosis, and contribute to myocardial remodeling key processes in the development and progression of HF.^{72,73} The impact of chronic airway inflammation on the cardiovascular system occurs through multiple mechanisms.⁷⁴ First, systemic hypoxia resulting from impaired gas exchange in COPD and severe asthma triggers compensatory polycythemia and pulmonary vasoconstriction, increasing right ventricular afterload and potentially leading to cor pulmonale.^{75,76} Second, the oxidative stress associated with chronic lung diseases promotes the release of reactive oxygen species that directly damage cardiomyocytes and impair cardiac contractility.^{77,78} Third, the increased mechanical load on the heart from pulmonary hypertension (common in advanced COPD) combines with systemic inflammation to promote left ventricular diastolic dysfunction, a precursor to HF with preserved ejection fraction (HFpEF).⁷⁹ This is particularly relevant in elderly patients with long-standing lung disease, where the cumulative burden of inflammation and hypoxia manifests as concurrent cardiac dysfunction.

Clinically, these interactions create diagnostic and therapeutic challenges. Patients may present with worsening dyspnea that could equally reflect an asthma/COPD exacerbation or acute HF decompensation.^{42,80} The inflammatory state of chronic lung disease also alters the cardiovascular response to therapy, for instance, beta-agonists used for bronchoconstriction may have reduced efficacy in the setting of myocardial inflammation while simultaneously increasing arrhythmia risk.^{40,81} Furthermore, corticosteroids, though effective for controlling airway inflammation, can exacerbate fluid retention and hypertension, potentially worsening cardiac function.^{82,83} Understanding these complex interactions is essential for managing the overlap syndrome. Biomarkers such as C-reactive protein (CRP) and NT-proBNP may help differentiate the relative contributions of inflammation versus cardiac strain, while imaging techniques like cardiac MRI can detect early myocardial fibrosis.⁸⁴ Therapeutic strategies must balance anti-inflammatory control of lung disease with cardioprotective approaches, potentially including targeted biologics for eosinophilic asthma or pulmonary vasodilators in COPD-associated pulmonary hypertension.⁸⁵ The recognition that chronic airway inflammation serves as both a driver and amplifier of cardiac dysfunction underscores the need for integrated care pathways in this high-risk population. Episodic asthma or chronic COPD, often with specific triggers (allergens, infections) and may improve with bronchodilators. Whilst, acute HF exerts exertional, orthopnea, paroxysmal nocturnal dyspnea (PND). HF has poor response to bronchodilator alone and improve with diuresis.

Effects of Pulmonary Hypertension and Right Heart Strain in COPD-HF Overlap

The development of pulmonary hypertension (PH) and subsequent right heart strain represents a critical pathway through which COPD exacerbates HF, creating a distinct phenotype within the overlap syndrome.^{21,86} In COPD, chronic alveolar hypoxia triggers hypoxic pulmonary vasoconstriction, which, when sustained, leads to vascular remodeling and increased pulmonary vascular resistance.^{87,88} This afterload elevation imposes significant strain on the right ventricle (RV), initially causing adaptive hypertrophy but eventually progressing to RV dilation and dysfunction - a condition termed cor pulmonale. The presence of concurrent HF further compounds this pathophysiology through multiple mechanisms: left ventricular diastolic dysfunction increases pulmonary venous pressures (post-capillary PH), while chronic systemic inflammation from COPD accelerates pulmonary vascular remodeling (pre-capillary PH).^{89,90}

Clinically, this manifests as worsening exertional dyspnea disproportionate to spirometric findings, peripheral edema, and elevated jugular venous pressure – symptoms that overlap substantially with both COPD exacerbations and HF decompensation.^{91,92} The diagnostic challenge is heightened because traditional echocardiographic measures of RV function may be unreliable in COPD patients due to hyperinflation, while NT-proBNP levels can be elevated from either RV strain or left-sided HF.^{93,94} Therapeutic implications are profound: bronchodilators, while essential for COPD management, must be carefully titrated to avoid further increases in pulmonary artery pressures.⁹⁵ Supplemental oxygen becomes crucial to break the cycle of hypoxic vasoconstriction, particularly in patients demonstrating nocturnal desaturation.^{96,97} Emerging evidence suggests a potential role for targeted PH therapies in select patients, though their use requires careful consideration of the underlying hemodynamics. This complex interplay underscores the need for comprehensive hemodynamic assessment in COPD-HF overlap patients presenting with disproportionate respiratory symptoms or exercise limitation.

