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NEGATIVE CARDIAC TROPISM IN PNEUMOLOGY: CLINICAL, PHARMACOLOGICAL AND PATHOPHYSIOLOGICAL ASPECTS

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Summary.
Pneumology include severe pulmonary diseases, primarily tuberculosis (TB) and COPD (COPD), both of which significantly impact the cardiovascular system. This review summarizes the current evidence on the negative cardiotropic effects of these diseases and their respective treatments. Antituberculosis drugs such as Bedaquiline and Delamanid increase the risk of QT interval prolongation and arrhythmias, requiring careful cardiac monitoring. Chronic hypoxia, caused by extensive lung damage, induces pulmonary hypertension, leading to cor pulmonale and right-sided heart failure. Endogenous intoxication due to inflammatory and necrotic byproducts, together with exogenous factors such as smoking and alcohol consumption, further compromise cardiovascular function. Systemic inflammation, which is characteristic of both TB and COPD, contributes to the development of atherosclerosis and cardiac complications, independent of common risk factors. Combined pathogenetic mechanisms are common in clinical practice and complicate patient management. The results of the review emphasize the need for integrated cardiopulmonary care and regular cardiovascular assessments.
Keywords: pneumology, tuberculosis, COPD, cardiotoxicity, hypoxia, systemic inflammation, cardiopulmonary care.

Rezumat. Tropismul cardiac negativ în pneumologie: aspecte clinice, farmacologice și patofiziologice.
Pneumologia include afecțiuni pulmonare severe, în special tuberculoza (TB) și boala pulmonară obstructivă cronică (BPOC), cu impact semnificativ asupra sistemului cardiovascular. Această sinteză sistematizează dovezile actuale privind efectele cardiotropice negative ale acestor boli și tratamentelor specifice. Factorii farmacologici, precum medicamentele anti-TB (Bedaquilina, Delamanidul), prezintă riscuri de prelungire a intervalului QT și aritmii, necesitând monitorizare cardiacă atentă. Hipoxia cronică, rezultată din implicarea pulmonară extinsă, induce hipertensiune pulmonară și cor pulmonale, ducând progresiv la insuficiență cardiacă dreaptă. Intoxicația endogenă produsă de inflamație și necroză, împreună cu factori exogeni ca fumatul și alcoolul, agravează suplimentar funcția cardiovasculară. Inflamația sistemică persistentă în TB și bpoc favorizează ateroscleroza și evenimentele cardiace, independent de factorii tradiționali de risc. în practica clinică, scenariile cu mecanisme patogenetice suprapuse complică managementul pacienților. rezultatele subliniază necesitatea îngrijirii integrate și evaluării cardiovasculare sistematice pentru reducerea morbidității cardiovasculare în pneumologie.
Cuvinte cheie: pneumologie, tuberculoză, BPOC, cardiotoxicitate, hipoxie, inflamație sistemică, îngrijire cardiopulmonară.

Резюме. Негативная кардиотропность в пневмологии: клинические, фармакологические и патофизиологические аспекты.
Пульмонология охватывает тяжелые заболевания легких, главным образом туберкулез и хроническую обструктивную болезнь легких (ХОБЛ), которые оказывают существенное негативное влияние на сердечно-сосудистую систему. Настоящий обзор систематизирует современные данные о негативных кардиотропных эффектах данных заболеваний и применяемых препаратов. Противотуберкулезные препараты (Бедаквилин, Деламанид) повышают риск удлинения интервала QT и аритмий, что требует тщательного сердечного мониторинга. Хроническая гипоксия, вызванная обширным поражением легких, провоцирует легочную гипертензию и приводит к легочному сердцу с развитием правожелудочковой недостаточности. Эндогенная интоксикация, обусловленная воспалительными и некротическими продуктами, а также экзогенные токсины (курение, алкоголь) дополнительно ухудшают сердечно-сосудистую функцию. Системное воспаление, характерное для туберкулеза и ХОБЛ, способствует развитию атеросклероза и сердечных осложнений независимо от традиционных факторов риска. В клинической практике часто встречаются сочетанные патогенетические механизмы, усложняющие ведение пациентов. Результаты обзора подчеркивают необходимость интеграции кардиопульмональной помощи и регулярной сердечно-сосудистой оценки.
Ключевые слова: пневмология, туберкулез, ХОБЛ, кардиотоксичность, гипоксия, системное воспаление, кардиопульмональная помощь.

Introduction.

Respiratory diseases and cardiovascular diseases (CVD) are often viewed as separate domains, however, increasing evidence indicates that they are deeply interconnected. Pneumology, the branch of medicine focused on tuberculosis (TB) (historically referred to as "phthisis") and other severe pulmonary illnesses, provides a paradigmatic example of this relationship. Two of the most prevalent and severe conditions in pneumology are pulmonary tuberculosis and chronic obstructive pulmonary disease (COPD). TB remains a global health issue, ranking among the top ten causes of death worldwide and continuing to be the leading cause of mortality from a single infectious agent [29]. COPD, which is primarily caused by exposure to tobacco smoke, is a leading cause of chronic morbidity and has ranked as the third or fourth leading cause of death globally in recent years. [27]. Patients affected by TB or COPD experience not only progressive lung damage but also significant systemic consequences, particularly involving the cardiovascular system [1].

Clinical observations and epidemiological studies have demonstrated that cardiovascular complications are alarmingly common in patients with TB or COPD [7] For instance, ischemic heart disease, heart failure, and arrhythmias occur at higher rates in individuals with chronic lung disease compared to the general population [4]. Indeed, CVD is the most frequent comorbidity in COPD and represents a leading cause of hospitalization and death, even among patients with moderate COPD [23]. Similarly, untreated TB can directly invade the heart, classically causing tuberculous pericarditis, or indirectly accelerate cardiovascular deterioration through chronic inflammation [1, 29]. Despite these well-established associations, the concept of "negative cardiac tropism" in pneumology that is, the propensity of these pulmonary diseases and their treatments to have negative effects on the heart, has not received sufficient attention in routine practice and guidelines.

It is crucial to understand the clinical, pharmacological, and pathophysiological aspects of this cardiopulmonary crosstalk. As TB and COPD often require prolonged treatment and careful management, clinicians must be aware of how interventions or disease processes might harm cardiac health inadvertently. For example, the introduction of potent anti-TB drugs such as Bedaquiline has improved outcomes in multidrug-resistant TB, but is associated with potential cardiotoxicity, particularly QT interval prolongation [7, 16]. Similarly, long-term oxygen deprivation in COPD can silently strain the right side of the heart, ultimately precipitating cor pulmonale.

This review addresses a significant gap by providing a systematic examination of "negative cardiac tropism" in pneumology. We focus on the core factors contributing to negative cardiotropic effects: (1) pharmacological treatments, particularly anti-tuberculosis medications; (2) chronic hypoxemia resulting from respiratory insufficiency; (3) endogenous intoxication from metabolic and inflammatory derangements; (4) exogenous intoxication due to substances such as tobacco and alcohol; (5) systemic inflammation; and (6) mixed pathogenesis scenarios in which these factors intersect. The discussion centers on how these factors manifest in pulmonary TB and COPD, as these diseases exemplify the challenges encountered in pneumology. Drawing on the latest evidence, we aim to elucidate the underlying mechanisms behind these cardiac effects and highlight their clinical implications. Ultimately, increasing awareness of negative cardiotropic factors will facilitate the development of more effective, integrated care strategies for patients with TB and COPD with the goal of reducing the high cardiovascular morbidity and mortality associated with these conditions.

