The interaction between respiratory diseases and cardiovascular system

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ABSTRACT

Background: The cardiovascular and respiratory systems function as a single unit and alteration in cardiorespiratory interactions can cause significant changes in cardiac function. Although LRTIs are traditionally regarded as a disease confined to the lungs, growing evidence suggests that pneumonia may have a negative impact on multiple organ systems, including the cardiovascular system. Diastolic dysfunction of the right ventricle is the earliest hemodynamic change found in patients with LRTIs due to the increase in the afterload imposed on the ventricle. Pulmonary disease affects the size, shape and function of the right ventricle, but altered respiratory function can also affect the left ventricle.

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Keywords*:* LRTIs, cardiovascular complications

1. INTRODUCTION

This interaction is complex. Changes in the structure and function of the right ventricle are associated with pulmonary hypertension. Recurring hypoxemia and hypercapnia associated with different mediators and cytokines related to chronic inflammation of the airways in patients with asthma cause pulmonary vasoconstriction and the development of pulmonary hypertension, with the consequent hypertrophy/dilatation of the right ventricle **(Allinson et al., 2023).**

There is increasing recognition that myocardial infarction (MI) can be precipitated by a respiratory infection, with evidence indicating that pneumonia, bronchitis and influenzas confer an increased transient risk of MI. This link may also contribute to the seasonal variation and winter peak of MI. However, much of the research linking respiratory infection to MI has been conducted using general practice records or regional registries **(Auld et al., 2024).**

Several studies have demonstrated the association between LRTIs and the risk of future cardiac complications. Pneumonia has been shown to predispose to several cardiac conditions including heart failure, cardiac arrhythmia and myocardial infarction **(Efros *et al.*, 2020).**

Acute respiratory distress syndrome (ARDS) has been associated to considerable cardiovascular strain, which may be related to severe respiratory compromise and hypoxemia. Elevated levels of cardiac biomarkers are associated with increased mortality and length of stay in critically ill patients, though the mechanism(s) responsible for biomarker elevations are still to be completely elucidated **(Green *et al.*, 2021).**

Also, animal models of severe pneumonia show that S. pneumoniae can invade the myocardium leading to cardiac injury and scarring. there have been few echocardiographic studies during severe pneumonia in humans. Autopsy studies suggest that myocardial injury, which is relatively rare in uncomplicated infections and may occur more often in fatal influenza **(Davidson and Warren-Gash, 2019).**

Understanding interactions between LRIs and CVD, is increasingly important as the global population ages and multimorbidity increases. Among LRIs, much focus has been given to influenza due to its severity but also because it is one of the only respiratory infections for which there is effective prevention and treatment. This focus is supported by findings from observational studies which confirm an association between laboratory-confirmed ARIs and cardiovascular complications. However, where infections other than preventable and treatable influenza or S. pneumoniae result in cardiovascular complications, other approaches to avert these outcomes are required **(Davidson and Warren-Gash, 2019).**

Novel coronavirus emerged in China in late 201.9 as a disease named coronavirus disease 2019. This pathogen was initially identified as causing a respiratory syndrome, but later, it was found that COVID-19 could also affect other body systems, such as the neurological and cardiovascular systems **(Sousa Rêgo *et al.*, 2023).**

By 12 May 2021, more than 130 million individuals had confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection worldwide with more than 3.3 million related deaths. SARS-CoV-2 and its interaction with the cardiovascular system is not entirely recognized and knowledge of the pathophysiological mechanisms behind such an interaction is still evolving **(Ghosh *et al.*, 2024).**

These mechanisms include direct SARS-CoV-2 cardiac and endothelial injury, and indirect heart damage by induced cytokine storm, hypercoagulable state and hypoxia, all of which are increasingly reported in individuals with COVID-19, especially severe cases. COVID-19 appears to be implicated in de novo post-recovery cardiac structural and functional changes and cardiac related symptoms **(Ramadan *et al.*, 2021)**.