Bronchoconstriction and Airway Remodeling in Asthma Exacerbating HF Symptoms

The interplay between asthma-related airway pathology and heart failure creates a particularly challenging clinical scenario within the overlap syndrome.^{10,98} In asthma patients with concomitant HF, bronchoconstriction and chronic airway remodeling impose significant additional burdens on an already compromised cardiovascular system through several distinct mechanisms.^{12,99} The acute bronchoconstriction characteristic of asthma exacerbations dramatically increases intrathoracic pressure fluctuations, which in turn elevate left ventricular afterload and reduce cardiac output.¹⁰⁰ This effect is particularly pronounced in HF patients with reduced ejection fraction, where the heart operates on the steep portion of the Frank-Starling curve.^{101–103} Chronic airway remodeling in long-standing asthma further compounds these effects through persistent airflow limitation and dynamic hyperinflation.^{103,104} The resulting increased work of breathing raises myocardial oxygen demand while simultaneously reducing diastolic filling time due to tachycardia – a dangerous combination for patients with existing coronary artery disease or ventricular dysfunction.^{105,106} Additionally, the inflammatory milieu of poorly controlled asthma (particularly eosinophilic inflammation) may directly contribute to myocardial inflammation and fibrosis, potentially accelerating HF progression.¹⁰⁷

These pathophysiological interactions create a vicious cycle where asthma exacerbations precipitate HF decompensation, and vice versa.^{108,109} The clinical presentation often manifests as refractory dyspnea that responds poorly to conventional bronchodilator therapy, with physical findings that may include both wheezing and pulmonary crackles.¹¹⁰ This overlap poses significant diagnostic challenges, as traditional markers like BNP may be elevated in both acute asthma exacerbations and HF decompensation.⁶⁴ Therapeutic approaches must therefore address both the bronchoconstrictive component and its cardiovascular consequences, requiring careful balancing of beta-agonist therapy (with its potential arrhythmogenic effects) against the need for adequate bronchodilation.^{27,111} Distinct inflammatory profiles in COPD (neutrophilic; IL-8/TNF- α) and asthma (eosinophilic; IL-4/5/13) converge to drive systemic hypoxia, endothelial dysfunction, and cor pulmonale, creating a self-amplifying cardiopulmonary syndrome that requires targeted anti-inflammatory and bronchodilator interventions¹¹² (Figure 3).

Identifying Treatable Traits: Eosinophilic Inflammation, Fluid Overload, and Bronchospasm

Within the COPD-asthma-HF overlap syndrome, a precision medicine approach focusing on identifiable and modifiable “treatable traits” offers a strategic framework for personalized management. Eosinophilic inflammation represents a particularly actionable target, as elevated blood or sputum eosinophil counts may predict responsiveness to inhaled corticosteroids (ICS) in asthma-COPD overlap while also indicating potential cardiac involvement, since eosinophilic myocarditis can worsen HF outcomes.¹¹³ However, distinguishing true Type 2 inflammation from HF-related eosinophilia requires correlation with clinical context and additional biomarkers like fractional exhaled nitric oxide (FeNO).^{48,114}