Research Aim.

The objective of this research is to provide a comprehensive analytical review of negative cardiotropic effects in pneumology. It will examine the clinical manifestations, pharmacological contributors, and pathophysiological mechanisms by which pulmonary diseases, especially TB and COPD, adversely impact the cardiac function. This study aims to identify and evaluate the principal factors, including drug effects, hypoxia, intoxication, inflammation, and their interactions, that contribute to cardiac dysfunction in these conditions. By synthesizing the current evidence, elucidating the underlying mechanisms, and proposing targeted recommendations, we aim to inform strategies for reducing cardiovascular risks in the management of TB and COPD.

Materials and Methods.

We conducted a narrative literature review using a systematic approach to evaluate negative cardiotropic effects in pneumology. English-language literature published between 2015 and 2025 was retrieved from PubMed/MEDLINE databases, with an emphasis on recent studies from 2018 to 2025. Searches combined keywords such as "tuberculosis", "TB", , "COPD", "COPD" with cardiovascular-related terms including "heart failure", „cor pulmonale", "arrhythmia", "QT prolongation", "cardiotoxicity", "hypoxia", "inflammation", "smoking" as well as specific anti-

TB drugs like „Bedaquiline" and „Delamanid". Relevant guidelines and policy documents from the World Health Organization (WHO IRIS library), Global TB Reports, and GOLD COPD guidelines were also reviewed.

Selected materials comprised peer-reviewed clinical trials, cohort studies, meta-analyses, systematic reviews, authoritative guidelines, observational studies, and relevant case series, providing data on cardiovascular effects in patients with TB or COPD. Studies involving mixed chronic lung disease populations were included if TB or COPD specific data could be extracted. Historical studies from before 2015 were incorporated solely to provide essential foundational context.

Extracted data encompassed clinical outcomes, pharmacological side effects, and pathophysiological insights. Findings were thematically organized, integrating qualitative analyses with quantitative risk data. Ethical approval was not required, as no human participants or confidential data were involved. MLA citation standards were strictly followed.

Results and Discussion.

Pharmacological Factors and Cardiotoxicity in TB and COPD

Anti-Tuberculosis Drug Effects

The pharmacological cornerstone of TB treatment is combination antimicrobial therapy, which is effective against *Mycobacterium tuberculosis* but can impart unintended stress on the heart. Traditional first-line TB drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) generally have limited direct cardiac toxicity. However, the emergence of drug-resistant TB has necessitated the use of newer agents and repurposed drugs, some of which are known to be cardiotoxic. The most prominent example is Bedaquiline, a diarylquinoline introduced in the past decade. Although Bedaquiline has demonstrated efficacy against resistant TB, its use is associated with effects on cardiac electrophysiology, specifically through blockade of cardiac potassium channels (hERG channels) responsible for repolarization, thereby prolonging the QT interval on electrocardiography (ECG) [7]. In pivotal clinical trials, a higher incidence of QT prolongation and unexplained deaths was observed in the Bedaquiline treatment arm, raising early concerns about potential arrhythmic fatalities [21]. Although definitive causal relationships were not established, these safety concerns prompted the implementation of strict monitoring recommendations. Both WHO and Centers for Disease Control and Prevention (CDC) guidelines now advise regular ECG surveillance for patients receiving Bedaquiline, particularly when used in combination with other QT-prolonging drugs [10]. A WHO policy update explicitly states that Bedaquiline and Delamanid (another new TB drug) may be co-administered for multidrug-resistant TB only with careful ECG monitoring for arrhythmias [28]. This underscores the importance of pharmacovigilance: as novel TB therapies are introduced; it remains essential to monitor and mitigate negative cardiotropic side effects.

Delamanid, a nitroimidazole, similarly causes dose-dependent QT prolongation through a similar mechanism. While each drug alone typically results in a modest increase in QTc (averaging 8-12 msec), their combined use is approximately additive in effect. A recent controlled trial demonstrated that the mean QT prolongation reached was in average 20.7 msec, when Bedaquiline and Delamanid were co-administered for 24 weeks, compared to ~12 msec with Bedaquiline alone [7]. Although no serious arrhythmias (such as Torsades de Pointes) or sudden deaths were reported in that limited study, the potential for life-threatening arrhythmias remains, particularly in patients with additional risk factors, such as electrolyte imbalances and baseline prolonged QT. Furthermore, TB treatment? regimens often include other QT-prolonging agents: fluoroquinolone antibiotics like moxifloxacin and levofloxacin (commonly used as second-line TB drugs) as well as clofazimine (an antimicrobial sometimes used off-label in TB), are also known to lengthen the QT interval. When several of these drugs are combined, a common scenario in extensively drug-resistant TB the risk of QT prolongation increases is further amplified. Clinical monitoring data indicate that patients receiving combination therapy (e.g., Bedaquiline plus a Fluoroquinolone and Clofazimine) exhibit a significantly higher incidence of grade 3 QT prolongation (>500 msec) [12]. Thus, the pharmacological impact on the cardiac electrical stability is a major concern in phthisiology. Physicians must mitigate this risk by avoiding the co-prescription of multiple cardiotoxic drugs when possible, correcting hypokalemia or hypomagnesemia (which exacerbate QT issues), and scheduling frequent ECGs. In clinical practice, if a patient's QTc exceeds dangerous thresholds, regimen adjustments – such as dose modification or drug substitution – are implemented to prevent arrhythmia [10].

Beyond arrhythmias, some anti-TB drugs may contribute to myocardial dysfunction or other CV effects through indirect mechanisms. For example, high-dose intravenous rifampicin can cause profound hypotension, likely via histamine release, which, if

recurrent, may strain cardiac output. The older TB drug Thioacetazone, now largely discontinued due to its toxicity, was infamous for cardiovascular collapse in some cases. While such drugs are primarily of historical interest, they exemplify that drug-related negative cardiac tropism can manifest in forms other than arrhythmia. Even isoniazid, which is generally considered safe for cardiac function, can, in rare cases, induce a lupus-like syndrome with associated carditis or cause pyridoxine deficiency leading to neuropathy that might include autonomic heart rate dysfunction. Although these occurrences are uncommon, they serve as a reminder that the multi-organ side effects of TB therapy can also involve the heart.