Since the beginning of the pandemic, cardiovascular disorders have been reported as the most common extrapulmonary manifestation of SARS-CoV-2 infection. It is estimated that approximately 20 to 30% of hospitalized COVID-19 patients develop cardiac complication **(Huseynov *et al.*, 2023),(Gupta, Marzook and Ahmad, 2022).**

Potential mechanisms of cardiovascular complications

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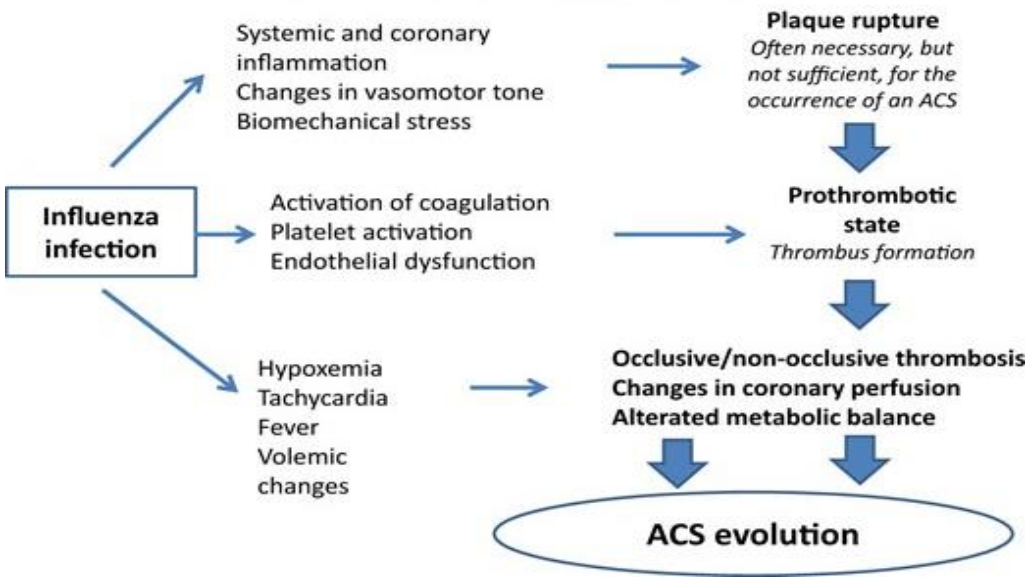

Fig 1: Influenza and acute coronary syndrome

(Muscente and De Caterina, 2020).

2- Ischemic complications

Myocardial infarction in children is extremely rare, with most suspected cases being in fact cases of fulminant myocarditis. Myocardial infarction is secondary to acute coronary thrombosis. The predisposition for the appearance of a thrombus depends on several factors: alteration of the vascular endothelium, modification of blood coagulation parameters by the appearance of thrombophilia, and hemodynamic changes of the blood vessel (stasis, turbulence). During the time of the COVID-19 pandemic, numerous cases of Kawasaki-like disease have appeared, many of them associating aneurysmatic dilations of the coronary artery after evolving as a multisystem inflammatory syndrome in children (MIS-C). MIS-C has an incidence of 0.2–0.6% of all pediatric SARS-CoV-2 infections **(Cinteză *et al.*, 2022).**

From a pathophysiological point of view, myocardial 'ischemia' results from an imbalance between myocardial oxygen demand/supply, whereas myocardial 'injury' is defined as any damage to myocardial cells that is accompanied by the release of cardiac necrotic biomarkers **(Davidson and Warren-Gash, 2019)**. It needs to be acknowledged that the prevalence of MI varies seasonally and is highest in the winter **(Franczuk *et al.*, 2022)**.

