



Cardiac Biomarkers in the Setting of Asthma Exacerbations: a Review of Clinical Implications and Practical Considerations

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Abstract

Purpose of Review The present paper aims to highlight clinical implications of elevated cardiac biomarkers and associated myocardial dysfunction in a variety of cardiac and non-cardiac scenarios in patients with an asthma exacerbation, and to propose a basic algorithm for cardiovascular evaluation and triage (and hence, for further management) of these patients primarily based on evaluation of cardiac biomarkers along with basic diagnostic modalities and specific cardiac symptoms in the hospital setting.

Recent Findings Elevation of cardiac biomarkers in the setting of an asthma exacerbation mostly signifies a new-onset subclinical myocardial dysfunction/injury generally associated with certain asthma-related factors including acute hypoxemia and bronchodilator therapy, and usually has a limited prognostic value in these patients. On the other hand, elevation of these biomarkers in patients with an asthma exacerbation might also denote a variety of certain life-threatening cardiac or non-cardiac conditions associated with significant myocardial dysfunction (acute coronary syndromes (ACSs), sepsis, etc.) that might be masked by the rampant course of the asthma exacerbation, and hence, might possibly go undetected potentially aggravating the prognosis in a portion of these patients.

Summary In patients with an asthma exacerbation, it seems imperative to timely diagnose and manage emerging diverse clinical conditions particularly through the guidance of cardiac biomarkers and associated myocardial dysfunction patterns in an effort to improve overall prognosis in these patients.

Keywords Cardiac biomarkers · Asthma · Asthma exacerbation · Troponins · Natriuretic peptides · N-terminal pro-brain natriuretic peptide (NT-proBNP) · Brain natriuretic peptide (BNP) · Clinical implications · Myocardial dysfunction · Prognosis

Introduction

In clinical practice, elevation of cardiac biomarkers has been encountered in the setting of acute pulmonary conditions including pulmonary embolism (PE), community-acquired pneumonia, exacerbations of chronic obstructive pulmonary disease (COPD), and asthma with important prognostic implications in most of these conditions [1•, 2, 3•, 4•, 5•, 6•,

7–10, 11•]. Furthermore, accompanying electrocardiographic (ECG) changes might further substantiate the presence as well as the severity of myocardial injury in this setting as well [1•, 3•, 5•]. Mechanistically, high levels of cardiac biomarkers in acute pulmonary conditions possibly denote the presence of new-onset (or occasionally pre-existing) subtle or overt myocardial dysfunction, and might be attributable to a variety of factors such as enhanced right ventricular (RV) strain (mostly due to acute increases in pulmonary vascular resistance (PVR)) severe hypoxemia, systemic inflammation (cytokine impact, etc.), hemodynamic alterations (tachycardia, etc.), high-dose bronchodilator therapy, and occasionally, acute cardiac complications including ACSs or pre-existing cardiac conditions including chronic left ventricular (LV) dysfunction and cor pulmonale (Fig. 1) most of which might be potentially associated, to some extent, with the severity of the underlying acute pulmonary disease and overall prognosis [1•, 2, 3•, 4•, 5•, 6•, 7–10, 11•].

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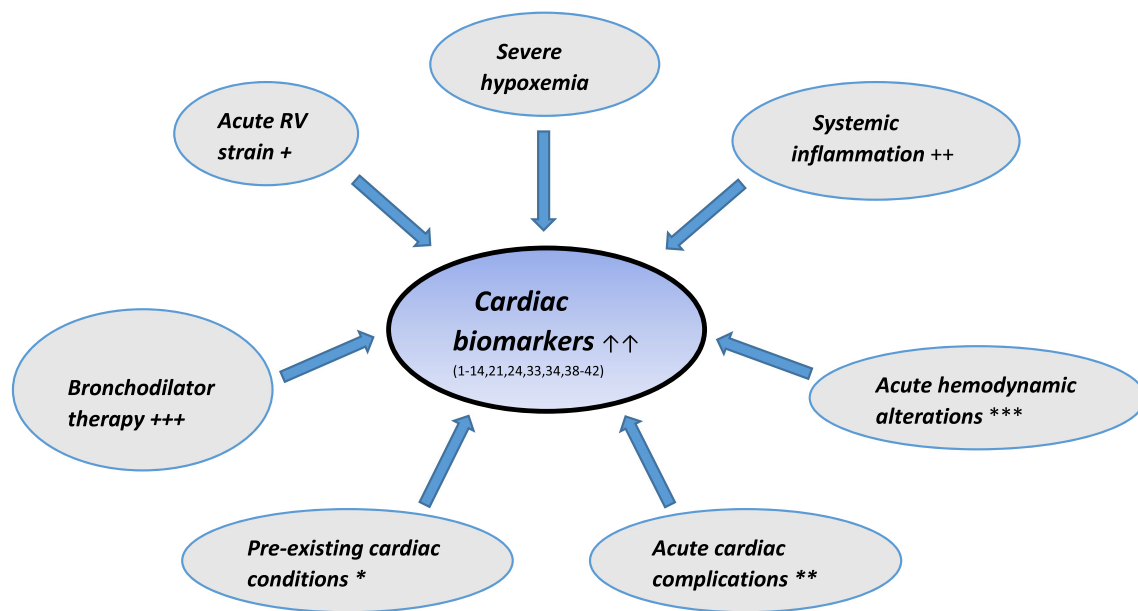