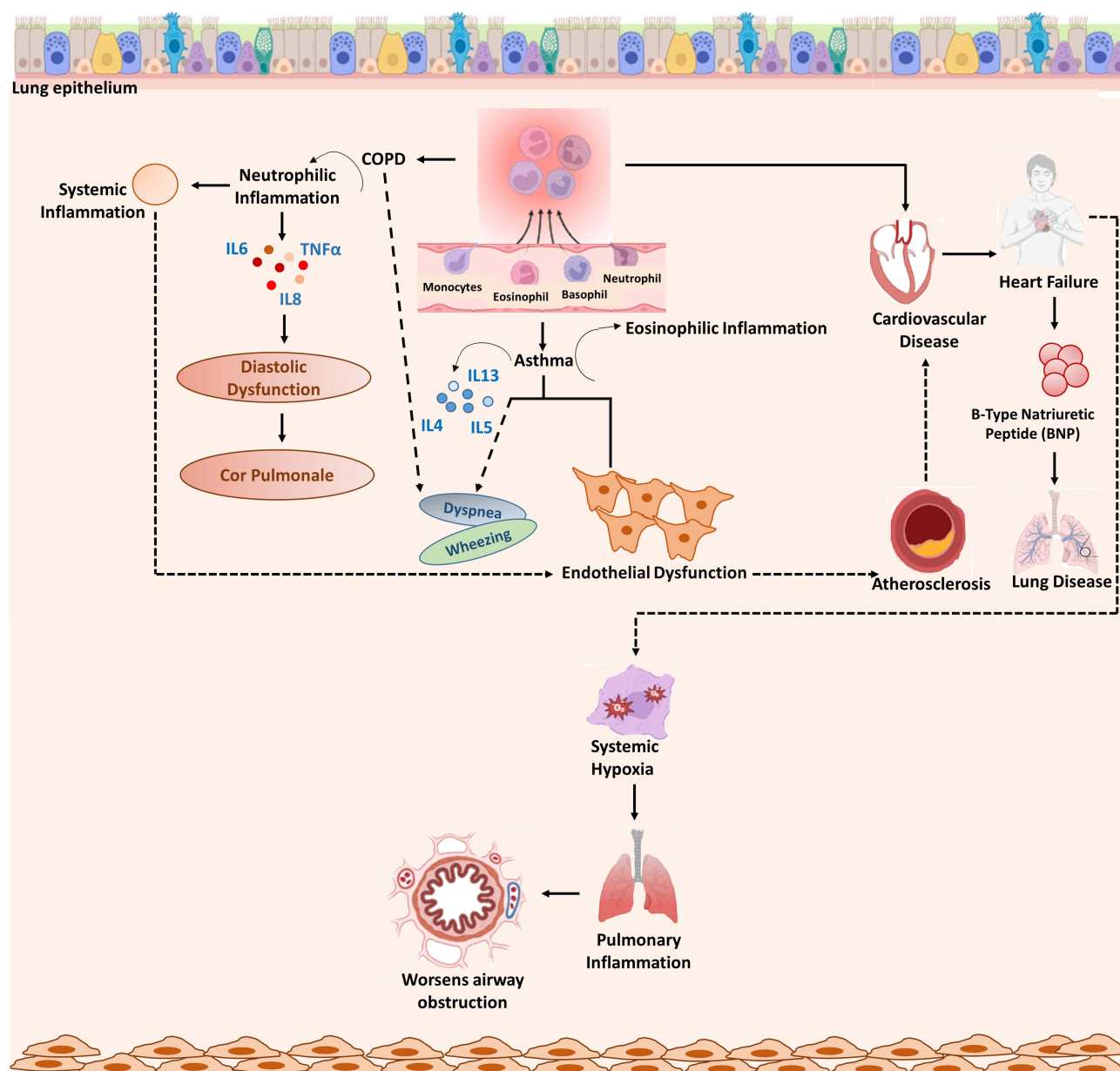


Figure 3 Inflammatory and cardiopulmonary interactions in COPD-asthma-heart failure overlap. COPD (neutrophil-driven, involving IL-8 and TNF- α) and asthma (eosinophil-driven, involving IL-4, IL-5, and IL-13) contribute to lung inflammation, systemic hypoxia, and airway blockage (causing dyspnea and wheezing), which worsen endothelial dysfunction and atherosclerosis. Systemic inflammation (mediated by IL-6) further aggravates cardiovascular disease (CVD) and heart failure, while cor pulmonale (indicated by elevated BNP) signals right heart stress. This disease triad accelerates progression through shared pathways, highlighting the need for optimized bronchodilators and ICS to reduce inflammation, hypoxia, and cardiopulmonary impairment.

Fluid overload, a cardinal feature of HF, frequently complicates respiratory symptoms in overlap patients.^{115,116} Careful assessment of jugular venous pressure, peripheral edema, and lung ultrasound B-lines helps differentiate cardiac from pulmonary causes of dyspnea.^{117,118} Notably, overzealous diuresis may worsen COPD by increasing mucus viscosity, while under-treatment perpetuates bronchial wall edema that mimics refractory asthma.¹¹⁹ Dynamic weight monitoring and natriuretic peptide trends provide objective measures to guide therapy. Bronchospasm, common to both asthma and COPD, requires nuanced management in HF patients.⁵⁰ Reversible airflow obstruction on spirometry supports bronchodilator use, but the choice of agent matters long-acting muscarinic antagonists may be preferable to beta-agonists in HF due to lower arrhythmogenic potential.^{120,121} Treatment response should be assessed with both pulmonary function and cardiac parameters, as bronchodilation may unexpectedly improve ventricular filling in patients

with hyperinflation-related diastolic dysfunction.^{122,123} By systematically evaluating these treatable traits, clinicians can develop targeted interventions that address the multifactorial pathophysiology of this high-risk overlap population.

