Invited Commentary

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Thoracic fluid accumulation and asthma symptoms: A new contributor mechanism

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Asthma is a chronic disease that affects about 300 million people worldwide.[1] Asthma is a heterogeneous disease, defined by variable expiratory airflow limitation and history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough.[2] The cardinal feature of asthma is excessive narrowing of the lower airways. Excessive airway narrowing accounts for the morbidity and mortality of asthma and it makes breathing difficult or, in the extreme, impossible.[3–5] Despite the advances in pharmacological treatment options, a large fraction of asthma sufferers has poor asthma control.[6] For example, in Canada, it is estimated that asthma is not well-controlled in 90% of asthmatics.[7] The presence of nocturnal symptoms is an important marker of poor asthma control.[8] Indeed, 50% to 68% of asthma attacks that led to death occur during night.[9–12] However, the mechanisms accounting for nocturnal worsening of asthma remain unclear.[3]

It is well known that sleep changes respiratory mechanics, including reductions in respiratory drive, pharyngeal dilator muscle tone, and lung volume.[13–15] However, the changes in respiratory mechanics during sleep do not account for all the nocturnal increases in airflow resistance in asthma. For example, maintaining lung volumes similar to the wakefulness values by continuous negative pressure applied to the chest during sleep does not prevent the overnight increase in airway resistance.[16,17] Moreover, whether awake or asleep, airway resistance increases overnight and doubles with sleep.[18] This shows independent contribution of sleep over circadian effects.

Recent evidences show that rostral fluid shift from the legs to the thorax during supine posture[19,20] and fluid overloading[21] are potential contributors to poor asthma control and nocturnal worsening of asthma symptoms. Fluid accumulation in the thorax may cause a cascade of events that exacerbate airway narrowing.[19] These events include increased blood volume and blood pressure in the bronchial circulation.[22,23] As a result, the pressure gradient from blood to interstitium increases, drives more fluid leak, and causes increased airway wall edema,[24–26] and peribronchial fluid cuffing.[24,25,27] These events can lead to the excessive airway narrowing[25–27] and airway hyper-responsiveness[26] that contribute to asthma severity and fatality.[28–31]

Our group has been investigating the effects of rostral fluid shift on lower airway narrowing in asthma.[19,20] In order to control for the confounding effects of sleep on airway resistance, we performed a daytime study in healthy controls and patients with asthma.[19,20] We simulated nocturnal rostral fluid shift by applying lower body positive pressure with inflatable trousers. After 30 minutes, lower body positive pressure moved similar amount of fluid out of the legs to that which happens overnight. We found that despite similar amount of fluid moving to the thorax in healthy controls and asthmatics with lower body positive pressure: (1) only in asthmatics, fluid accumulation in the thorax increased lower airway narrowing[19]; (2) changes in lower airway resistance were directly related to the amount of fluid moving to the thorax[19]; and (3) the effects of fluid shift were larger in women than in men.[20]

Airway resistance is inversely related to the forth power of airway diameter. For similar amount of fluid accumulating in the airway wall, airway wall becomes thicker in smaller airways than larger airways. Thus, airway lumen narrows more and its resistance increases more in patients with narrower airways at baseline. Women have narrower airways than men even at similar lung volumes[32] and women are at higher risk of nocturnal asthma than men.[33,34] Thus, rostral fluid shift may have larger effects in airway narrowing in asthmatics with smaller airways, such as women, obese patients, and those with more severe asthma.