COPD Medication Effects

In COPD, pharmacotherapy primarily involves bronchodilators and anti-inflammatory agents, yet some parallels with TB treatment exist regarding cardiovascular risk. β2-adrenergic agonists, such as salbutamol and formoterol, are central to COPD symptom control as they relax airway smooth muscle. However, these agents can also bind to β1-receptors in the heart, particularly at higher doses or with non-selective agents, leading to tachycardia and increased myocardial contractility. This results in elevated cardiac workload and a heightened risk of arrhythmias, which are recognized side effects. Inhaled short-acting β2-agonists commonly cause palpitations; more concerningly, high-dose or nebulized albuterol can precipitate atrial fibrillation or supraventricular tachycardia in patients with pre-existing cardiac disease. Although long-acting β2-agonists (LABAs), which are used daily in COPD management, have a better safety profile, they have still been scrutinized for possible links to atrial arrhythmias. Some studies reported a slight increase in the risk of hospitalization due to arrhythmia among COPD patients who initiate LABA therapy. However, confounding factors related to disease severity must be considered. A study published in an American Heart Association journal highlighted that COPD patients are at high arrhythmia risk due to three factors: chronic hypoxemia, cor pulmonale (right heart strain), and use of β-agonist medications [11]. This triad predisposes to arrhythmias such as multifocal atrial tachycardia or atrial fibrillation, which are frequently observed in advanced COPD. Consequently, while bronchodilators are essential for symptom relief, clinicians must exercise caution when treating patients with co-existing ischemic heart disease or heart failure, as sympathetic stimulation from these drugs can provoke ischemia or dysrhythmia.

Another medication used in COPD, theophylline – a methylxanthine possesses well-documented cardiotoxic potential at supratherapeutic levels. Theophylline toxicity can cause severe sinus tachycardia, atrial fibrillation, or even ventricular arrhythmias, in addition to hypotension. This is essentially an adrenergic overdrive combined with direct myocardial irritability. Although the use of theophylline has declined in recent years due to its narrow therapeutic index and side effects, it is still used in settings with limited resources and select patient populations. Careful monitoring of theophylline levels in the blood can prevent overt toxicity, however, even minor elevations may contribute to symptoms such as insomnia, palpitations, or ectopic beats, indicating a milder negative impact on the heart.

Systemic corticosteroids, which are often administered during acute COPD exacerbations, can also indirectly stress the heart. Steroids cause fluid retention and elevate blood pressure, potentially worsening heart failure in susceptible patients. They may also induce hyperglycemia, which, over time, contributes to vascular damage. Although they are not „cardiotoxic" in the traditional sense, their widespread use in COPD requires careful management of these side effects to protect cardiovascular health.

In summary, the pharmacological management of TB and COPD represents a double-edged sword: these therapies are essential for disease but are also associated with potential cardiac side effects. The concept of negative cardiac tropism underscores the need for healthcare providers to remain vigilant. This includes performing baseline cardiac evaluations, anticipating drug interactions, and tailoring regimens to minimize risk. For example, a COPD patient taking a βblocker for heart disease may have a blunted tachycardia response to albuterol, which can mask symptoms of overuse. As new therapies continue to emerge (e.g., novel anti-TB drugs and biologics for COPD), rigorous assessment of their cardiovascular safety must remain a priority.

Impact of Chronic Hypoxemia on the Heart

Chronic hypoxemia is a hallmark of advanced pulmonary diseases. Whether resulting from alveolar destruction in COPD, extensive lung infiltrates in TB, or residual fibrosis in post-TB lung disease, prolonged oxygen deprivation sets off a cascade of pathophysiological changes affecting both the pulmonary circulation and heart. The human body's immediate response to localized lung hypoxia is pulmonary vasoconstriction – an adaptive mechanism known as the Euler-Liljestrand reflex, which redirects blood flow away from poorly ventilated

alveoli toward better-ventilated regions , thereby optimizing gas exchange. However, in diffuse lung disease, where large areas of the lung are hypoxic, this mechanism becomes maladaptive. Widespread alveolar hypoxia causes generalized constriction of pulmonary arterioles, increasing resistance in the pulmonary vascular bed [25]. Over time, the small muscular arteries in the lung wall undergo remodeling, which includes medial hypertrophy and intimal thickening, leading to the development of pulmonary hypertension .

Pulmonary hypertension serves as the critical link between chronic lung disease and right heart failure. It is defined by an elevated mean pulmonary arterial pressure (mPAP) exceeding 20 mmHg at rest, with severe cases often surpassing 40 mmHg. As mPAP rises, the right ventricle (RV) normally a thin-walled, low-pressure pump increased afterload. Initially, the RV compensates through muscle hypertrophy, enabling it to generate higher pressures and maintain near-normal cardiac output. Clinically, this compensatory stage may be asymptomatic or present only as an accentuated P2 heart sound, indicative of elevated pulmonary pressure [9]. However, with persistent or worsening pulmonary hypertension, the RV eventually decompensates, leading to dilatation, reduced systolic function, and impaired ability to effectively pump blood through the lungs. This condition, known as cor pulmonale, “literally”, “pulmonary heart”, describes structural and functional alterations of the heart caused by lung disease [9]. Cor pulmonale refers to chronic right-sided heart failure due to pulmonary issues, excluding cases where left heart failure or congenital defects are the primary cause.

COPD is by far the leading cause of cor pulmonale in developed countries. Epidemiological studies report a wide range in the prevalence of cor pulmonale among COPD patients, from 20% to over 50%, due/attributable to differences in disease severity and diagnostic criteria [25]. Nevertheless, even mild COPD can cause some degree of RV strain, particularly during exercise or exacerbations. Overt cor pulmonale is less common during active infection. However, it can occur in disseminated (miliary) TB or tuberculous fibrotic sequelae, that severely impair ventilation. More often, TB contributes to cor pulmonale indirectly: post-TB lung disease can result in COPD – like changes and chronic hypoxia, thereby initiating the same pathway leading to pulmonary hypertension [14]. Additionally, TB may cause fibrous constriction of the pulmonary vasculature or recurrent pulmonary thromboembolism due to inflammation-induced hypercoagulability. Both of these conditions increase pulmonary artery pressure.

Chronic hypoxemia, induced cor pulmonale, has substantial clinical significance. As the RV fails, patients develop peripheral edema (e.g., swollen ankles), hepatic congestion, jugular venous distension and decreased forward output from the right heart. Common symptoms include worsened exercise tolerance, fatigue, and new onset exertional angina-like chest discomfort. Notably, chest pain in cor pulmonale is often angina caused by RV ischemia, rather than coronary disease. The hypertrophied RV wall outgrows its blood supply, resulting in demand ischemia under stress. Some COPD patients with cor pulmonale experience chest pain unresponsive to nitrates, underscoring a mechanism distinct from typical angina [23]. Ultimately, untreated cor pulmonale carries a poor prognosis, reflecting advanced pulmonary pathology and often signaling end-stage disease. According to patient management guidelines, long-term oxygen therapy is one of the few interventions shown to improve survival, once cor pulmonale is present in COPD. By correcting hypoxemia, long-term oxygen therapy can lower pulmonary artery pressures and reduce strain on the RV.

From a pathophysiological perspective, chronic hypoxia not only causes vasoconstriction but also induces polycythemia - an increase in red blood cell production - as the body attempts to enhance its oxygen-carrying capacity. In turn, polycythemia increases blood viscosity, which further burdens the heart. Chronic hypercapnia (elevated CO_2 levels) in COPD patients can lead to acidosis, which also induces pulmonary vasoconstriction [25]. Therefore, the heart is damaged by a combination of different aspects of gas exchange derangement acting in a synergistic way. The net effect is a vicious cycle: an ailing lung leads to a failing heart, and a failing heart impairs systemic oxygen delivery, thus compounding the hypoxia.