Pharmacological Management Strategies: Bronchodilators in the Triad

The use of bronchodilators in the COPD-asthma-HF overlap requires careful balancing of pulmonary benefits against cardiovascular risks, necessitating an individualized approach based on dominant phenotypes.¹²⁴ For patients with asthma-COPD predominance, long-acting β_2 -agonists (LABAs) remain foundational, but their cardiovascular effects demand particular caution in HF.^{125,126} Studies demonstrate that while selective β_2 -agonists improve FEV1 by 12–15% in overlap patients, they may increase heart rate by 8–10 bpm and potentially exacerbate arrhythmias in vulnerable individuals.^{81,127} This has led to preferential use of long-acting muscarinic antagonists (LAMAs) in HF-associated cases, which show comparable bronchodilation with superior cardiac safety profiles. Emerging evidence suggests tiotropium may reduce HF exacerbations in COPD patients by 21% compared to LABAs, possibly through reduced dynamic hyperinflation and improved cardiac filling.⁵⁰

Dual bronchodilation (LAMA/LABA) presents a therapeutic dilemma – while highly effective for airflow limitation, the combination may compound risks in severe HF.^{128,129} Current guidelines recommend a stepwise approach: initiating LAMA monotherapy in high-risk cardiac patients, then cautiously adding LABAs while monitoring for tachycardia or arrhythmias.¹³⁰ Ultra-LABAs like indacaterol, with faster onset and lower peak serum concentrations, may offer improved safety margins. Importantly, bronchodilator response should be assessed not just by spirometry, but through comprehensive evaluation including dyspnea scores, exercise tolerance, and cardiac biomarkers, as pulmonary decompression may unexpectedly improve ventricular function in some patients with significant hyperinflation. This nuanced approach underscores the need for close cardiopulmonary monitoring when optimizing bronchodilator therapy in this complex triad.

Role of LABAs/LAMAs in COPD-Asthma Overlap with HF

The therapeutic application of long-acting bronchodilators in patients with COPD-asthma-heart failure overlap requires careful consideration of both pulmonary efficacy and cardiovascular safety.¹³¹ LAMAs (eg, tiotropium, glycopyrronium) have emerged as preferred first-line agents due to their neutral cardiac profile, demonstrating comparable bronchodilation to LABAs without significant effects on heart rate or arrhythmia risk. Importantly, LAMAs may improve ventricular filling in HF patients by reducing dynamic hyperinflation, with studies showing a 15–20% improvement in cardiac output in responders.^{132,133}

For LABA therapy (eg, salmeterol, formoterol), current evidence suggests cautious use in HF, particularly in patients with pre-existing arrhythmias or ischemic cardiomyopathy.¹³⁴ While LABAs provide superior symptom relief in asthma-predominant overlap, their β_2 -adrenergic activity may increase myocardial oxygen demand and potentially worsen outcomes in advanced HF.¹³⁵ Recent pharmacokinetic studies indicate that the newer ultra-LABAs (eg, indacaterol, olodaterol) with faster receptor dissociation may offer improved cardiac safety profiles.¹³⁶

Risks of Beta-Agonists in HF and ICS Benefits in Eosinophilic Inflammation

The use of beta-agonists in HF requires careful risk stratification due to their potential to exacerbate cardiovascular instability.²⁶ By stimulating β_2 -adrenergic receptors, these agents can induce tachycardia (increasing heart rate by 10–15 bpm) and lower serum potassium levels, thereby predisposing patients to atrial and ventricular arrhythmias particularly dangerous in those with pre-existing ischemic cardiomyopathy or reduced ejection fraction.¹³⁷ Observational data suggest that frequent SABA use is associated with a 27% increased risk of HF hospitalization, while LABAs may elevate the relative risk of cardiovascular events by 1.3-fold in vulnerable populations. Key precautions include: (1) preferential use of cardioselective beta-agonists (eg, salmeterol over formoterol), (2) continuous cardiac monitoring during exacerbations, and (3) avoidance in decompensated HF (NYHA Class IV).^{50,138}