Fig. 1 Primary mechanisms underlying elevation of cardiac biomarkers (associated with myocardial dysfunction) in the setting of acute pulmonary conditions. RV, right ventricle; cardiac biomarkers denote troponins and natriuretic peptides. Acute pulmonary conditions mostly denote pneumonia, acute pulmonary embolism (PE), and exacerbations of chronic obstructive pulmonary disease (COPD) and asthma. +, largely

due to acute increases in pulmonary vascular resistance (PVR). ++, largely due to cytokine-mediated cardiomyocyte injury. +++, including β agonists. * including chronic left ventricular (LV) dysfunction and cor pulmonale. **, including acute coronary syndromes (ACSs), Takotsubo cardiomyopathy (TTC), and myocarditis. ***, including tachycardia and acute increases in blood pressure (BP)

In particular, asthma and COPD appear to be the most common and similar forms of obstructive pulmonary disorders (both harboring a chronic inflammatory background and usually presenting with acute exacerbations and remissions), and also have a variety of diverse characteristics with regard to etiologic triggers, disease course, and response to therapeutic regimens, etc. as [12]. In contrast to COPD, generally known as a later-onset and progressive pulmonary disease presenting with variable degrees of both airway and parenchymal involvement, asthma is mostly regarded as an earlier-onset pathology that exclusively involves proximal and distal airways, and is generally characterized by recurrent bouts of reversible airway obstruction in response to a variety of triggers including specific allergens [12]. Importantly, oxidative stress and classical systemic inflammation as demonstrated with involvement of neutrophils and certain pro-inflammatory mediators (tumor necrosis factor- α (TNF- α), interleukin-8(IL-8), etc.) generally appear to be less pronounced in the setting of asthma as compared with COPD [12]. Conversely, asthma is predominantly characterized by the preponderance of eosinophils and mast cells within the airways primarily accounting for the release of certain bronchoconstrictor substances including histamine and basic proteins associated with epithelial damage [12]. However, despite these generalizations, neutrophilic and eosinophilic pathways, to some extent, overlap in these two conditions [12]. On the other hand, more detailed information on asthma may be found elsewhere [12], and is beyond the scope of this paper.

Notably, even though meta-analyses [13•, 14] have demonstrated substantial impact of certain biomarkers including troponins and brain natriuretic peptide (BNP) on morbidity and mortality in patients with COPD, prognostic implications of these biomarkers in the setting of asthma, as compared with other acute pulmonary conditions, are still nebulous, and have yet remained to be established in the clinical setting. Accordingly, the present paper aims to highlight clinical implications of elevated cardiac biomarkers and associated myocardial dysfunction in the setting of diverse cardiac and non-cardiac scenarios in patients with an asthma exacerbation, and to propose a basic algorithm for cardiovascular evaluation, triage, and management of these patients primarily based on evaluation of cardiac biomarkers along with certain basic tools (including ECG) and specific symptomatology in the hospital setting.

Elevation of Cardiac Biomarkers in Asthma Exacerbations: Potential Triggers and Mechanisms

In the clinical setting, cardiac biomarkers, unless stated otherwise, universally refer to cardiac troponins and natriuretic peptides that have been widely used over the past years particularly for the diagnosis and risk stratification of various cardiovascular diseases around the globe [15–17]. Troponins (troponin-I, T, and C (TnI, TnT, TnC)) are well-known to serve as regulatory proteins that orchestrate the process of calcium-induced interaction of actin and myosin, and are

generally elevated in the setting of acute or chronic myocyte injury [16]. A value of above the 99 percentile of the upper reference limit (URL) is generally considered abnormal with substantially higher sensitivity and specificity values as compared with creatine kinase-MB and myoglobin for the detection of cardiomyocyte injury (and even much higher for high-sensitivity troponin assays) [15]. Importantly, the specificity of troponins for the detection of cardiomyocyte injury significantly increases at higher levels (particularly levels $> 5 \times$ URL) [15].

On the other hand, natriuretic peptides used in clinical practice comprise a variety of biologically active and inactive proteins (mid-regional pro-atrial natriuretic peptide (MR-pro-ANP), BNP, and N-terminal pro-brain natriuretic peptide (NT-pro-BNP)) predominantly released from atrial and ventricular myocardium in response to enhanced wall stress, myocardial injury, etc. [17]. Importantly, normal values of these peptides might safely rule out heart failure (HF) due to their very high sensitivity values in clinical practice [17]. On the other hand, their positive predictive value (and hence, specificity) for the diagnosis of HF also increases significantly with increasing values [17]. More detailed information on these biomarkers is beyond the scope of this paper, and may be found elsewhere [16, 17].

In patients with an asthma exacerbation, there might exist a variety of cardiac and non-cardiac clinical scenarios primarily accounting for the elevation of cardiac biomarkers. In other terms, even though these biomarkers are well-known to increase in the setting of certain pathologies directly involving myocardium including ACS, heart failure (HF), hypertensive emergencies, and myocarditis [15–17], they might also elevate in certain non-cardiac conditions primarily associated with the asthma exacerbation itself (hypoxemia, bronchodilator therapy, etc.) or occasionally in the setting of certain complications including renal failure, sepsis, cerebrovascular events, hypothyroidism, and hyperthyroidism in these patients [15–17]. However, it should be borne in mind that the primary mechanism of biomarker elevation might still be attributable to myocardial injury in most of these non-cardiac diseases [16]. For instance, cytokine impact along with hemodynamic alterations and hypoxemia in sepsis and adrenergic upsurge in stroke might possibly induce myocardial injury leading to elevation of cardiac troponins [16]. However, the absolute mechanisms of troponin rise in renal failure remain to be established [16]. On the other hand, natriuretic peptide levels might significantly increase in patients with renal failure as a consequence of reduced renal elimination, yet might also increase in the setting of hypoxemia as a result of myocardial injury [17]. Temporally, elevation of cardiac biomarkers might evolve acutely (for instance, due to acute and severe hypoxemia or acute renal failure), or might be due to pre-existing comorbidities (for instance, co-existing and chronic LV dysfunction) in patients with an asthma exacerbation. However, it