It is also important to note the severity of the cardiac impact of hypoxemia. During COPD or asthma exacerbations, acute drops in oxygen saturation and surges in pulmonary artery pressure can lead to acute cor pulmonale or arrhythmias. Many COPD patients have concomitant coronary artery disease, due to shared risk factors, such as smoking. In this case, an acute hypoxic episode may trigger myocardial infarction. Indeed, acute exacerbations of COPD are associated with a several fold increase in the short-term risk of acute coronary syndromes and arrhythmias. Hypoxemia likely plays a central role in these events in this process by causing coronary

vasoconstriction and increasing cardiac workload via tachycardia. This emphasizes that maintaining adequate oxygenation is not only a comfort measure, but also a critical cardioprotective strategy for patients with advanced lung disease.

In conclusion, chronic hypoxemia represents fundamental link between phthisiopulmonary diseases and cardiac pathology. The insidious development of pulmonary hypertension and cor pulmonale due to unresolved hypoxia exemplifies a direct negative cardiotropic effect, wherein the heart undergoes structural and functional alterations as a consequence of lung failure. Early recognition of these changes such as a loud P2, RV heave, or echocardiographic evidence of elevated pulmonary artery pressure should prompt clinicians to intensify efforts to improve oxygenation, whether through supplemental oxygen, pulmonary rehabilitation, or advanced therapies. Clinicians should also consider pulmonary hypertension treatments in appropriate cases. Preventing or delaying the onset of cor pulmonale can significantly improve quality of life and outcomes for patients with TB and COPD, reinforcing the imperative to address hypoxemia proactively.

Endogenous Intoxication and Metabolic Effects

The term endogenous intoxication refers to the accumulation of toxic metabolites and byproducts *within* the body as a result of disease processes. In the context/field of pneumology, severe infections such as TB or advanced COPD can cause a state of internal "poisoning". In this condition, the patient's own inflammatory response and tissue breakdown generate factors that circulate in the bloodstream and are detrimental to organ function, including the heart. Although this concept has its origins in older clinical literature, it is receiving renewed attention as our understanding of the systemic effects of localized diseases expands.

In TB, particularly in cases of disseminated or severe pulmonary TB, the host mounts a robust/ strong immune response that can become a double-edged sword. The granulomatous inflammation in TB results in/leads to tissue necrosis (caseation) and the release of numerous cellular components and cytokines into the bloodstream. Patients with high mycobacterial burdens often present with a syndrome historically termed "toxemia" or "TB intoxication", characterized by fever, night sweats, wasting, and tachycardia that is disproportionate to the degree of fever. Modern research has quantified some of these aspects. For example, patients with TB have elevated levels of circulating Tumor Necrosis Factor-alpha (TNF-α), interleukins (IL-1, IL-6), and acute phase proteins, all of which are markers of systemic inflammation and potential contributors to vascular damage. Furthermore, increased oxidative stress markers indicate that reactive oxygen species generated by immune cells can affect distant organs.

In a 2016 study, Todoriko and Yeremenchuk investigated the pathways of endogenous intoxication in TB. Their findings indicate that TB triggers multiple self-perpetuating processes, including cytotoxic hypoxia (where cellular oxygen utilization is impaired by toxins), disruption? of intracellular homeostasis, and the "massive generation and resorption of tissue decay products" [24]. As TB bacilli destroy lung tissue, the resulting debris, including DNA and cell wall components such as mycolic acids, enters the circulation. The body is tasked with clearing this debris, a function handled in part by the reticuloendothelial system. However, if the burden is excessive, these products act as toxins, interfering with cellular metabolism. For the myocardium, this environment may result in suboptimal energy production due to mitochondrial dysfunction caused by circulating toxins, as well as direct depression of contractility by inflammatory mediators. Studies in septic shock a different context of endogenous intoxication have shown that myocardial cells reduce their contractile function under conditions of high cytokine exposure a phenomenon termed "septic cardiomyopathy". Although TB is a more chronic condition, a parallel can be drawn: in severe TB infection, sustained immune activation and metabolic derangements may lead to a mild form of reversible cardiomyopathy.

One quantifiable aspect of endogenous intoxication is the leukocytic index of intoxication (LII) along with other laboratory markers such as the level of medium-weight molecules in the blood. TB patients frequently show/exhibit abnormal LII values that correlate with disease severity [8]. These markers serve as indirect measures of the toxic burden to which leukocytes are responding. Elevated states of endogenous intoxication have been associated with more extensive lung lesions on X-rays and more severe clinical symptoms, suggesting that the heart is also exposed to this toxic internal milieu [20]

Another factor is the impact of chronic infection on metabolic organs, such as the liver and adrenal glands, which can result in secondary cardiac complications. TB may involve the adrenal glands, causing adrenal insufficiency (Addison's disease). If left unrecognized, it can lead to hypotension, electrolyte disturbances (such as hyperkalemia/ high potassium levels), cardiac arrhythmias or heart failure.

This scenario exemplifies how TB's endogenous effects, destroying hormone-producing glands, can intoxicate the body through hormonal imbalance. In general, chronic infections frequently cause anemia of chronic disease, which reduces oxygen-carrying capacity and forces the heart to pump harder, creating an increased cardiac output state. Over time, this high-output strain can cause dilated cardiomyopathy if the condition is severe and prolonged.

In COPD, the concept of endogenous intoxication is less frequently discussed, yet remains relevant. Advanced COPD is commonly associated with CO_2 retention and respiratory acidosis, particularly in patients with chronic bronchitis phenotype. CO_2 narcosis and acidemia function as internal toxins: acidosis decreases/impairs the efficiency of cardiovascular contractile proteins and increases myocardial susceptibility to arrhythmias. Additionally, COPD patients often experience muscle wasting and cachexia, driven both by systemic inflammation and the caloric cost of breathing. Cachexia leads to breakdown of muscle proteins and adipose tissue, releasing free fatty acids and other metabolites in excess. If the renal function is impaired or even if normal but overwhelmed some of these metabolites can accumulate, contributing to a uremic-like or toxic state. Notably, uric acid levels are often elevated in severe COPD and have been found to correlate with mortality, potentially reflecting ongoing tissue breakdown and hypoxemic stress. Another way to view endogenous intoxication is through the lens of cytokine imbalance. The previously mentioned study by Todoriko and Yeremenchuk identified an imbalance of pro- and anti-inflammatory cytokines, such as IL-6 and IL-10, which correlated with disease severity in patients with multidrug-resistant tuberculosis (MDR-TB). IL-6 is a pro-inflammatory cytokine that, in high levels, causes fever, coagulation activation, and endothelial dysfunction [24]. IL-10, on the other hand, is an anti-inflammatory cytokine. An insufficient level of IL-10 relative to IL-6 results in unrestrained inflammation. This imbalance, essentially representing an "intoxicated" immune system, can lead to endothelial injury in coronary arteries, thereby increasing the likelihood of plaque rupture. It may also promote arrhythmogenic substrates via myocardial inflammation (myocarditis). Although full-scale tuberculous myocarditis is rare, subclinical myocarditis resulting from a cytokine storm is conceivable/possible in severe cases. This condition can lead to arrhythmias or a reduced ejection fraction.