Conversely, ICS demonstrate particular value in asthma-COPD overlap patients with eosinophilic inflammation (blood eosinophils ≥ 300 cells/ μ L), where they reduce exacerbation frequency by 30–40%.¹³⁹ ICS mitigate airway inflammation through NF- κ B inhibition, which may also beneficially modulate systemic inflammation contributing to HF

progression.¹⁴⁰ However, their use requires careful patient selection: ICS should be avoided in non-eosinophilic COPD phenotypes due to increased pneumonia risk, and in HF patients with fluid retention tendencies, as corticosteroids may worsen edema.¹⁴¹ Practical strategies include: (1) confirming eosinophilic inflammation via CBC or sputum analysis, (2) using the lowest effective ICS dose (eg, fluticasone 100 mcg BID), and (3) combining ICS with LAMAs rather than LABAs in HF patients to minimize β -adrenergic stimulation.^{142,143} Regular reassessment of both respiratory control and cardiac status ensures optimal benefit-risk balance in this complex triad. While LAMA/LABA combinations effectively alleviate airflow obstruction and hyperinflation in COPD-asthma-heart failure overlap, their cardiovascular safety profile necessitates individualized use, particularly avoiding LABAs in arrhythmia-prone patients to optimize cardiopulmonary outcomes^{3,144} (Figure 4).

Potential Risks of Pneumonia and Fluid Retention in HF Patients

The use of ICS in COPD-asthma-HF overlap patients introduces two critical safety considerations that require vigilant monitoring: pneumonia risk and fluid retention.¹²⁴ ICS therapy increases the relative risk of pneumonia by 1.5- to 2-fold in COPD patients, with this risk being particularly pronounced in those with concurrent HF due to pre-existing immune dysfunction and pulmonary congestion.^{145,146} Mechanistically, ICS impair alveolar macrophage function and mucociliary clearance, creating a permissive environment for bacterial colonization.¹⁴⁷ This risk is further amplified in HF patients who frequently exhibit compromised respiratory defenses secondary to chronic pulmonary edema. Clinically, this necessitates careful screening for recurrent pneumonia (≥ 2 episodes/year) as a potential indication for ICS dose reduction or discontinuation, particularly in non-eosinophilic patients.¹⁴⁸

Fluid retention represents another ICS-associated complication that may destabilize HF management. Corticosteroids enhance renal sodium reabsorption and potentiate mineralocorticoid effects, which can precipitate peripheral edema and worsen pulmonary congestion even at moderate doses.⁸² This effect is particularly problematic in patients with pre-