3- Viral Myocarditis

Myocarditis is defined as an immunological inflammatory reaction of various etiologies occurring within the myocardium, occurring in 10 to 20 cases per 100,000 people **(Krych et al., 2024)**. Acute myocarditis covers a wide spectrum of clinical presentations, from uncomplicated myocarditis to severe forms complicated by hemodynamic instability and ventricular arrhythmias; however, all these forms are characterized by acute myocardial inflammation. AM is caused by a direct pathogen insult and/or exaggerated immune response. It represents the most typical case of myocardial inflammatory disease, **(Uccello et al., 2023).**

After the initial acute phase presentation of viral myocarditis, the virus may be cleared, resulting in full clinical recovery; the viral infection may persist; or the viral infection may lead to a persistent autoimmune-mediated inflammatory process with continuing symptoms of heart failure. As a result of these 3 possibilities, the diagnosis, prognosis, and treatment of viral myocarditis can be extremely unpredictable and challenging for the clinician **(Olejniczak *et al.*, 2020).**

Myocarditis is common during viral infection with cases described as early as the influenza pandemic of 1917, and COVID-19 pandemic is no exception. The hallmark is elevated troponin, which occurs in 36% of COVID patients, with electrocardiogram, echocardiogram, and cardiac magnetic resonance being valuable tools to assist in diagnosis. Cases of cardiac inflammation during the current epidemic are either related to direct viral invasion of the myocardial cells or to intense cytokine storm **(Rezkalla and Kloner, 2021).**

4- Pericardial Disease

Acute pericarditis is the most common inflammatory heart disorder, a head of acute myocarditis and infective endocarditis. Acute pericarditis is an overall benign and self-limiting disease In developed countries, viral etiology is the most common in both acute pericarditis and pericardial disease as a whole**(Lazarou et al., 2022).**

Acute pericarditis is an inflammatory disease characterized by infiltrates of immune cells into the pericardium triggered mainly by viruses and resulting in a clinical syndrome characterized by typical signs and symptoms (pericarditis type of chest pain, specific electrocardiogram (ECG) abnormalities, and pericardial effusion). The common course of the disease is benign with mild to moderate symptoms that can be successfully treated out patiently with non-steroidal anti-inflammatory agents and colchicine. More severe complications, including cardiac tamponade with a worse prognosis, are rather rare. 33% of patients with acute pericarditis have a history of a recent upper respiratory tract infection **(Franczuk *et al.*, 2022).**

Vaccination studies

Vaccination studies provide further evidence of a link between acute respiratory infections and ACS. In particular this support the notion that influenza infections, not just bacterial infections, are an

important part of this association. Randomized control trials have reported a reduced risk of coronary events following influenza vaccination in patients known to have cardiovascular disease **(Bazaz et al., 2013).**

'Indirect' evidence of a possible association between influenza and AMI derives from studies showing that influenza vaccination is effective in the prevention of ischemic heart disease. This, in addition to strengthening the causality between the two factors, would highlight the important clinical repercussion from the association. The results of some observational studies show that the protective efficacy of influenza vaccination from new coronary events in secondary prevention is between 19% and 45%. This is a range of effectiveness substantially similar to that obtained with other cardiovascular prevention measures widely accepted in clinical practice **(Muscente and De Caterina, 2020).**

Future research directions

More research focused on who is at risk of cardiovascular complications triggered by LRIs is needed. Predicting future CVD, particularly in people with different combinations of co-morbid conditions, will assist in providing targeted personalized interventions. Any expansion to current vaccine recommendations resulting from new patient groups being identified as high risk for cardiovascular complications following ARI will require effectiveness and cost-effectiveness studies. While prevention of ARIs themselves is likely to result in the greatest clinical and public health benefit, treatment during the acute phase of infection could also prevent cardiovascular complications **(Davidson and Warren-Gash, 2019).**

Evaluation of cardiac function

Evaluation of cardiac function requires good image quality and multiples parameters in order to deliver accurate and reliable information. The evaluation of cardiac function can be easily performed by bedside cardiac ultrasound in the intensive care setting and physiological information gained may help in taking timely and accurate therapeutic decisions (Counseller and Aboelkassem, 2023).