is noteworthy that since the overall incidence of pre-existing comorbidities in the setting of asthma seems to be relatively low (due to younger age, low incidence of cor pulmonale, etc.) as compared with COPD, elevation of cardiac biomarkers emerge as an acute phenomenon in the setting of most asthma exacerbations. More importantly, elevation of biomarkers in the setting of non-cardiac conditions that even do not lead to significant myocardial injury, also seems to denote relatively unfavorable prognosis [16] in patients with an asthma exacerbation possibly due to systemic adverse effects of the co-existing non-cardiac condition (including renal failure) associated with biomarker elevation in this setting.

Myocardial Dysfunction Associated with Elevated Cardiac Biomarkers in Patients Having an Asthma Exacerbation: Clinical Patterns and Prognostic Implications

As categorized and described below, acutely evolving or pre-existing triggers accounting for the elevation of cardiac biomarkers in patients with an asthma exacerbation mostly elicit variable degrees of myocardial injury, and manifest as either subclinical or overt myocardial dysfunction with a variety of diverse prognostic implications in these patients:

Subclinical Myocardial Dysfunction/Injury: a Common Phenomenon in the Setting of Asthma Exacerbation

In the setting of asthma exacerbation, a variety of cardiac biomarkers including CK-MB, TnI, and BNP as part of subclinical myocardial dysfunction/injury have all been demonstrated to be significantly elevated in certain pediatric cases at admission (almost completely returning to normal levels at discharge) [4•]. Similarly, subclinical myocardial dysfunction as measured with NT-proBNP and Tn-T levels was previously found to be significantly increased in the setting of COPD exacerbation, and was largely attributed to the adverse impact of bronchodilator therapy [3•]. Interestingly, natriuretic peptides including BNP and NT-pro-BNP, that are well-known to increase in response to enhanced myocardial wall stress, might also increase substantially in the setting of severe hypoxia [17], and might have important implications in the setting of COPD exacerbations [18, 19•, 20]. However, whether these findings might also apply to the setting of asthma has yet remained to be established.

In general, elevation of cardiac biomarkers in the setting of an asthma exacerbation mostly refers to a newly emerging subclinical myocardial dysfunction/injury that, by definition, refers to normal LV and RV systolic and diastolic functions [5•] accompanied by a variety of subtle abnormalities as demonstrated with basic modalities including ECG [21•, 22, 23] and possibly certain specific echocardiographic techniques including tissue Doppler and strain rate. Importantly,

subclinical myocardial dysfunction, unless arising as part of an ACS scenario, generally appears to be a silent phenomenon with no specific symptomatology. On the other hand, as described later, significant elevation of myocardial enzymes including troponins ($> 5 \times \text{URL}$) particularly with a “rise and fall” pattern, irrespective of accompanying clinical findings, should also be labeled as acute myocardial infarction (AMI) [15] rather than myocardial injury in the clinical setting. Taken together, certain asthma-related factors including hypoxemia, bronchodilator therapy, and tachycardia generally appears to serve as the dominant trigger of subclinical myocardial dysfunction characterized by sole elevation of cardiac biomarkers with or without non-specific ECG findings (as described below). However, it should be borne in mind that ACSs, infections, and other serious conditions including cerebrovascular events [2, 15–17] might occasionally account for this phenomenon as well.

Notably, reversible ECG changes including ST segment and T wave alterations, P pulmonale, right axis deviation, and right bundle branch block (RBBB) might also arise in a portion of cases presenting with an asthma exacerbation [21•, 22, 23]. Certain ECG changes including T wave and ST segment changes, though they were previously ascribed to reversible autonomic changes, in this setting [23], might particularly substantiate an existing subclinical myocardial dysfunction in these patients. However, it seems quite likely that these ECG changes might arise in isolation in the absence of elevated biomarkers due to a variety of factors including hyperinflation of lungs leading to cardiac positional changes [23], or might precede elevation of these biomarkers in certain asthma cases. More importantly, these changes, unless associated with a full-blown ACS pattern, might be regarded as quite non-specific in the clinical setting.

Prognostically, asthma exacerbation has been considered a serious clinical condition particularly during childhood [5•]. However, the issue of whether subclinical myocardial dysfunction as demonstrated with elevation of cardiac biomarkers (and ECG changes) has prognostic significance still remains to be fully established; accordingly, some authors previously reported no association of TnI elevation with acute disease severity in the setting of pediatric asthma [6•]. Similarly, in another study comprising children with asthma exacerbation, raised TnI levels were largely ascribed to bronchodilator therapy rather than acute disease severity [5•] that might possibly correlate with blood gas analysis, length of hospital stay, and hemodynamic parameters. Interestingly, it was recently suggested that natriuretic peptides might exert bronchoprotective and bronchodilator effects on bronchial muscle cells largely through a variety of indirect mechanisms in patients with asthma [18] and hence might be expected to substantially increase as part of counterbalancing mechanisms in more severe clinical presentations of asthma exacerbations. This might indirectly substantiate the potential prognostic relevance of these peptides in asthma as well.

