

Cardiac Asthma: An Old Term That May Have New Meaning?



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Should asthma join the ranks of smoking, obesity, hypertension, and diabetes as a major risk factor for cardiovascular disease?

Several recent studies suggest that it should, including a report in this issue of *The Journal of Allergy and Clinical Immunology: In Practice* by Bang et al.¹ In a case-control study of myocardial infarction among mostly older adults in Olmstead, Minn, they found that active asthma was associated with a more than 2-fold higher risk of myocardial infarction; 8% of the 543 myocardial infarction cases had a history of active asthma, compared with 3% of age-matched controls. This relationship persisted after controlling for traditional cardiovascular risk factors, including body mass index, hypertension, diabetes, and smoking history, as well as other comorbid conditions, and remained significant when adjusting for diagnosed chronic obstructive pulmonary disease (COPD), although the magnitude of the association decreased. This work joins several other studies in a variety of cohorts that have also found a significant association between asthma and cardiovascular disease.²⁻⁶

It is biologically plausible that asthma could be a risk factor for myocardial infarction. Although the respiratory and cardiovascular systems are distinct, common biological pathways including inflammation and endothelial dysfunction lead to deterioration in each of these systems.^{7,8} It has been previously established that lung function decline is a predictor of cardiovascular disease and mortality in the general population and among those with COPD.^{8,9} COPD itself is an important risk factor for cardiovascular disease, even independent of smoking history.¹⁰ It is believed that systemic inflammation underlies the excess risk of cardiovascular disease that COPD confers on top of shared environmental risk factors. Chronic pulmonary inflammation leads to production of inflammatory mediators in the lung, and these mediators may have direct effects on vascular endothelium, as well as indirectly cause systemic inflammation through effects on the liver. This inflammation leads to a procoagulant state,

setting the stage for cardiovascular events.¹⁰ Inflammation associated with asthma may similarly contribute to cardiovascular disease, as individuals with severe asthma tend to have higher levels of markers of systemic inflammation, such as c-reactive protein and fibrinogen, than those with less severe or no asthma.¹¹ In addition, the 5-lipoxygenase pathway, a source of key proinflammatory mediators in asthma, also plays a role in atherosclerotic plaque stability.² Thus, it may not be surprising that among older adults, persistent asthma is associated with more cardiovascular events.

However, as acknowledged by the authors, it is also possible that misclassification of COPD as asthma led to a biased estimate of the relationship between active asthma and myocardial infarction. COPD is often underdiagnosed, and distinguishing asthma and COPD can be difficult, especially in older adults. Approximately 20% of COPD in the United States occurs in never smokers and smoking is more prevalent among those with asthma than the general population, so history of smoking cannot distinguish between the 2 diseases.¹² Because COPD is associated with cardiac disease, such misclassification would tend to be differential and inflate the relationship between asthma and myocardial infarction. Although asthma was still significantly associated with myocardial infarction even when adjusting for diagnosed COPD in Bang et al's study, the attenuation of the relationship when COPD was included suggests that with more precise phenotyping the relationship may have diminished further.

On the other hand, there is increasing recognition that confusion between asthma and COPD may not be entirely due to misclassification but may reflect the need to refine our understanding of the overlap between these diseases. The asthma COPD overlap syndrome (ACOS) is a clinical entity that captures the intersection between these 2 diseases. As with both asthma and COPD in general, it is believed that there are several pathways that lead to this overlap condition, with identifiable subphenotypes such as eosinophilic predominant, neutrophilic predominant, asthma in smokers, and nonsmokers exposed to biomass.¹³ Perhaps because of this heterogeneity, there is no generally agreed upon definition for this syndrome, and estimates of the prevalence of this overlap among those with asthma or COPD range from 15% to more than 50% in select populations.¹³ Those with ACOS have been reported to suffer greater respiratory morbidity than those with COPD or asthma alone and ACOS may underlie some of the increased risk of cardiovascular disease among those with asthma seen in this and other studies. Both the ACOS and obese-comorbid phenotypes of asthma, the other adult-onset persistent asthma phenotype identified by latent class or clustering analyses of asthmatics, are associated with a generalized inflammatory state, multiple comorbidities, and shared risk factors with cardiovascular disease,

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such as smoking.^{14,15} In the study by Bang et al, only adult-onset but not childhood-onset asthma was associated with myocardial infarction, supporting the idea that these but not other phenotypes of asthma may confer greater risk of cardiovascular disease. Compared with the more classic childhood onset allergic asthma, these phenotypes of asthma have received relatively less attention and the treatment options are less clear.^{13,14}

It is not only COPD that can be confused with asthma. Misclassification of cardiovascular disease symptoms as asthma may have even greater epidemiologic and clinical consequences. So-called “cardiac asthma” describes the common presentation of heart failure with wheeze, cough, and dyspnea.¹⁶ Coronary artery disease is the most common cause of heart failure in adults, and both coronary artery disease and heart failure are frequently underdiagnosed. In historical studies, it has been estimated that approximately 10% of cases of dyspnea referred to a pulmonary specialist may have a cardiac cause for their symptoms.¹⁷ In the study by Bang et al, active asthma was defined as a combination of cough, wheeze, and dyspnea occurring in an intermittent recurrent pattern. Although this definition may have high sensitivity and specificity for asthma in younger individuals, in older subjects there is a substantial risk for misclassification of the symptoms of cardiovascular disease. Even a small rate of misclassification of cardiovascular symptoms as asthma could lead to a false epidemiologic association between asthma and cardiovascular disease given the strength of the relationship between cardiovascular disease and myocardial infarction. Although such misattribution has important research implications, the clinical effects are even more pernicious. Not only may such patients miss important opportunities for treatment of their cardiovascular disease, but they may also receive asthma treatments that are not indicated and have been linked to potentially harmful cardiac effects.¹⁸ Although the exploration of the relationship between asthma medication use and myocardial infarction in this study did not suggest an effect of inhaler medication, this warrants further study.

Prospective studies with rigorous pulmonary and cardiac phenotyping will be needed to understand the true relationship between asthma and cardiovascular disease and whether asthma should be considered a cardiovascular risk factor. To substantially improve clinical care of patients with significant pulmonary morbidity at risk for cardiovascular disease, interventional studies are needed. Although two-thirds of those older than 65 have multiple medical comorbidities, too often clinical trials for both asthma and cardiovascular disease exclude those with significant comorbidity.^{19,20} The findings of Bang et al highlight the importance of including those with significant pulmonary disease in cardiovascular studies, and also including those with risk factors for or existing cardiac disease in asthma studies.

For health care providers, these findings emphasize the need for a high index of suspicion for cardiovascular disease among older adults with persistent asthma or asthma-like symptoms, especially when such symptoms are of recent onset. Whether

patients with true persistent asthma without cardiac disease should be treated differently with respect to cardiovascular disease prevention remains an open question.

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