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Epithelial Damage in Children with Sleep-disordered Breathing

Sleep-disordered breathing (SDB) in children is very common. The hallmark symptom of SDB is snoring, and studies using parental questionnaires have reported that over a third of preschool children snore often or always (1). Snoring is also very common in older children, affecting more than 15% (2). SDB forms a spectrum of severity of disease from simple or primary snoring at the mild end to obstructive sleep apnea (OSA) at the severe end. Sleep disruption, hypoxia/hypercapnea, and/or swings in intrathoracic pressure are the features of SDB believed to underpin the adverse cardiovascular effects associated with this condition. All of these alterations lead to disturbances in autonomic nervous system function and manifest as increased sympathetic nervous system tone, increased sympathetic responsiveness, and the presence of sympathetic–parasympathetic imbalance. In adult patients with OSA, the causal association between intermittent hypoxemia and elevated sympathetic nervous

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tone has now been conclusively and repeatedly demonstrated (3). In addition to the autonomic nervous system changes, the systemic inflammatory pathways activated in the presence of OSA induce functional and structural disruption of the endothelium and lead to alterations in vasomotor tone and promote vascular remodeling, which is characterized by arterial stiffening and reduced vascular compliance (4). As a result of increased blood flow velocity, epithelial damage occurs. As a protective response, surface receptors and adhesion molecules are upregulated on the plasma membrane of platelets (5), which then adhere to the epithelial walls. In adults, OSA as an independent risk factor for hypertension and reduced nocturnal dipping of blood pressure, both of which are associated with cardiovascular and cerebrovascular disease (6, 7).

Although studies have reported that primary snoring in children is not associated with hypoxia, hypercapnia, or sleep disruption, there are now numerous reports of adverse cardiovascular effects, including elevated heart rate and blood pressure and impaired cardiovascular control (8).

In this issue of the *Journal*, Kontos and colleagues (pp. 1560–1566) provide new evidence that SDB in children leads to epithelial damage (9). The study was designed to reflect clinical practice and recruited 30 children who were assessed by experienced pediatric ear, nose, and throat clinicians as having SDB of a severity requiring treatment with adenotonsillectomy. Control children ($n = 20$) with no history of snoring were recruited from the community. All children (mean age, 10 yr) underwent overnight polysomnography to determine SDB severity as defined by the obstructive apnea–hypopnea index (OAHI), and parents completed a questionnaire about their child's snoring at home. In the morning, a fasting blood sample was taken, and whole blood platelet aggregation was measured using impedance aggregometry.

As expected, the children recruited from the ear, nose, and throat clinic had more severe SDB (7.9 ± 16.9 events/h [mean $\pm$ SD]) than the control group (0.6 ± 0.5 events/h). The children with SDB also had more frequent parental reports of snoring. The study found that children with SDB had increased platelet aggregation, and although OAHI was not correlated with platelet aggregation measures, parental report of snoring was. It must be noted that this relationship would not have reached statistical significance if the data had been adjusted for multiple testing, and further studies in a larger cohort are required to confirm these findings. In addition, the study found that body mass index (BMI) percentile was significantly correlated with parental report of snoring, however it was not correlated with any measure of platelet aggregation.

Under normal conditions, platelets do not adhere to epithelial cells; however, if the blood vessel epithelial cells are damaged because of increased blood flow velocity or reduced vascular compliance, both of which increase shear stress, then platelet plugs are formed at the site of epithelia damage. Thus, the findings of the study by Kontos and colleagues (9) suggest that SDB in these young children is associated with endothelial damage. The authors speculate that this epithelial damage may be a sign of early vascular aging, which may lead to cardiovascular and cerebrovascular disease in adulthood.

As highlighted by the authors, the findings are concerning. First, pediatric SDB is significantly underdiagnosed because many parents and clinicians consider snoring to be benign, and second, many of the children in the SDB group had only mild disease. Third, the conventional measure of SDB severity as assessed by polysomnography, the OAHI, was not correlated with platelet aggregation measures. Other studies have also shown that SDB of any severity, including primary snoring (OAHI of 1 event/h or less) is associated with adverse cardiovascular outcomes (8). Importantly, a recent study that followed-up children recruited from the community found that primary school–aged children with moderate to severe OSA at baseline had a 2.5-fold increased risk of hypertension and 1.3-fold risk of reduced nocturnal dipping 10 years later (10). A second paper from the same cohort of children reported that in 30% of children, OSA spontaneously resolved (OAHI of less than 1 event/h) (11). The 22% who continued to have OSA were predominantly male and had a higher BMI *z*-score at baseline. Furthermore, the study showed that more severe OSA in children older than 10 years of age tended to persist, whereas OSA diagnosed in younger children was less likely to correlate with the persistence of OSA. There is now evidence that any improvement in SDB severity lowers blood pressure (12) and improves autonomic control (13), and the reduction in blood pressure is more marked in children with a higher BMI (14). Further studies are required to ascertain whether platelet aggregation measures are also normalized after the resolution of SDB.