In the general context, it is noteworthy that certain factors (severe systemic inflammation, acute RV strain, etc.) associated with serious pulmonary conditions (pneumonia, PE, and severe COPD exacerbation), besides eliciting significant myocyte injury [11•], are also well-known to have direct adverse effects on myocardium (induction of arrhythmogenesis, electromechanical dissociation, etc. [1•, 24]) possibly in correlation with serum levels of cardiac biomarkers. This might, in part, explain the stronger relation of cardiac biomarkers with prognosis in these conditions as compared with an asthma exacerbation. Taken together, current evidence regarding the association of elevated cardiac biomarkers (as part of subclinical myocardial dysfunction) with clinical outcomes still appears to be inconsistent in the setting of asthma exacerbation potentially warranting further studies in this setting.

Acute Coronary Syndromes Manifesting as Subclinical Myocardial Dysfunction

In particular, elevation of cardiac biomarkers might portend a variety of worse clinical scenarios in a specific subgroup of patients with asthma: Within this context, elevation of cardiac troponins might occasionally signify a co-existing ACS (mostly presenting with subclinical myocardial dysfunction) as a potential complication in certain cases (for instance, troponins $> 5 \times \text{URL}$ and/or specific cardiac symptoms (angina, ECG changes, etc.) on admission or during the hospital course [15]). Current guideline on non-ST segment elevation ACSs (NSTEMI) [15] particularly highlights that an elevation of $> 5 \times \text{URL}$ in troponin levels particularly with a “rise and fall” pattern should suggest an acute myocardial pathology including acute myocardial infarction (AMI). However, specific signs and symptoms (typical angina, ECG changes) [15] even in the absence of these specific troponin changes should mandate further analysis for a potential ACS. Therefore, these cases should, in a timely manner, receive ACS medication, and undergo coronary imaging modalities (invasive or non-invasive coronary angiogram (CAG)) in an effort to diagnose and manage a grossly visible coronary pathology, if any, in this setting. Within this context, specific ACS medications along with timing and necessity of invasive coronary procedures in the setting of NSTEMI may be found in the current guideline in a detailed manner [15], and are beyond the scope of this review. However, certain clinical factors including malignant ventricular arrhythmias, hemodynamic instability, and intractable chest pain strongly warrant emergent coronary intervention in this setting [15] in a similar manner to the setting of ST segment elevation myocardial infarction (STEMI).

According to the universal definition of AMI [15], evolution of AMI might pathophysiologically be attributable to an acute atherosclerotic plaque rupture with subsequent thrombus superimposition (type 1) or due to a variety of other

triggers including coronary vasospasm, and acute supply-demand mismatch including severe hypoxemia and tachycardia, particularly in the presence of pre-existing critical plaques (type 2). The other types in a variety of specific clinical settings (types 3, 4, and 5) may be found elsewhere [15], and are beyond the scope of this article. Within this context, type 2 AMI mostly arising as a NSTEMI seems to be the dominant form of ACSs in patients with an asthma exacerbation, and might possibly be associated with certain factors including significant hemodynamic changes, bronchodilator therapy, and coronary vasospasm; accordingly, coronary vasospasm in the presence of normal coronary arteries was previously suggested as an important trigger of AMI in the setting of an asthma exacerbation [21••].

As expected, these cases might have a worse prognosis, even if treated in a timely and proper manner with the initiation of certain ACS medications and percutaneous coronary intervention (PCI) [15], where necessary (in the rare instance of a severe culprit stenosis), in the clinical setting. Contraindication of life-saving drugs including β blockers in this particular setting might further aggravate the prognosis in the short- and long-term as well. More interestingly, it also seems plausible that elevation of cardiac biomarkers as part of ACSs might also portend future cardiac events (arrhythmias due to potentially persistent myocardial changes) in the long-term suggesting close supervision of these patients even after discharge. Of note, the issue of whether significant elevation of all cardiac biomarkers (both troponins and natriuretic peptides) in a single patient at admission or during the hospital stay might be associated with a worse outcome as compared with a single marker positivity has yet remained to be fully established.

Bronchodilator Therapy: a Potential Trigger of Subclinical Myocardial Dysfunction on Top of its Direct Arrhythmogenic Impact

Impact of certain therapeutic regimens on cardiac biomarkers should also be taken into consideration in patients with an asthma exacerbation. Bronchodilators have long been regarded as the mainstay of therapy, and might significantly contribute to the elevation of cardiac biomarkers in these patients as well [3••, 4••, 5••, 6••] particularly when used in high doses and long duration. Within this context, “ β_2 adrenergic receptor agonist” therapy (salbutamol, terbutaline, etc.) was previously demonstrated to have direct and dose-dependent cardiomyotoxic effects (leading to myonecrosis) in clinical and experimental studies [5••]. Moreover, potential impact of salbutamol on myocardium was previously suggested to be an age-dependent phenomenon: accordingly, cardiomyocytes of elder children might be more vulnerable to the detrimental impact of β agonist therapy including sustained tachycardia [5••]. This vulnerability might also be

more striking in a particular gender category as well. In more severe scenarios, bronchodilators might also be implicated in the evolution of silent or symptomatic AMIs [21••, 25] as detected with substantial increments in cardiac biomarkers and/or specific ECG signs through a variety of mechanisms including coronary vasospasm.