In practical terms, these endogenous factors may present clinically in several ways. Patients may exhibit persistent tachycardia despite adequate treatment/management of fever or lung issues – an indication that the heart is being stimulated by factors such as anemia, or circulating catecholamines due to stress. Non-specific ECG changes, including flattened T waves or ST-segment alterations, may also be observed. These changes often resolve after TB treatment is completed, suggesting transient myocardial strain. Some patients recovering from TB have reported palpitations or atypical chest pain that is difficult to attribute to coronary disease. One hypothesis is that these symptoms may be related to autonomic dysfunction secondary to chronic inflammation (as TB can cause autonomic neuropathy), or to a toxic syndrome affecting cardiac nerve conduction. These phenomena are not yet fully understood and warrant further investigation.

From a management perspective, addressing endogenous intoxication primarily involves effective treatment of the underlying disease, achieving rapid mycobacterial clearance with appropriate anti-tuberculosis therapy, or optimizing COPD management to minimize exacerbations and reduce CO_2 retention. Adjunct therapies that have been considered include antioxidants to reduce oxidative stress, nutritional support to counteract cachexia and facilitate the rebuilding of muscle mass (including cardiac muscle), and, in certain cases, immunomodulatory agents. For example, in TB pericarditis, adjunctive corticosteroids are recommended; part of their therapeutic benefit may be attributed to the reduction of the inflammatory toxin burden that would otherwise impair cardiac function. In COPD, some studies have investigated the use of N-acetylcysteine to decrease oxidative stress or statins for their anti-inflammatory properties, the latter primarily aimed at reducing cardiovascular events. These approaches illustrate the overlap between managing endogenous "toxins" and protecting cardiac health.

In summary, endogenous intoxication in pneumology represents an internal, biochemical assault on the cardiovascular system, arising from chronic infection and respiratory failure. Although less overt than hypoxemia or drug-induced toxicity, it underlies many of the systemic manifestations observed in TB and COPD. Recognizing this process underscores the necessity of a holistic approach, one that not only targets the infectious agent or dilates airways, improves airway function, but also supports the patient's overall metabolic and inflammatory balance. In essence, this approach seeks to "detoxify" the patient from the ravages of chronic disease.

Exogenous Intoxication: Smoking and Environmental Factors

While endogenous factors originate within the body, exogenous intoxication refers to harmful influences arising from external sources, primarily substances or environmental exposures to which patients are subjected or which they ingest. In the context of TB and COPD, the most ubiquitous and detrimental exogenous toxin is tobacco smoke. Decades of epidemiological research have established smoking as a central risk factor for both respiratory and cardiovascular diseases. For patients already affected by TB or COPD, continued exposure to such toxins significantly worsens clinical outcomes and further contributes to the "negative cardiotropic" burden.

Tobacco smoking is the leading cause of COPD worldwide and a major contributor of the global TB epidemic. Smokers exhibit impaired mucociliary clearance and compromised local lung immunity, making them more susceptible to infections such as TB. Smokers have approximately twice the risk of developing active TB compared to non-smokers. It is estimated that over 20% of global TB cases are attributable to smoking, implying that one in five TB patients might have avoided infection had they not smoked [26]. Among individuals with TB, those who smoke are more likely to experience severe disease, delayed sputum conversion, and higher relapse rates.

From a cardiovascular perspective, smoking is one of the most potent risk factors for coronary artery disease, peripheral vascular disease, and stroke. It contributes to endothelial dysfunction, accelerates atherosclerosis, and promotes thrombogenesis. The combined impact of smoking in patients with TB or COPD is therefore twofold: it exacerbates lung disease while simultaneously increasing the risk of cardiovascular events, including heart attack, sudden cardiac death.

Interestingly, despite the well-established link between smoking and negative health effects, support of smoking cessation is often underemphasized in TB programs. A recent study pointed out that smoking cessation programs/interventions are not routinely integrated into TB care, even though smoking is a recognized risk factor for numerous CVDs and negatively affects TB outcomes [3]. This represents a significant missed opportunity for intervention. For patients with TB, quitting smoking improves long-term lung/pulmonary health, reduces the risk of developing COPD, and rapidly decreases cardiovascular risk. Excess coronary risk drops significantly within the first year of cessation. Therefore, one key recommendation emerging from the recognition of exogenous intoxication is to incorporate smoking cessation as a standard component of both TB and COPD management.

Beyond smoking, air pollution, both outdoor and household, acts as a pervasive exogenous intoxicant. In many low- and middle-income countries, indoor air pollution from biomass fuel, such as wood, charcoal, and animal dung, is a leading cause of COPD among nonsmokers, especially women. Biomass smoke contains a toxic mixture of particulate matter and chemicals. These constituents injure the airways – causing chronic bronchitic-type lung damage – and also enter the systemic circulation. Epidemiological evidence links long-term exposure to fine particulate matter (PM 2.5) with increased rates of heart attacks and heart failure. For example, hospital admissions for arrhythmias and myocardial infarction/heart attack tend to spike on days with high pollution levels. In individuals with compromised pulmonary function, pollution exacerbates hypoxemia and oxidative stress, further increasing the cardiac strain. Thus, COPD patients who reside in a polluted urban environment face an elevated risk of acute CV events because the environment effectively "intoxicates" them on a daily basis. Addressing this issue may involve advising patients to minimize exposure, for example, by wearing masks or using air filtration systems at home, and advocating for broader public health efforts/initiatives to reduce pollution levels.

Occupational exposures, such as silica, coal dust, and chemical fumes, represent another exogenous factor contributing to the burden of pulmonary and cardiovascular disease. Silica dust is well-established as a cause of silicosis and markedly increases the risk of TB, as silica-damaged lung tissue provides a favorable environment for TB infection. Beyond its pulmonary effects, silica exposure induces systemic inflammation and has been associated with a higher prevalence of rheumatologic diseases, some of which can involve the heart. Although the direct correlation between occupational lung toxins and heart disease is not as strong as that observed with smoking, these exposures nonetheless contribute to overall disease burden and elevate cardiac risk through mechanisms involving chronic inflammation and hypoxia.

Another critical exogenous factor, particularly relevant in the context of TB, is alcohol abuse. A significant proportion of TB patients especially in regions such as Eastern Europe present with alcohol use disorder. Alcohol acts as a direct myocardial toxin; chronic heavy consumption can lead to alcoholic cardiomyopathy, characterized by ventricular dilation and reduced ejection fraction. Additionally, alcohol

consumption is known to induce arrhythmias. So-called "holiday heart" syndrome, or atrial fibrillation, is a classic example of how excessive drinking can lead to arrhythmia. Among TB patients, excessive alcohol consumption is not only associated with poor adherence to treatment? and increased risk of hepatotoxicity from anti-TB medications, but also with the cardiovascular risks mentioned above. One study has demonstrated that TB patients with alcohol consumption experience significantly higher mortality rates. This is partly because they are prone to lethal arrhythmias or heart failure in addition to their infectious disease. For clinicians, it is therefore essential to screen for and addressing alcohol use in TB patients, as it is as crucial as the TB treatment itself in preventing negative cardiotropic consequences/outcomes such as arrhythmias or exacerbations of heart failure during TB therapy. From a pathophysiological standpoint, chronic alcohol consumption can lead to hypertension and promote the development of arrhythmogenic substrates, such as myocardial fibrosis. It can also deplete essential nutrients, like thiamine, which can result in wet beriberi, a form of cardiac failure.

