

Asthma Attacks and Cardiovascular Events: Earthquakes and Tsunamis



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Tsunamis are giant sea waves produced by a large earthquake beneath the ocean floor, underwater landslides, or undersea volcanic eruption. The shaking motion of an earthquake is due to a sudden release of energy, and the first sign may be a loud bang or a roar. The ground may start to pitch and roll like the deck of a ship during a squall for several seconds to several minutes. But it is important to remark that tsunamis are rare events and not all earthquakes will generate a tsunami, so the first step to safety is identifying existing hazards.

In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, Raita et al¹ investigates the association between asthma exacerbations (earthquakes) and cardiovascular events (tsunamis) by applying a self-controlled case-series design to population-based data. This is an epidemiological model in which individuals act as their own control and, because only cases are included (controls are not required), it is economically efficient compared with a cohort design, especially when the outcome of interest is a rare event. Data were obtained from the Healthcare Cost and Utilization Project State Inpatient Database. The Healthcare Cost and Utilization Project represents the largest collection of all-payer hospital data in the United States. The State Inpatient Database includes all hospital discharges during the calendar year within the study states (Florida, Nebraska, New York, and Washington). The authors first selected all adults 40 years or older with at least 1 hospitalization for asthma exacerbation and then, among these patients, they further identified patients with a first event of acute myocardial infarction or ischemic stroke. The aim was to compare each patient's incidence rate of the outcome (a composite of these 2 cardiovascular events) during 3 sequential risk periods (1-7, 8-14, and 15-28 days after asthma exacerbation) with that of the reference period (ie, the nonexposure period, before and after the

3 risk periods). Among 4851 adults hospitalized for an asthma attack who had a first episode of acute myocardial infarction or ischemic stroke, the incidence rate of outcome significantly increased during the first risk period (133.2/100 person-years) compared with the reference period (25.0/100 person-years), with a corresponding adjusted incidence rate ratio of 5.21 (95% CI, 4.46-6.05; $P < .001$). The incidence rate declined but remained high in the 2 subsequent risk periods.

These results are in accordance with previous findings showing a higher incidence of cardiovascular events in patients with asthma.²⁻⁶ This association was evident only among patients with late-onset (but not with early-onset) asthma in several previous reports, with^{3,5} or without⁶ effect modification by sex. However, it should be pointed out that previous investigations focused on patients with chronic asthma and the present study is the only one to examine the relationship between asthma exacerbations and cardiovascular events.

Several plausible mechanisms (which could be considered jointly or separately) may explain the association between asthma attacks and cardiovascular events. First, on the one hand, it has been reported that blood eosinophil count correlates with the severity of respiratory failure in asthma attacks.⁷ On the other hand, eosinophils have been histologically identified in intracoronary thrombi,⁸ and preliminary studies have shown an association between this cell count and a worse prognosis after myocardial infarction.⁹ Moreover, Rios-Navarro et al¹⁰ found that in a large series of patients with ST-segment elevation myocardial infarctions and in a swine model, eosinophils exhibited important dynamic changes, both in peripheral blood and in the infarcted area. Taken together, these findings suggest a role for this cell in ischemic heart disease. Second, although the evidence for systemic inflammation is scarcer in asthma than in chronic obstructive pulmonary disease, cross-communication between the airways and bone marrow through inflammatory mediators can lead to systemic propagation of local inflammation, and several proinflammatory cytokines such as IL-6, TNF- α , and C-reactive protein were found to be elevated in the blood of a person with asthma in comparison to healthy controls.¹¹ Complex interactions between platelets, endothelial cells, and blood granulocytes can further stimulate the production of proinflammatory cytokines, resulting in the development and progression of atherosclerosis. In fact, it has been reported that increased arterial stiffness (a strong predictor of future cardiovascular events) is positively related to C-reactive protein levels in severe asthma.¹² It remains to be elucidated whether systemic inflammation is increased in asthma exacerbations compared with a stable condition. Third, asthma is in part a spastic condition of the airways, and it is well known that vasospastic myocardial infarction can occur in angiographically normal coronary arteries. Although there is a clear analogy between the pathophysiology of bronchospasm and vasospasm, the

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mechanisms that link both processes are still unknown. Coronary artery spasm is predominantly caused by hyperreactivity of vascular smooth muscle cells and, probably, by endothelial dysfunction. In addition, the presence of mast cell infiltration at the site of angiographic documentation of coronary spasm and focal infiltration of inflammatory cells in the adventitia of the coronary arteries in patients with vasospastic myocardial infarction have been described.¹³ Thus, local inflammation of the artery wall is likely to play a role in the pathogenesis of coronary spasm, and this hypothesis is supported by the fact that patients with vasospastic angina, refractory to the usual treatment (calcium antagonists, nitrates, and nicorandil), can be successfully treated with corticosteroids.¹⁴ Fourth, patients with a severe asthma exacerbation (in the present study, all the asthma attacks resulted in hospitalization) can experience hypoxemia to a greater or lesser extent; the myocardial oxygen supply can thus be compromised and an imbalance between supply and demand may occur, leading to ischemia. Fifth, the therapeutic approach to asthma exacerbation (excessive use of β_2 -agonists and theophylline and discontinuation of β -blockers, antiaggregant drugs, and statins) may contribute to an increased risk of subsequent cardiovascular events. And finally, sixth, viral respiratory infections (the most frequent cause of asthma exacerbations) can induce the release of many proinflammatory cytokines (TNF- α , IL-1, IL-6, IL-8, etc).¹⁵

The tsunami arrival time in some risk areas may vary between 5 and 30 minutes after the earthquake. The best warning is the earthquake itself and residents in risk areas should be prepared to seek higher ground or go inland immediately. Besides, tsunamis are instrumentally recorded by sea-level recorders, which can detect them before they arrive at a coast, giving some lead time for issuing tsunami warnings. Raita et al provide convincing data on the association between asthma attacks and cardiovascular events, and clinicians should draw some lessons from them: it is important to keep in mind that cardiovascular risk factors have to be assessed in detail and optimally addressed and cardiovascular agents must be maintained throughout hospital admissions for asthma exacerbations to minimize the risks of a cardiovascular tsunami.

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