Moreover, β agonist therapy might even be associated with sudden cardiac death (SCD) particularly in the presence of pre-existing structural heart disease including cardiomyopathies [21••, 25, 26]. More specifically, bronchodilator therapy, even in apparently normal hearts, might also exert significant and direct arrhythmogenic effects [3••, 6••, 25] in susceptible subjects particularly with a potential genetic basis [27–30] even without cardiomyocyte injury (and hence, with normal levels of cardiac biomarkers) potentially serving as a significant confounding factor when evaluating the association between cardiac biomarkers and prognosis in the setting of an asthma exacerbation. Mechanistically, these putative arrhythmogenic effects of β agonist therapy might be attributable to QT interval (QT_i) prolongation, decreased effective refractory period (ERP) in myocardium along with enhancement of certain indices associated with myocardial repolarisation heterogeneity including QT dispersion and T wave alternance (TWA) that all might be associated with a variety of life-threatening arrhythmias including torsades de pointes (TdP) [25, 29]. Therefore, it may be suggested that bronchodilator therapy, including β agonists, exerts detrimental effects on myocardium through a wide range of mechanisms with or without acute myocardial injury in the clinical setting [3••, 4••, 5••, 6••, 21••, 25–30].

Taken together, since the primary determinant of cardiac biomarker rise (as part of subclinical myocardial dysfunction) in patients with an asthma exacerbation mostly appears to be the severity of acute disease course (generally with a completely reversible nature) and use of bronchodilator therapy rather than certain accompanying factors with stronger prognostic value including systemic inflammation and acute hemodynamic load, the overall prognostic efficacy of cardiac biomarkers in most of these patients currently seems to be limited, and needs to be further investigated in the clinical setting. On the other hand, certain life-threatening conditions including ACSs, as potential triggers of biomarker elevation, should also be particularly sought and managed accordingly in certain patients with high-risk features including substantial elevation of biomarkers and ischemic ECG changes.

Overt Myocardial Dysfunction: a Stronger Determinant of Prognosis in the Course of an Asthma Exacerbation?

New-onset overt myocardial dysfunction (presenting with significant myocardial wall motion abnormalities, systolic and/or diastolic dysfunction on top of ECG and biomarker changes)

as part of well-known clinical phenomena including certain ACSs, takotsubo cardiomyopathy (TTC), and myocarditis [6••] might occasionally complicate the disease course in more severe clinical scenarios. Certain forms of ACSs including STEMI (generally with complete occlusion of the culprit coronary artery) are more likely to elicit significant and acute myocardial dysfunction on various imaging modalities as compared with NSTEMIs [31•]. However, diagnosis of acute STEMI mostly relies on initial ECG changes and symptomatology [31•] rather than evaluation of myocardial dysfunction on imaging modalities, and might very rarely go undetected in the hospital setting. In the setting of an asthma exacerbation, evolution of STEMI might be attributable to atherosclerotic plaque rupture (type 1 AMI) possibly as a consequence of adrenergic hyperactivity (hypoxia, anxiety, β agonists, etc.). Based on similar mechanisms, coronary vasospasm with normal coronary arteries (type 2 AMI) also serves as a trigger of STEMI in certain cases with an asthma exacerbation [21••]. In particular, STEMI equivalents (acute left bundle branch block (LBBB), etc.) and mimickers (acute pericarditis, early repolarization pattern, and metabolic disturbances) [32] should particularly be taken into account when evaluating asthma patients suggestive of having ACS. However, these advanced ECG interpretations are beyond the scope of this review, and may be found elsewhere [32]. As in the general population, STEMI in the setting of an asthma exacerbation is an emergency that mandates a variety of coronary reperfusion strategies including primary PCI or thrombolytic therapy [31•].

Similarly, TTC has been regarded as a catecholamine-mediated reversible myocardial disease (possibly triggered by a variety of emotional and physical stressors) that strongly mimics STEMI, and is primarily characterized by the absence of significant coronary artery disease (CAD) on coronary imaging [33]. Within this context, cases of TTC in patients with an asthma exacerbation were previously reported, and have been mostly attributed to the severe stress and β agonist therapy used in this setting [34••, 35]. However, invasive CAG with left ventriculography is mostly indicated in patients suggestive of having TTC to fully establish the final diagnosis [33]. In an analogous manner to the setting of ACSs, acute medication mostly comprises anticoagulation, blockade of β receptors, and renin-angiotensin-system (RAS) along with management of specific complications (arrhythmias, outflow gradient, etc.) [33]. Interestingly, STEMI and TTC might occasionally co-exist in certain patients with specific risk factors including frailty, very old age, and severe systemic inflammation on admission [36–38]. However, since these specific risk factors are rarely encountered in the setting of asthma (particularly in comparison to COPD) [12], co-existence of these two phenomena might be quite unlikely in this setting.

More specifically, viral pathogens that might have the potential to induce an asthma exacerbation [12] have also been

regarded as substantial triggers of acute myocarditis, a clinical phenomenon generally presenting with elevation of myocardial enzymes along with non-specific ECG changes as well as regional or global contractile dysfunction and wall thickening on imaging modalities [39, 40]. In other terms, it seems likely that asthma exacerbation and myocarditis might possibly co-exist in a portion of cases. On the other hand, more sophisticated tools including cardiac magnetic resonance imaging (MRI) (with late gadolinium enhancement (LGE)) might be necessary in ambiguous cases of overt myocardial dysfunction (TTC, myocarditis, etc.) where a definitive diagnosis cannot be fully established [38, 39]. Of note, in rare instances, acute myocarditis might possibly arise as a subclinical phenomenon characterized by apparently normal myocardial functions on conventional imaging modalities (echocardiogram, etc.) potentially mandating the use of MRI for a definitive diagnosis in this setting.