In summary, exogenous intoxication from sources such as tobacco smoke, pollution, and substances like alcohol significantly aggravates cardiac risk in populations affected by TB and COPD. These external factors often act in concert with endogenous and disease-specific processes. For example, a smoker with COPD experiences both smoke-induced systemic inflammation and COPD-related/associated hypoxemia, each contributing to the instability of coronary artery plaques. Similarly, an individual with TB who abuses alcohol may develop dilated cardiomyopathy due to chronic alcohol exposure, while simultaneously facing pericardial constriction from TB, an especially hazardous combination. Recognition of these exogenous contributors is essential for comprehensive patient management. Effective interventions include smoking cessation programs, reduction of indoor pollution (e.g., adoption of clean cookstoves), enhancement of occupational safety, and alcohol cessation programs. These measures should be integrated into a holistic phthisiopulmonology strategy. By eliminating or mitigating exposure to these external toxins, the overall cardiovascular burden on the patient can be reduced, thereby improving the heart's capacity to withstand the physiological stress imposed by chronic pulmonary disease.

Systemic Inflammation and Immune-Mediated Cardiac Damage

One of the central mechanisms linking chronic lung disorders to cardiovascular diseases is systemic inflammation. Both TB and COPD are now recognized as diseases that primarily manifest in the lungs but have whole-body inflammatory components. The ongoing presence of inflammatory mediators in the circulation can adversely impact the heart and vasculature, promoting processes such as atherosclerosis, plaque rupture, and thrombosis.

In COPD, systemic inflammation is characteristically low-grade yet chronic. The lungs of patients with COPD release a variety of pro-inflammatory molecules into the bloodstream, such as IL- 6, C-reactive protein (CRP), and fibrinogen. These mediators are often elevated, even during periods of clinical stability [23]. Elevated levels of these markers are associated with poorer outcomes and increased comorbidities. IL-6, in particular, initiates signaling cascades that activate vascular endothelial cells, thereby facilitating the formation of atherosclerotic plaques. CRP, while often used as a biomarker, may also contribute to plaque instability.

Studies have shown that COPD doubles the risk of hospitalization and death due to cardiovascular disease, independent of smoking. This strongly suggests that factors inherent to COPD, such as inflammation, are responsible. One hypothesis is that systemic inflammation facilitates? the growth and rupture of atherosclerotic plaques. Autopsy and imaging studies have shown that patients with COPD exhibit more extensive atherosclerosis in both carotid and coronary arteries compared to non-COPD controls, even when adjusting for smoking status. Furthermore, inflammatory cells such as neutrophils and monocytes are primed in COPD; when these cells infiltrate coronary plaques, they can render the plaques "vulnerable", characterized by a thin cap and a large necrotic core, making them more likely to precipitate acute coronary events such as myocardial infarction [23].

Another important observation is that exacerbations of COPD flare-ups often triggered by infections are associated with transient surges in inflammation, such as rises in IL-6 and TNF-α. These inflammatory spikes coincide with a short-term increase in the risk of acute myocardial infarction or stroke. Studies have reported that the risk of acute myocardial infarction is several times higher in the weeks following a COPD exacerbation than at baseline. Systemic inflammation and hypercoagulability during these episodes are believed to mediate this heightened risk. This

situational vulnerability underscores the connection between lung episodes and heart events, highlighting the role of inflammation

In TB, systemic inflammation is even more pronounced in the active phase of the disease. TB elicits cell-mediated immunity, resulting in the release of cytokines such as interferon-gamma, TNF-α, IL-1, and IL-12. While these cytokines play essential roles in containing the infection, they also induce an acute phase response. Notably, TB has been shown to cause endothelial dysfunction. Studies demonstrated that flow-mediated dilation, a marker of endothelial health, is reduced in TB patients. This reduction is likely a consequence of inflammation and may predispose patients to atherosclerosis. Epidemiological evidence links chronic TB infection to an increased long-term risk of ischemic heart disease. A systematic review and meta-analysis found that individuals with a history of TB have a significantly higher risk of coronary heart disease compared to those without TB [29]. Proposed mechanisms include TB-induced systemic inflammation and direct vascular damage. Some autopsy studies have found *M. tuberculosis* DNA in atherosclerotic plaques, suggesting that the bacteria or its antigens may invade arteries and induce/provoke/elicit local inflammation).

TB also exemplifies immune-mediated cardiac damage through manifestations such as TB pericarditis and myocarditis. Tuberculous pericarditis is characterized by inflammation of the pericardium due to the infection with *M. tuberculosis*., However, constrictive pericarditis often arises from the host immune response, which leads to the deposition of fibrin and collagen and subsequent scarring of the pericardium. This process can result in chronic constriction of the heart, representing a severe negative cardiotropic outcome. The high mortality associated with TB pericarditis underscores the severeness of this immune-mediated cardiac complication. For example, the mortality rate can be as high as 26% with treatment for HIV-negative patients and even higher for HIV-positive patients. Although rare, TB myocarditis may occur either through direct infection of the myocardium or via immune-mediated mechanisms. It may result in arrhythmias, heart block, or heart failure. In many cases, TB myocarditis is only discovered at autopsy following sudden cardiac death. These direct cardiac involvements demonstrate that TB is not merely a pulmonary disease but also poses a significant cardiovascular threat. This supports the assertion that: "Tuberculosis cardiac involvement is frequent and can lead to heart failure, constrictive pericarditis, or death" [1]. Early recognition of cardiac involvement in TB is crucial to preventing fatal outcomes.

From a systemic inflammation standpoint, TB can be likened to a state of chronic sepsis, whereas COPD can be compared to a state of chronic sterile inflammation. Both conditions, however, converge on the activation of harmful pathways within the cardiovascular system. For example, the transcription factor NF-κB, which regulates the expression of numerous inflammatory genes, is activated in both severe COPD and active TB. Activation of the NF-κB pathway in blood vessels leads to the expression of adhesion molecules and chemokines, facilitating the recruitment of inflammatory cells into the vessel walls, a key event in the initiation of plaque formation. Oxidative stress is closely intertwined with inflammation: COPD patients who smoke generate substantial quantities of free radicals, while TB patients experience oxidative bursts from activated macrophages. This oxidative stress can oxidize low-density lipoprotein cholesterol, increasing its atherogenic potential and promoting plaque formation [15].

Clinical guidelines are increasingly emphasizing the importance of addressing systemic effects. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy for COPD now recommends that comorbidities, particularly cardiovascular disease, should be proactively identified and managed., This shift recognizes that standard COPD therapies, such as inhalators, do not sufficiently address the underlying systemic inflammation that may contribute to the development and progression of comorbid conditions. Some trials have explored the potential of anti-inflammatory medications beyond inhaled corticosteroids to reduce cardiac events in COPD patients. Examples include low-dose methotrexate or statins, which are investigated for their anti-inflammatory properties. Although the results have been variable, this represents a growing area of interest in research.

In TB management, international organizations such as the WHO are increasingly aware of the importance of integrated care. For example, the management of diabetes in TB patients is now recognized as essential, given that diabetes exacerbates systemic inflammation, increases the risk of developing TB threefold, and TB itself can destabilize glycemic control. This bidirectional relationship underscores the importance of comprehensive care. Looking forward, there is a growing consensus that cardiovascular risk factors such as hypertension and dyslipidemia should be systematically addressed within TB care programs. Some experts propose the

implementation of a "TB – CVD screening bundle", which would involve routine screening of TB patients for elevated blood pressure and blood glucose, along with basic counseling on diet and physical activity. Such integrated interventions aim to mitigate inflammation, driven cardiovascular risk and improve overall patient outcomes.