Kantor et al[21] investigated the relationship between fluid overload and asthma exacerbation. In children admitted for asthma exacerbation, they performed a large retrospective cohort study over 7 years to evaluate fluid balance and clinical outcomes. In particular, they investigated length of in-hospital stay and duration of administration of beta agonist and supplemental oxygen.[21] They calculated the percentage of fluid overload as the difference between fluid intake and fluid output normalized by the admission weight in the first 72 hours of hospitalization. They found that peak fluid overload ≥7% was associated with worse clinical outcomes, such as longer length of hospital stay, longer treatment duration, and increased risk of supplemental oxygen use.[21] Kantor et al validated their results in a sample of subjects with multiple hospitalizations, finding similar results in matched sample.[21]

The same study[21] investigated the physiological mechanisms that may contribute to worse clinical outcomes in patients with asthma and fluid overload. In a prospective observational cohort, they showed that patients with peak fluid overload ≥7% had more negative swings in inspiratory intrapleural pressure and evidence of extravascular lung water, as assessed, respectively, by the variation in peak aortic velocity and the cumulative number

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of B-lines in ultrasound images of lung.[21] Their findings were in agreement with their hypothesis that during asthma exacerbation, the excessive airway narrowing increases the negative pleural pressure which pulls part of the extra fluid to the lungs and increases extravascular lung water.

The findings from Bhatawadekar et al[19,20] and Kantor et al[21] have important clinical implications, especially for the patients with difficult-to-treat asthma. So far, the recognized risk factors for asthma exacerbation include severe nasal sinus disease, gastroesophageal reflux, recurrent respiratory infection control, physiological dysfunctioning (such as depression and anxiety), and obstructive sleep apnea (OSA).[35] Among the recognized risk factors for asthma exacerbation, OSA is one with unclear pathophysiological mechanism. Asthma and OSA coexist in up to 30% of patients with either disorder.[9,36–38] Moreover, in patients with difficult-to-control asthma, prevalence of OSA is about 90%.[39] Interestingly, previous studies have shown that overnight rostral fluid shift is associated with worsening of OSA by increasing fluid accumulation in the neck that narrows the pharynx, increasing its resistance and collapsibility.[40–57]

During OSA, the pharynx collapses; causing strong inspiratory efforts against the occluded pharynx to resume inspiration. The result is large negative (subatmospheric) intrapleural pressures that increase venous return. The OSA events associated with the overnight rostral fluid shift may increase even more the accumulation of fluid in the chest, aggravating the airway narrowing and hyper-responsiveness. Indeed, OSA is associated with up to 7 times greater risk of having severe asthma[38,58] and 3.4 times increased risk of asthma exacerbations.[35] However, the overlap between asthma and OSA is poorly recognized. Thus, both patients and physicians may not attribute sleep problems and poor asthma control to the OSA.

Recognizing fluid accumulation in the thorax as a risk factor for poor asthma control, difficult-to-treat asthma, and worse clinical outcomes in asthma has the potential to reveal new treatments to improve asthma control and change the clinical management of asthma. Asthma patients may benefit from simple treatments to reduce fluid retention in the legs such as wearing compression stockings or physical exercise. In fact a recent systematic review from our group showed that physical exercise improves nocturnal asthma in children and adults by reducing the prevalence and frequency of nocturnal symptoms.[59] In our review, we could not determine the mechanisms by which physical exercise could improve nocturnal asthma. However, the reduction of rostral fluid shift by reducing fluid retention in the legs may be one of the mechanisms related with the improvements in nocturnal asthma.

While rostral fluid shift occurs in everyone during sleep, it is likely to exert detrimental effects on airway narrowing in other high-risk populations including: (i) pregnant women, postoperative patients, and patients with heart or renal failure; (ii) individuals with limited mobility or sedentary lifestyle; and (iii) the elderly who have stiffer arteries and/or compromised cardiac function. Finally and importantly, in patients with asthma exacerbation, controlling the fluid balance to avoid fluid overload can potentially improve the clinical outcomes, reducing the risks and costs associated with long-term hospitalization.

In conclusion, in asthma, fluid overload and fluid accumulation in the thorax can be potential contributing factors for worsening of asthma symptoms and poor clinical outcomes. More studies are needed to understand the mechanism of asthma worsening due to fluid accumulation in the thorax and to identify the specific asthma phenotypes in adults and children who are at higher risk of asthma worsening due to the fluid accumulation in the thorax. A better understanding of these mechanisms has the potential to facilitate development of new treatments and prevent the pernicious effects of asthma exacerbations.

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Conflicts of interest

The authors declare no conflicts of interest.

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