Of note, in a recent meta-analysis comprising fifty-one studies, elevation of natriuretic peptides in the setting of COPD has been ascribed to concomitant cardiac conditions including cor pulmonale and LV systolic dysfunction generally in strong correlation with pulmonary artery pressure (PAP) and left ventricular ejection fraction (LVEF) values, but not pulmonary function [14]. Moreover, these peptides also had a significant association with early adverse outcomes along with high negative, yet with relatively lower predictive values in the prediction of LV systolic function in this setting [14]. This might denote that elevation of natriuretic peptides might also suggest pre-existing cardiac comorbidities potentially associated with adverse outcomes in a portion of cases with COPD [14]. However, these findings still need to be established in patients with asthma.

In rare instances, a specific form of overt myocardial dysfunction, namely reversible myocardial dysfunction in the critically ill patient (RMDCIP), might arise as part of a variety of clinical complications including sepsis [41, 42] in the course of an asthma exacerbation. Mechanistically, certain factors including substantial levels of cytokines and NO (nitric oxide) appear to play a pivotal role in the evolution of this phenomenon that usually has a worse prognosis (despite its potentially reversible nature) largely due to the serious nature of the underlying trigger [41, 42].

Since the abovementioned clinical syndromes (mostly with overt myocardial dysfunction) in patients with an asthma exacerbation are significantly associated with a much worse prognosis in both the short- and long-term [31•, 32, 39–42], they should also come to the attention of the treating physician potentially suggesting further diagnostic and therapeutic modalities to improve overall prognosis in these patients. On the other hand, these syndromes might be potentially masked by the rampant clinical manifestations of the asthma exacerbation, and might go unnoticed in certain settings. Therefore, we strongly suggest routine assessment of cardiac biomarkers

and ECG on admission and during follow-up (at least daily and during specific cardiac symptoms) in patients with an asthma exacerbation. Timely use of these basic tools along with further cardiac and coronary imaging modalities, where necessary, might significantly aid in the diagnosis of these syndromes, and hence improve overall prognosis of asthma patients with the initiation of disease-specific management strategies. Table 1 demonstrates a general comparison between subclinical and overt myocardial dysfunction/injury in patients with an asthma exacerbation.

Cardiovascular Evaluation and Triage of Patients with an Asthma Exacerbation: Guidance of Cardiac Biomarkers on top of Basic Tools for Risk Stratification and Management

In clinical practice, asthma exacerbation is well-known to have a fully reversible nature in a large portion of cases [12]. Interestingly, in-hospital mortality in these patients generally appears to be due to superimposed complications including infections, cardiovascular syndromes, etc. rather than the severity of the asthma exacerbation. Accordingly, a variety of cardiovascular conditions [5•, 21•, 25, 26, 34•, 35] that might potentially go undetected in the acute setting, might account for a significant portion of adverse clinical outcomes in the short- and long-term in asthma patients.

Within this context, cardiovascular evaluation of patients with an asthma exacerbation based on cardiac biomarkers and certain basic modalities including ECG and echocardiogram might help establish subsequent management strategies, and

might significantly diminish adverse events in these patients. Accordingly, asthma patients with life-threatening ischemic ECG changes particularly with specific ischemic symptoms on admission or during hospital stay (including ST elevation or severe depression, etc.), irrespective of cardiac biomarker levels, should undergo invasive CAG for a potential diagnosis of ACS, and be treated according to recent guidelines [15, 31•]. Invasive CAG may be deferred in certain ACS patients with intermediate or low-risk features [15]. This also holds true for asthma patients who may undergo invasive or non-invasive coronary imaging after stabilization of their pulmonary status.