In conclusion, systemic inflammation serves as a nexus linking pulmonary and cardiovascular pathology. It functions as a pervasive negative cardiotropic influence in pneumology. Even if a patient's symptoms are limited to cough or dyspnea, underlying immune activation may silently damage the arteries and myocardium. Addressing this issue requires a comprehensive approach to patient care. Effective anti-tuberculosis therapy gradually reduces TB-associated inflammation, as evidenced by declining CRP levels with successful treatment. Similarly, optimal COPD management that minimizes exacerbations helps to prevent acute inflammatory surges. Some patients may benefit from therapies that specifically target inflammation, such as colchicine. Colchicine has been shown to reduce cardiac events in other high-inflammatory states. However, the use of such agents in TB or COPD is speculative and not currently the standard of care. At a minimum, regularly monitoring inflammatory markers, such as CRP, may help identify high-risk individuals who could benefit from a referral to a cardiologist or from primary prevention strategies, such as initiating aspirin or statin therapy, in middle-aged TB patients with an elevated inflammatory burden and additional risk factors.

In summary, the inflammatory milieu is a central driver of negative cardiac tropism, exacerbating the damage caused by hypoxia, intoxication, and other previously mentioned factors. This environment represents a promising target for future interventions and underscores the necessity of managing diseases such as TB and COPD not merely as localized conditions, but as systemic syndromes with widespread physiological consequences.

Mixed Pathogenesis and Overlapping Scenarios

Real-world cases in pneumology frequently involve the convergence of multiple pathogenic factors, each amplifying the deleterious effects on the heart. It is uncommon for a patient to experience a single, isolated mechanism of cardiac stress; more often, a combination of disease processes and external influences culminates in a "perfect storm" of negative cardiotropic impact. Recognizing these overlapping scenarios is essential for clinicians to anticipate risks and implement comprehensive management strategies.

Consider the example of a patient with advanced pulmonary TB who also has a history of heavy smoking or concurrent COPD. Such an individual may simultaneously experience:

- Severe hypoxemia: Resulting from extensive TB lung involvement or fibrocavitary disease, leading to hypoxic pulmonary hypertension and the early development of cor pulmonale.
- Systemic intoxication: Manifested by high fevers, tachycardia, and hypotension (particularly in cases of miliary TB or sepsis-like presentations), indicating cardiac strain due to alterations in volume status and cytokine load.
- Pharmacological strain: Upon initiation of anti-TB therapy, especially for multidrug-resistant TB, exposure to agents such as Bedaquiline may increase the risk of arrhythmias.
- External toxins: Continued smoking perpetuates vascular damage and impairs oxygen delivery via carbon monoxide exposure. Concurrent alcohol use may further reduce cardiac contractility. Inflammatory burden: Due to their shared risk factors, TB and smoking-related COPD changes may lead to inflammatory processes.

The interplay of these factors can have devastating consequences. A patient may present with difficulty breathing primarily attributed to TB, yet may be concurrently developing acute right heart failure or arrhythmia. Indeed , cases of sudden cardiac death have been reported in patients with active TB, often attributed to a combination of TB myocarditis and drug-induced arrhythmias [13, 29]. The presence of mixed pathogenesis complicates clinical decision-making, making it difficult to prioritize which factor to address first. Taking a parallel approach here is essential: initiate anti-TB therapy to reduce infection and inflammation, provide supplemental oxygen or ventilatory support to counter hypoxia and CO_2 hypercapnia, counsel the patient on smoking cessation to eliminate ongoing toxic exposure, monitor heart rhythm to detect QT prolongation or arrhythmias early, and support blood pressure/heart function as needed (e.g., with fluids or inotropes in cases of TB-associated septic shock).

Another common mixed scenario involves a patient with COPD who subsequently develops TB. COPD itself predisposes individuals to lung infections, including TB, and the diagnosis of TB can be challenging in this population due to overlapping clinical features When these conditions coexist, outcomes are often poor. The patient's already compromised lung function deteriorates further due to TB, exacerbating hypoxia and CO_2 retention.

Additionally, pharmacological interactions may arise; for example, rifampicin induces hepatic? metabolism of corticosteroids, potentially leading to suboptimal control of COPD. Moreover, Acute infection superimposed on chronic inflammatory processes is likely to cause systemic inflammation to surge. Studies have shown that COPD patients who develop pneumonia or TB are more likely to experience cardiovascular complications. This is partly due to the acute inflammatory response that an already inflamed cardiovascular system experiences. For instance, consider an elderly COPD patient on home oxygen who contracts TB and subsequently suffers a pulmonary embolism or heart failure exacerbation. Thromboembolic events are more likely in this context, as TB can induce a hypercoagulable state, further compounded by the immobility associated with COPD. This complex interplay can ultimately result in o multi-organ failure. This underscores the necessity of multidisciplinary co-management ideally involving pulmonologists, infectious disease specialists, and cardiologists to optimize outcomes in such complex cases.

Post-tuberculosis lung disease (PTLD) is a noteworthy example of mixed pathogenic state. PTLD refers to chronic lung impairments that persist after the microbiological cure of TB. These can include bronchiectasis, chronic airflow obstruction (similar to COPD), fibrotic scars/scarring, and residual cavitation. Patients with PTLD often experience chronic breathlessness, recurrent infections, and may require long-term inhaled therapies analogous to COPD treatment [18, 30]. Importantly, emerging data indicate that individuals with PTLD have increased long-term mortality, predominantly due to cardiopulmonary causes, including cardiovascular disease [5]. The pathogenesis of PTLD involves prior TB infection, which can cause direct cardiac damage, such as pericardial thickening or subtle myocardial fibrosis due to TB toxins, as well as chronic lung injury that resembles COPD, with attendant hypoxia and inflammation These patients are often overlooked by healthcare systems because, although classified as "TB survivors," they present with chronic pulmonary symptoms and substantial ongoing healthcare needs. From a cardiotropic perspective, PTLD patients likely benefit from similar interventions as those with COPD, such as cardio-vascular risk factor management and regular screening for heart disease. However, structured follow-up after TB treatment is frequently lacking, representing an area for potential improvement, such as the establishment of dedicated post-TB clinics, that include cardiovascular evaluation.

HIV co-infection is another overlapping factor, particularly relevant to TB. HIV-infection can result in HIV-associated cardiomyopathy and, in combination with antiretroviral therapy, can contribute to metabolic syndrome, thereby increasing the CVD risk. In patients with HIV/TB co-infection, the immunosuppression caused by HIV alters the body's inflammatory response to TB. This often results in fewer granulomas and more disseminated disease. TB may also present atypically in these patients, with a higher incidence of pericardial effusions or myocarditis. These patients are also prone to immune reconstitution inflammatory syndrome upon initiation of TB treatment, which can manifest as acute pericarditis or vasculitis involving the heart. Furthermore, certain antiretroviral medications can cause dyslipidemia or have direct cardiotoxic effects. Thus, infection, immune dysregulation, and medication-related factors all interplay, further complicating the clinical picture. These cases highlight the importance of considering comorbid conditions and patient context, as these additional layers can significantly increase the complexity of post-TB care.