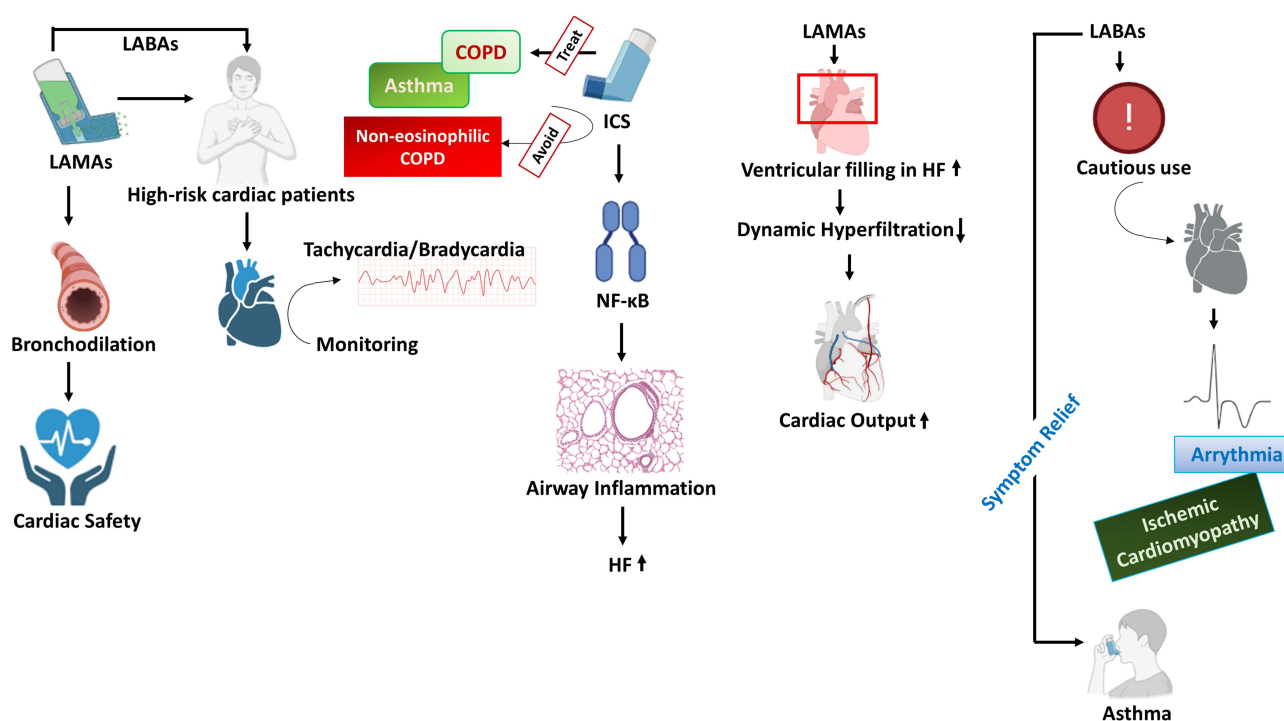


Figure 4 Cardiopulmonary Effects of LAMA/LABA Therapy in COPD-Asthma-Heart Failure Overlap. LAMAs exhibit cardiovascular neutrality, offering safe bronchodilation while enhancing ventricular filling and cardiac output in heart failure patients. Their combination with LABAs improves symptom control in asthma/COPD, though requires careful use in patients with arrhythmias or ischemic cardiomyopathy due to potential tachycardia risks. While reducing dynamic hyperinflation may improve cardiac function, LABAs necessitate vigilance for arrhythmic effects. Effective bronchodilator therapy in this high-risk patient group requires careful selection to optimize airway benefits (alleviating obstruction and hypoxia) while maintaining cardiac safety, underscoring the need for personalized treatment to prevent cardiovascular complications stemming from systemic hypoxia.

existing right heart failure or renal impairment. Monitoring parameters should include daily weight measurements (alert threshold: >2 kg gain in 3 days), regular assessment of jugular venous pressure, and periodic BNP monitoring.¹⁴⁹ Mitigation strategies include: (1) preferential use of ciclesonide (which has lower systemic bioavailability), (2) co-administration with diuretics, and (3) strict sodium restriction (<2 g/day).¹⁵⁰ These precautions are especially crucial during acute exacerbations when systemic steroid bursts are required, as even short courses (eg, prednisone 40 mg × 5 days) can significantly worsen fluid balance in decompensated HF patients.¹⁵¹

Diuretics and Cardiac Medications: Loop Diuretics for HF with Pulmonary Congestion

In patients with the COPD-asthma-HF triad, loop diuretics play a pivotal yet nuanced role in managing pulmonary congestion while requiring careful titration to avoid exacerbating respiratory symptoms. These agents (eg, furosemide, torsemide) effectively reduce pulmonary vascular congestion by inhibiting the Na-K-2Cl transporter in the loop of Henle, thereby decreasing pulmonary capillary wedge pressure and improving gas exchange.^{152,153} However, their use in this overlap population presents unique challenges: over-aggressive diuresis may lead to excessive bronchial mucus dehydration, increasing sputum viscosity and exacerbating airflow obstruction in COPD, while electrolyte imbalances (particularly hypokalemia and hypomagnesemia) can lower the threshold for ventricular arrhythmias when combined with beta-agonist therapy.^{154,155} Optimal management requires a balanced approach, initiating with low-to-moderate doses (eg, furosemide 20–40 mg IV or equivalent oral dosing) and titrating based on both cardiac (eg, jugular venous pressure, daily weights) and respiratory (eg, sputum characteristics, oxygen saturation) parameters. Combination therapy with thiazide diuretics may be considered in refractory cases, though this necessitates close monitoring of renal function and electrolytes.¹⁵⁶ Importantly, clinicians must remain vigilant for drug interactions - beta-agonists may counteract diuretic efficacy by promoting sodium retention, while corticosteroids can exacerbate fluid retention through mineralocorticoid effects. Emerging strategies such as lung ultrasound-guided diuresis, which allows real-time assessment of pulmonary edema resolution through B-line quantification, may help strike the crucial balance between alleviating cardiac congestion and maintaining adequate bronchial hydration in these complex patients.^{5,157} (Table 2).