Echocardiography

Echocardiography is a precious tool in the hands of an expert operator to improve diagnostic procedures and therapeutic management of patients with LRTIs, aiding clinicians in early recognizing subtle cardiac damage and providing adequate treatment for infected subjects. The use of trans thoracic echo (TTE) could change the diagnostic workup of acute coronary syndromes, myocarditis, acute left or right ventricular failure, and secondary myocardial damage due to sepsis or mechanical ventilation, allowing noninvasive assessment and monitoring (Soliman-Aboumarie et al., 2021). Echocardiography provides important information on the severity of the disease, the decision-making process for treatment strategies, prognosis prediction, and treatment response evaluation (Lee and Park, 2023). Echocardiography is a non-invasive, relatively safe, cost effective and easily accessible

method for the right ventricle assessment. Tissue Doppler imaging (TDI) has been demonstrated to furnish a quantitative measure of regional velocities in the myocardium as well as systolic and diastolic intervals. TDI can detect subclinical abnormalities of the right ventricle in a phase when conventional echocardiographic findings are still within normal ranges, thereby enabling the detection of right ventricular dysfunction in the early stage of a disease (De-Paula et al., 2018). Doppler echocardiography has become the standard imaging modality for the assessment of heart valve disease severity and heart physiology, specifically diastolic function (Tissot, Singh and Sekarski, 2018).

cardiac markers

Cardiac biomarkers have evolved as essential tools in cardiology over the last 50 years, that is, for primary and secondary prevention, the diagnosis and management of acute myocardial infarction (AMI), and the diagnosis and risk stratification of heart failure (HF). We are beginning an era when it may be possible for biomarkers to direct treatment to optimize patient management (Mair et al., 2015). Cardiac markers, including brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-pro BNP), troponin, and aspartate aminotransferase (AST), are frequently used clinical parameters to predict the progression of deterioration in earlier phases. Natriuretic peptides are primarily synthesized in the heart and upregulated by myocardial stress. BNP and its precursor hormone NT-pro BNP are suitable laboratory cardiac markers for the diagnosis and risk stratification of heart failure (Zhao et al., 2021).

1-Natriuretic peptides

Atrial naturetic peptide and brain naturetic peptide are primarily produced in cardiac cells, namely atrial and ventricular cardiomyocytes. The cardiac natriuretic hormones are synthesized by cardiomyocytes as prohormones (Rahbar Kouibaran et al., 2023). The main mechanical stimulus for atrial naturetic peptide and brain naturetic peptide secretion is atrial and ventricular distension respectively, although studies suggest multiple other proteins/hormones can promote secretion including endothelin-1, α-adrenergic agonists, and angiotensin II, glucocorticoids, vasopressin, growth factors and cytokines (Rahbar Kouibaran et al., 2023). Both atrial naturetic peptide and brain naturetic peptide functionally antagonise the renin angiotensin aldosterone system (RAAS) and have antifibrotic and antihypertrophic effects (McGinn, Casey, et al., 2023).

2-Creatine Kinase and Creatine Kinase-MB

The earliest biomarker to increase is the muscle enzyme, CK or CPK, which is present in the cytosol of the myocytes and predominantly released into the bloodstream from the necrosed myocardium. The CK-MB fraction being more specific to the myocardium quickly replaced the CK and is considered the gold standard. CK-MB forms nearly 30% of CK in the myocardium, and a rise of > 5% of the total CK activity suggests damage to the cardiac muscle (Jacob and Khan, 2018). CK-MB still holds some

diagnostic value in cardiac and noncardiac conditions. CK-MB is detected in the serum 4 hours after myocardial injury, peaks by 24 hours, and normalizes within 48 to 72 hours. CK-MB is a useful biomarker for detecting AMI as it has a relative specificity for cardiac tissue but can still become elevated in noncardiac conditions, such as skeletal muscle injury, hypothyroidism, chronic renal failure, and severe exercise

3-Troponin

Since 2000, worldwide guidelines have recommended cardiac troponins (cTn) be regarded as the biomarkers of choice for the diagnosis of acute coronary syndrome (ACS) in adults. In 2018, the Fourth Universal Definition of Myocardial Infarction (MI) defined myocardial injury as elevated cTnI or cTnT concentrations with at least one value above the 99th percentile of the distribution of biomarker values in a reference population of apparently healthy individuals (99th percentile Upper Reference Level, URL) (Jaffe et al., 2023).