The study by Kontos and colleagues (9) adds weight to the growing body of evidence that supports the urgent need to screen and treat all children for SDB as young as possible. Importantly, those children who are overweight or obese require particular attention and follow-up to reduce the chances of OSA persisting into adulthood and increasing the risk of hypertension, cardiovascular and cerebrovascular disease, and end-stage renal disease. ■

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Rosemary S. C. Horne, Ph.D., D.Sc.
Department of Paediatrics
Monash University
Melbourne, Australia

ORCID ID: 0000-0003-3575-0461 (R.S.C.H.).

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Supporting a Comprehensive International Approach to Global Tuberculosis Eradication Is the Right Thing to Do

In recent years, we have seen several dramatic examples of localized infectious disease outbreaks spreading regionally or globally and requiring concerted international public health containment responses.

The 2014–2016 Ebola outbreak led to immense suffering and more than 11,000 deaths in West Africa and created widespread concern about the potential of spread to other regions, including the United States. Coordination and financial support from international partners, including the United States CDC, enabled West African governments and health officials to use sound public health practices to stem the epidemic and prevent widespread transmission in the United States and a number of other countries (1). Earlier, the world came together to fight polio, one of the most feared diseases of the 20th century. Jonas Salk, who created the first polio vaccine, did not patent it, asking, "Would you patent the sun?" (2). From the distribution of the polio vaccine to current efforts to eradicate the virus, the struggle against polio has become an example of how a collective global effort can save lives and reduce suffering. Now, the coronavirus disease (COVID-19) pandemic is causing enormous disruption of health systems and the global economy, highlighting again the importance of infectious disease surveillance and the ability to respond collectively and effectively. The message from these examples—and many others—is clear: effective control of many public health threats requires local, national, and international cooperation and investment.

One challenge that has languished in the last half century is the eradication of tuberculosis (3, 4). Although there has been a reliable cure for the disease since the early 1950s and a robust epidemic control strategy since the late 1950s, tuberculosis has persisted globally and continues to kill more than 4,000 people every day. This is because until recently, low- and middle-income countries have not been supported to deploy the epidemic control strategies that have been so successful in high-income settings (5). The largest omissions have been in the areas of early identification of tuberculosis (active case finding using highly sensitive tests and contact investigation) (6, 7), treatment of active disease (prompt initiation of effective medical regimens), infection control, identification of exposed contacts, and treatment of tuberculosis infection (8, 9). These are not so much knowledge gaps as they are a lack of political will and funding (10).

In this issue of the *Journal*, Menzies and colleagues (pp. 1567–1575) use a modeling approach to estimate the benefit to the United States of a comprehensive global tuberculosis eradication strategy (11). Such an approach, which is reflected in the global End Tuberculosis Strategy—and was affirmed by the Secretary of Health and Human Resources at the United Nations High Level Meeting on Tuberculosis in 2018—is widely seen as the only way to reduce tuberculosis incidence globally by 90% by 2035 (1, 12). Menzies and colleagues show that if the United States directs funding toward an effective epidemic control strategy globally—or even simply focuses on the five countries from which the greatest number of non–U.S.-born tuberculosis cases arise in the United States—two significant positive outcomes would result. First, death and suffering would be reduced both in the United States and globally. Second, there would be direct health-system savings in the United States (between eight and 32 billion dollars between 2020 and 2035). Their argument is both morally and fiscally compelling (13).

The rationale for investing in local tuberculosis control by supporting public health systems outside the United States is straightforward (14). Because the majority of new tuberculosis cases and infections in the United States are detected in people born abroad (15), ensuring that other countries can build tuberculosis prevention and control programs based on sound medical science is of critical importance to tuberculosis eradication at home. Menzies and colleagues add to previous analyses by using global tuberculosis epidemiology and a sophisticated model to demonstrate the merits of a shared epidemic control strategy for stopping the epidemic. By highlighting dramatic differences

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