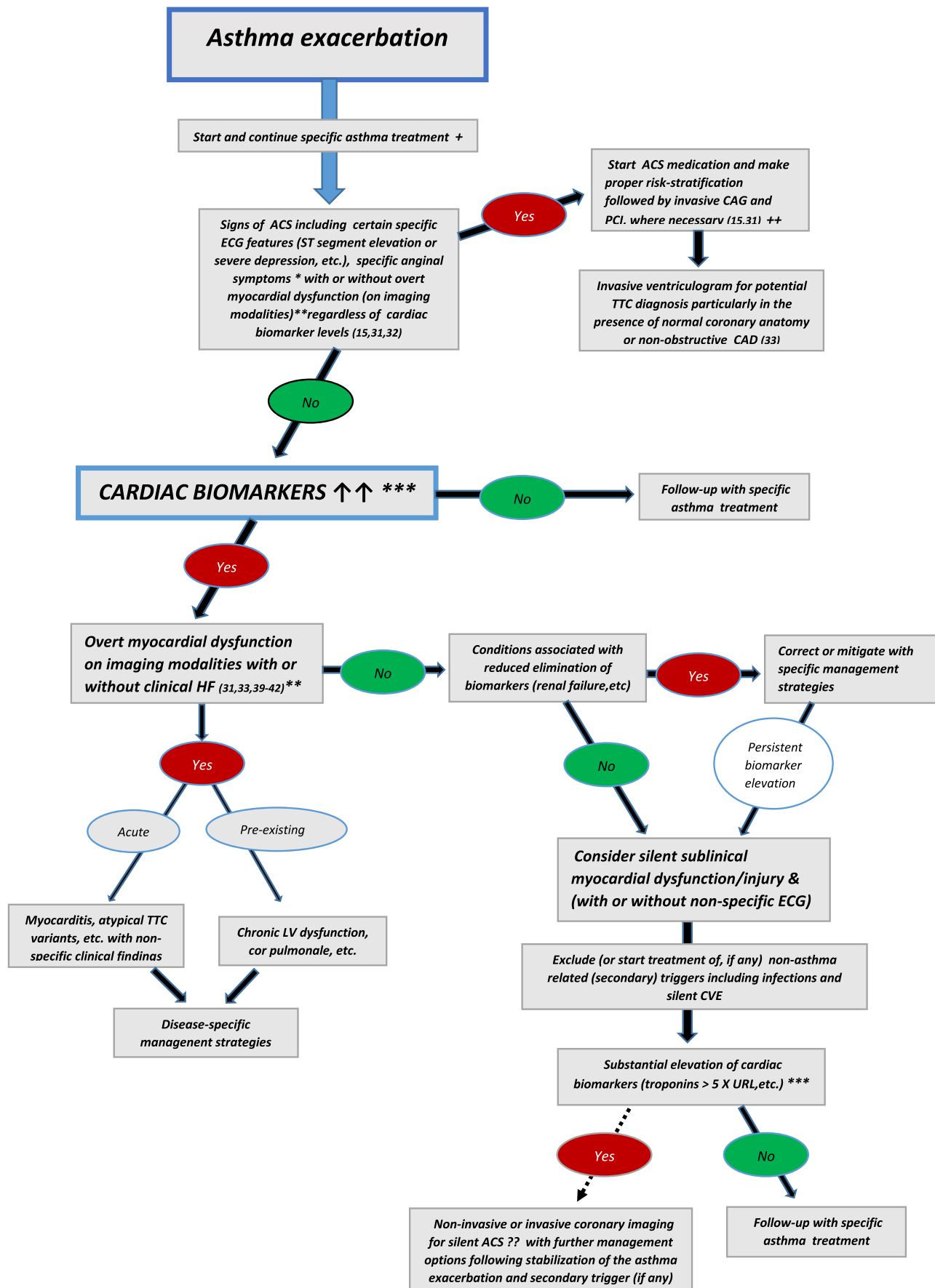
In the absence of an overt ACS presentation, the sole elevation of cardiac biomarkers (natriuretic peptides, troponins) should mandate a variety of imaging modalities including echocardiogram and magnetic resonance imaging (MRI). In an effort to timely detect and manage acute or pre-existing conditions, if any, with overt myocardial dysfunction including TTC, myocarditis, or chronic HF [31•, 33, 39, 40]. After safe exclusion of potential causes of overt myocardial dysfunction (as well as certain conditions associated with reduced elimination of biomarkers including renal failure), it seems reasonable to consider subclinical myocardial dysfunction/injury as the most likely cause of biomarker elevation in patients with an asthma exacerbation.

Among patients suggestive of having subclinical myocardial dysfunction, certain non-asthma-related (secondary) triggers including infections and silent cerebrovascular events (CVEs) [16, 17, 41, 42] should also be carefully sought and safely excluded beforehand. Specific management strategies

Table 1 A general comparison between subclinical and overt myocardial dysfunction/injury in patients with an asthma exacerbation

	Myocardial dysfunction in asthma exacerbations [3•, 4•, 5•, 6•, 14, 15, 21•, 22, 23, 31•, 32, 33, 34•, 35–42]	
	Subclinical	Overt
Cardiac biomarkers	Constantly high with non-specific variation in serum levels (unless associated with ACSs)	Substantially high and with a specific “rise and fall” pattern of troponins particularly in ACSs
Etiology	Mostly due to common asthma-related factors (hypoxemia, bronchodilator therapy, tachycardia, etc.) and occasionally new-onset ACSs	Acute cardiac (ACSs, TTC, myocarditis) or non-cardiac (sepsis, etc.) complications as well as pre-existing chronic conditions (cor pulmonale, chronic LV dysfunction)
Specific cardiac symptoms (angina, etc.)	None (unless associated with ACSs)	Generally present
Myocardial functions on conventional cardiac imaging (echocardiogram, etc.)	Normal (possibly with subtle abnormalities on specific modalities including strain, strain rate, and dobutamine stress echocardiogram)	Overt systolic and/or diastolic dysfunction, segmentary or global wall motion abnormalities
ECG	Mostly non-specific or normal	Specific in the setting of ACSs and TTC
Reversibility	Generally reversible	Reversible, partly reversible, or irreversible
Prognostic impact	Mostly none or limited	Significant
Need for further diagnostic and therapeutic strategies	None unless associated with ACSs	Mostly warrants further cardiac and/or coronary imaging modalities followed by disease-specific management strategies

ACS acute coronary syndrome, TTC Takotsubo cardiomyopathy, ECG electrocardiogram, LV left ventricle