Myocardial injury in a setting compatible with cardiac ischemia identifies a MI, but myocardial injury can occur without infarction in several cardiac and systemic pathologies. The most important consequence of the application of this statement to current clinical practice is that cTnI or cTnT are measured using high-sensitivity methods (hs-cTnI and hs-cTnT) in all adult individuals with chest pain (Krychtiuk and Newby, 2024). Furthermore, over the last 10 years, several clinical studies (including some meta-analyses) have demonstrated that pathophysiological and clinical relevance of hs-cTnI and hs-cTnT measurement can predict incident heart failure and major cardiovascular events in adult individuals from the general population (Clerico, Aimo and Cantinotti, 2022). Highly sensitive troponin is a gold-standard necrotic biomarker for myocardial risk assessment worldwide. It is released virtually exclusively in the myocardium in the presence of myocardial injury irrespective of the mechanism of insult. Other biomarkers of myocardial injury that are of diagnostic value include creatine kinase-myocardial band (CK-MB) and BNP (Aboughdir et al., 2020). Troponins are cardiac-specific proteins which make up thin filaments, which along with thick filaments, form the sarcomere which is the contractile apparatus of cardiomyocytes. When cardiomyocytes are damaged, troponin is released into the blood stream and can be detected almost immediately following an ischemic or hypoxic event (McGinn, Casey, et al., 2023). Cardiac troponin I is a structural protein in myocardial cells and is a highly specific and sensitive laboratory parameter well known to reflect acute and chronic myocardial cell death. It is an important biomarker in patients with acute myocardial infarction for rapid diagnosis that enables us to take patients to the interventional catheterization laboratory as soon as possible after presentation in the emergency room is a marker that displays cardiac injury quickly and accurately. In adults, troponin elevation is usually associated with coronary artery disease and requires urgent cardiac catheterization (McGinn, Waterfield, et al., 2023). In healthy children, myocardial injury is rare and may develop due to many different causes., there has been growing

interest in the use of troponin I in pediatrics and its value in assessing cardiac injury in children. Elevations in this biomarker reflect myocardial injury; they do not indicate its mechanism. Troponin is released into the circulation in response to ischemic and non-ischemic cardiac injury (Yoldaş and Örün, 2019).

Cardiac troponin (cTn) measurements are an essential component of the evaluation of adult patients who present to the emergency department (ED) with suspected acute coronary syndrome. Because of their superior analytical performance, high-sensitivity cardiac troponin (hs-cTn) assays are the preferred choice for these evaluations. Using hs-cTn assays, very low cTn concentrations have a high negative predictive value for acute myocardial infarction in adults, but high concentrations lack specificity for a specific etiology of the increase (Kozinski et al., 2017).

In fact, the majority of cases with increased hs-cTn concentrations above the 99th percentile upper-reference limit (URL) are due to myocardial injury secondary to some systemic illness that involves the heart indirectly, rather than reflecting a primary cardiac abnormality. This reflects the fact that many disease states other than ischemic heart disease can cause acute and/or chronic damage to the myocardium (Wang et al., 2022).

High sensitive troponin provides remarkable prognostic value for patients at increased risk of worsening outcomes and in-hospital mortality, though studies have also shown the association of raised CK-MB and BNP levels with more severe symptoms of COVID-19. Raised serum cTnT (Aboughdir et al., 2020). Data on the clinical significance of elevated levels of blood biochemical markers of myocardial necrosis in ARDS patients are so far scarce and discrepancies exist among investigations especially because of different timing of troponin measurements and the incorporation of electrocardiogram (ECG) testing and echocardiograms in the analysis (Lazzeri et al., 2016).

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