Non-Pharmacological Interventions

Non-pharmacological approaches are vital and complement pharmacological approaches. Higher improvements of these strategies have been found to enhance quality of life and reduce the risk of disease initiation. The primary and secondary non-pharmacological strategies are pulmonary rehabilitation, long-term oxygen therapy, non-invasive ventilation, smoking cessation, and patient education.¹⁶⁸ Long-term oxygen therapy contributes to alleviate hypoxia, vasoconstriction, ventricular afterload, and pulmonary hypertension. Non-invasive ventilation provides massive support through unloading respiratory muscles, improving gas exchange, and reducing ventricular afterload.¹⁶⁸ Therefore, risk of concomitant cardiac failure can be avoided in patients. Cigarette smoke initiates lung injury by enhancing airway inflammation,

Table 2 Pharmacological Management Strategies for the Triad

Medication Class	Benefits in Triad	Risks in Overlap	Special Considerations	Monitoring Parameters	References
LAMAs (eg, tiotropium)	Improves FEV1; cardiac neutral	Dry mouth, constipation	First-line in HF; may improve ventricular filling	Spirometry, heart rate, HF symptoms	[158,159]
LABAs (eg, salmeterol)	Better asthma control	Tachycardia, arrhythmias	Avoid in unstable HF; use ultra-LABAs if needed	ECG monitoring, exercise tolerance	[160,161]
ICS (eg, fluticasone)	Reduces eosinophilic exacerbations	Pneumonia, fluid retention	Only if eosinophils >300; combine with LAMAs in HF	Sputum eosinophils, weight, JVP	[162,163]
Loop Diuretics (eg, furosemide)	Relieves pulmonary congestion	Mucus dehydration, electrolytes	Titrate to lowest effective dose; time dosing	Daily weights, sputum viscosity, electrolytes	[164,165]
Beta-blockers (eg, bisoprolol)	HF mortality benefit	Bronchospasm risk	Start very low dose in asthma-COPD; monitor PFTs	Respiratory symptoms, FEV1	[166,167]

chronic hypoxia, and oxidative stress. Thereby, these series of events drive bronchial obstruction and endothelial dysfunction. Therefore, smoking cessation is highly effective to prevent further pulmonary damage and mitigate disease progression. Furthermore, patient education is a vital self-management which includes regular self-checkup, promoting smoking cessation, and mitigating exacerbations. Precisely, non-pharmacological interventions are promising alternatives to develop quality of life, mitigate disease progression, and to reduce hospitalizations.¹⁶⁹

Conclusion

The COPD-asthma-HF overlap represents a high-risk clinical triad with shared pathophysiology, including chronic inflammation, airway obstruction, and cardiac dysfunction, leading to worsened outcomes. Diagnosis is challenging due to overlapping symptoms (dyspnea, wheezing, exercise intolerance) and limitations of conventional tests, necessitating a multimodal approach. Phenotyping patients based on treatable traits such as eosinophilic inflammation, fluid overload, or bronchospasm enables precision medicine strategies. Early diagnosis of HF is suggested for COPD patients to avoid recurrent exacerbation. NT-proBNP test is recommended in routine blood test for patients having HF symptoms. Patients with higher NT-proBNP are referred for further monitoring for suspected HF. Pharmacological management requires careful balancing: LAMAs are preferred in HF for their cardiac safety, while beta-agonists pose arrhythmia risks. ICS benefit eosinophilic inflammation but increase pneumonia and fluid retention risks in HF. Diuretics must be titrated carefully to avoid exacerbating COPD. Emerging strategies, including lung ultrasound-guided therapy and targeted pulmonary hypertension treatments, show promise. A multidisciplinary, patient-centered approach is essential to optimize care. Future research should refine diagnostic algorithms, explore novel biomarkers, and develop therapies that simultaneously target pulmonary and cardiovascular pathways. Improved recognition and tailored management of this complex overlap syndrome are crucial for reducing hospitalizations and mortality.

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