◀ **Fig. 2** A proposed algorithm for cardiovascular evaluation, triage, and management of patients with an asthma exacerbation based on cardiac biomarkers, basic diagnostic modalities, and specific symptomatology. ACS, acute coronary syndrome; CAD, coronary artery disease; ECG, electrocardiogram; CAG, coronary angiogram; PCI, percutaneous coronary intervention; TTC, Takotsubo cardiomyopathy; LV, left ventricle; CVE, cerebrovascular events; URL, Upper reference limit; +, including oxygen therapy, bronchodilators (anticholinergics and/or β agonists), steroids, methylxanthines, non-invasive or invasive mechanical ventilation, and prophylactic antibiotics [12]. ++, indication and timing of invasive coronary angiogram (CAG) are largely determined by clinical risk factors in the setting of non-ST segment elevation acute coronary syndromes (NSTEMI). Accordingly, intractable angina, hemodynamic compromise, and malignant arrhythmias mandate an emergency, while factors including ECG changes and biomarker elevation and high-risk clinical scores (grace, etc.) signify an urgency (within 24 h) for CAG evaluation in NSTEMI. ST segment elevation acute myocardial infarction (STEMI) is an emergency, and mandates reperfusion of the culprit coronary artery via percutaneous coronary intervention (PCI) or thrombolytic agents (mostly as a bridge therapy to rescue or early PCI) [15, 31]. *, Symptoms including new-onset or worsening angina (tightness in chest, etc.) or angina equivalent (epigastric pain, etc.) as defined in guidelines [15, 31] on admission or during hospital stay. ACS on admission might possibly arise either as a coincidental phenomenon (preceding asthma exacerbation) or due to the detrimental impact of acute pulmonary condition (ACS following asthma exacerbation) with a wide range of symptoms (accelerated angina, bouts of angina at rest, or severe and prolonged angina at rest). ACS arising during hospital stay mostly presents with angina at rest and is largely an asthma-triggered phenomenon [21]. ECG might be completely normal in the setting of an ACS. However, ischemic ECG changes during symptoms might confirm an existing ACS. Therefore, ECG should be obtained within 10 min on admission, and during specific symptoms in the hospital setting [15, 31]. Daily ECG evaluation, in the absence of specific cardiac symptoms, may also be recommended to detect silent and persistent ischemic changes in patients hospitalized for an asthma exacerbation. **, Denotes segmentary myocardial wall motion abnormalities and diastolic or systolic dysfunction on modalities including echocardiogram, magnetic resonance imaging (MRI), and computed tomography (CT). ***, Denotes natriuretic peptides and troponins, and signify a value above 99 percentile of the upper reference limit (URL) for troponins ($> 5 \times$ URL) particularly with a rise and fall pattern strongly suggests cardiac etiology including acute coronary syndromes (ACSs) [15]. Natriuretic peptides work better as rule-out markers with high sensitivity in the setting of heart failure (HF). However, very high levels also denote an existing chronic or acute HF. Accordingly, cut-off values for N-terminal pro-B type natriuretic peptide (NT-proBNP) were previously reported as 450, 900, and 1800 pg/ml in patients of < 50 , $50-75$, and > 75 years of age, respectively for the diagnosis of acute HF with specificity and sensitivity values of 84% and 90%, respectively [17]. &, generally refers to silent elevation of cardiac biomarkers in the absence of overt ventricular dysfunction on various imaging modalities, and might be attributable to asthma-related factors (hypoxemia, tachycardia, and bronchodilator therapy), or, occasionally, to certain complications including ACSs, infections, and cerebrovascular events [2, 16]

(antibiotics, anticoagulation, etc.) targeting these secondary triggers, if any, should be immediately initiated along with asthma treatment. Quantitatively, those with substantial elevation of cardiac biomarkers (including troponins $> 5 \times$ URL) might undergo non-invasive or invasive coronary imaging modalities regardless of ECG changes or symptomatology

following stabilization of the asthma exacerbation and secondary trigger (if any). On the other hand, substantial elevation of these biomarkers might also be attributable to the severity of asthma-related primary factors including profound and/or persistent hypoxia and substantial doses of bronchodilator therapy (or due to a severe secondary trigger including sepsis), and hence might not necessarily signify a silent ACS in these patients. Therefore, indication for coronary imaging in this setting might be left to the discretion of the treating physician who might possibly determine the next step (follow-up or coronary imaging) according to the existing atherosclerosis risk factors of the patient (diabetes mellitus, family history, etc.).

Lastly, mild elevation of biomarkers (troponins $< 5 \times$ URL, supranormal levels of natriuretic peptides) as part of subclinical myocardial injury appears to be a quite common finding in patients with an asthma exacerbation (regardless of secondary triggers of biomarker elevation) [3•, 4•, 5•, 6•], and does not necessitate further cardiovascular diagnostic modalities and therapeutic strategies. Figure 2 demonstrates a proposed algorithm for cardiovascular evaluation, triage, and management of patients with an asthma exacerbation primarily based on cardiac biomarkers, specific symptoms, and certain diagnostic modalities.

Conclusion

In patients with an asthma exacerbation, elevation of cardiac biomarkers mostly signifies an existing silent subclinical myocardial dysfunction/injury possibly as a consequence of multifaceted pathophysiological triggers including hypoxemia, bronchodilator therapy, and hemodynamic alterations (that all appear to be associated with the severity of the acute pulmonary pathology), and, in general, has limited prognostic value as compared with their value in other acute pulmonary conditions including PE.

On the other hand, elevation of these biomarkers, in certain settings, might also denote a variety of more severe clinical scenarios including ACSs (manifesting as subclinical or overt myocardial dysfunction) and other cardiac conditions presenting with overt myocardial dysfunction (with or without HF) that might suggest important prognostic and therapeutic implications in patients with an asthma exacerbation. However, these life-threatening conditions might be potentially masked by the rampant nature of the asthma exacerbation itself, and hence might be easily overlooked in the hospital setting. Accordingly, thorough cardiovascular evaluation and triage of patients with an asthma exacerbation mostly based on cardiac biomarkers along with other adjunctive tools including ECG (evaluated at regular intervals and during specific symptoms) and certain imaging modalities, where necessary, might be regarded as of utmost importance for proper management

and hence improvement of cardiovascular and overall prognosis in the setting of an asthma exacerbation. However, further studies are still warranted to fully establish cardiovascular strategies and practical considerations along with clinical implications of cardiac biomarkers in patients with an asthma exacerbation.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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