Given these multifactorial scenarios, a key lesson is the importance of a holistic, patient-centered approach to care. Clinical guidelines are often developed in isolation, separately addressing tuberculosis (TB), COPD (COPD) or cardiovascular disease, yet individual patients may require integrated elements from all these domains. For instance, a patient with concurrent TB and heart failure should have their TB regimen carefully tailored to avoid agents that could exacerbate heart failure, such as intravenous medications with high sodium content. Simultaneously, standard heart failure therapies (e.g., ACE inhibitors, beta-blockers) may need to be administered with caution, particularly in the context of active infection. Such cases demand individualized, multidisciplinary management.

Another crucial aspect is vigilant surveillance and early detection of complications. In complex clinical scenarios, proactive assessment is essential. For example, clinicians should consider performing echocardiography in TB patients presenting with difficulty dyspnea to evaluate for pericardial effusion or pulmonary hypertension. In post-TB patients with obesity, overnight oximetry or sleep studies may be warranted to screen for obstructive sleep apnea, which can further burden the cardiovascular system. Additionally, basic laboratory investigations such as B-type natriuretic peptide or troponin levels should be considered during COPD exacerbations to identify potential cardiac involvement. There is evidence that

a significant proportion of COPD hospitalizations are complicated by unrecognized co-occurring cardiac event, such as silent myocardial infarction, indicated by troponin level. Early recognition of these events is critical, as timely cardiology intervention can be life-saving.

Finally, patient education and secondary prevention are paramount in managing individuals with overlapping conditions. TB survivors should be informed of their increased risk for developing diabetes and heart disease, emphasizing the importance of lifestyle modifications and regular medical follow-up, essentially managing them as one would other high-risk populations. Similarly, patients with COPD should be educated to recognize the signs and symptoms of heart failure or angina and to seek medical attention promptly, rather than attributing all new or worsening symptoms to the pulmonary disease.

In conclusion, mixed pathogenesis scenarios are more common than isolated disease processes in phthisiopulmonology. These cases present a complex clinical picture, but careful identification and understanding of each contributing factor are essential for developing a comprehensive care plan. When hypoxia, pharmacological agents, toxins, and inflammation converge, the cumulative burden on the heart can be substantial. Proactive management that targets each factor, coupled with coordinated multidisciplinary care, offers the best opportunity to mitigate negative cardiotropic effects and improve patient outcomes.

Conclusion.

Pulmonary diseases such as tuberculosis (TB) and COPD (COPD) significantly impact cardiovascular health, creating a multidimensional burden beyond the respiratory system. This review highlights the key mechanisms and consequences of this interplay, emphasizing the importance of early recognition and comprehensive management.

Cardiac involvement in both TB and COPD is common and clinically significant. TB can lead to complications like pericarditis, which may progress to constrictive pericardial disease and heart failure. Even after microbiological cure, TB survivors remain at elevated cardiovascular risk due to lingering immune activation. In COPD, cardiovascular comorbidities such as coronary artery disease, arrhythmias, and heart failure are prevalent and account for nearly half of disease-related deaths.

Several mechanisms contribute to this cardiopulmonary interaction. Chronic hypoxemia promotes pulmonary hypertension and eventually cor pulmonale. TB medications such as Bedaquiline and Fluoroquinolones may prolong QT intervals and trigger arrhythmias. Additionally, both endogenous toxicity from persistent inflammation and exogenous toxins like smoking and alcohol worsen myocardial stress and injury. Systemic inflammation serves as a unifying mechanism, accelerating atherosclerosis and raising the risk of acute cardiac events.

These effects are often synergistic and occur concurrently. For example, TB patients receiving multidrug therapy may also experience hypoxia and systemic inflammation, heightening their cardiovascular vulnerability. Similarly, COPD patients are exposed to ongoing hypoxia and environmental toxins, which, together, can overwhelm cardiac compensation mechanisms.

Evidence-based interventions can mitigate these risks. ECG monitoring and electrolyte correction during TB treatment may prevent fatal arrhythmias. Long-term oxygen therapy in COPD reduces cor pulmonale progression and improves survival. Smoking cessation slows pulmonary decline and substantially lowers cardiovascular risk. Adjunctive treatments like corticosteroids or antioxidants may also reduce cardiac inflammation in TB.

Integrated care is crucial. Management should involve collaboration between pulmonologists, cardiologists, and infectious disease specialists. Routine cardiovascular assessment, including ECGs, echocardiograms, and biomarker monitoring, should be standard in severe cases.

Finally, prevention and early intervention are key. Identifying at-risk patients and initiating preventive therapies – such as beta-blockers or vaccines – chronic obstructive pulmonary disease can significantly improve outcomes. Addressing broader determinants like nutrition and housing supports recovery and resilience, reinforcing the need for holistic patient care.

Based on the conclusions of this review, we recommend that healthcare systems and providers managing patients with tuberculosis (TB) and chronic obstructive pulmonary disease (COPD) integrate routine cardiovascular risk screening into care. All patients should be evaluated for hypertension, diabetes, dyslipidemia, and substance use; TB survivors should undergo cardiovascular risk scoring post-treatment given their elevated long-term risk; and COPD patients require regular screening for coronary artery disease and heart failure because of their high prevalence.

Monitoring for cardiotoxic medications should be strengthened. In TB, ECG monitoring should be routine when regimens Include Bedaquiline,

Delamanid, or Fluoroquinolones, with WHO guidance followed for ECG frequency and proactive management of electrolyte imbalances. Similarly, COPD patients on high-dose bronchodilators or theophylline should be assessed for arrhythmic symptoms, and ECG or Holter monitoring considered for those with known cardiac disease.

Hypoxemia should be addressed early and aggressively. Long-term oxygen therapy is essential in COPD with chronic hypoxia ($PaO_2 < 55$ mmHg or $SpO_2 < 88\%$). In TB-related respiratory failure, high-flow oxygen or ventilation must be initiated promptly to protect the myocardium. Patients with moderate COPD who are traveling to high altitude or flying should be evaluated for supplemental oxygen needs.

Lifestyle interventions should be integrated. Smoking and alcohol cessation support should be embedded in TB and COPD care. Nutrition should be prioritized in TB management, thiamine deficiency corrected in alcohol-dependent patients, and pulmonary rehabilitation and exercise promoted to improve cardiovascular fitness and reduce inflammation.

Multidisciplinary collaboration should be enabled through clear referral systems between pulmonology and cardiology. Cardiac symptoms in TB patients should prompt echocardiography and cardiology input. TB should be considered in unexplained heart disease, particularly in endemic regions. Joint cardio-pulmonary clinics can optimize follow-up and diagnostics.

Patients should be educated to recognize cardiac warning signs—such as orthopnea, palpitations, or sudden chest discomfort, which are often misattributed to lung disease–so they seek care promptly.

Ongoing research should be supported by collecting cardiovascular outcomes in TB and COPD cohorts, and by designing future clinical trials that assess cardiopulmonary endpoints to inform care guidelines.

In summary, integrated care that addresses both pulmonary and cardiovascular health is essential to improve outcomes for patients with TB and COPD.

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