carefully designed prospective, propensity-matched study of PAP therapy in patients with COPD-OSA overlap. Justification for such studies comes from the inherent limitations and additional questions posed by previous studies, such as the Sleep Apnea cardiovascular Endpoints (SAVE) trial, which indicated limited benefit to cardiovascular outcomes from PAP therapy in patients with moderate/severe OSA, although this study was limited by the exclusion of sleepy patients and by the poor PAP adherence (10). A future trial in COPD-OSA overlap patients should ideally include patients reporting mild/moderate sleepiness, which is a factor associated with increased likelihood of comorbidity and which may impact PAP compliance. The report by Sterling and colleagues should help in the design of such a study, capable to more reliably assess the potential health benefits of PAP therapy in this important patient group. ■

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Coughing Is Not Required to Transmit *Mycobacterium tuberculosis*
Another Nail in the Coffin

For nearly a century, coughing has been deemed central to the transmission of *Mycobacterium tuberculosis* (1). Even as subclinical tuberculosis (TB) has more recently drawn attention as a potential source of transmission (2), it has been argued that the major driver of transmission might be unrelated or unrecognized coughing (3). But even though coughing is the cardinal symptom of TB, its importance in transmission has never been confirmed (4). In 1969, Loudon and Spohn found that nocturnal cough frequency among patients hospitalized with pulmonary TB was not strongly associated with tuberculin status among those patients' household contacts (5). This finding was not revisited until 2018, when Turner and colleagues again found that 24-hour cough frequency was only weakly associated with tuberculin positivity in contacts of individuals with smear-positive TB (6). High *M. tuberculosis* counts in cough aerosols do correlate with infection in contacts (7), but this finding does not

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demonstrate that coughing itself was the method of transmission. Thus, even though coughing is widely thought to likely be the primary mechanism by which *M. tuberculosis* is transmitted, data supporting this "commonsense" belief are remarkably scant.

An alternative hypothesis is that *M. tuberculosis* is commonly transmitted not only during coughing (or other maneuvers like singing [8]), but also during simple tidal breathing. In support of this hypothesis, patients with pulmonary TB were found to generate bioaerosols of the appropriate size for transmission (1–5 μm) during tidal breathing, and to do so at a higher rate than people without TB (9). However, until now, it has been uncertain whether those aerosols contain viable *M. tuberculosis*—and how those aerosols compare with those generated by coughing. In this issue of the *Journal*, Dinkele and colleagues (pp. 206–216) provide a compelling piece of evidence that tidal breathing may be an important, if not the major, mechanism of transmission for this airborne pathogen (10). Specifically, these authors performed comprehensive bioaerosol evaluation of 38 people with untreated, Xpert-positive pulmonary TB, including not only particle counts but also counts of viable *M. tuberculosis*. Their key finding was that the rate of *M. tuberculosis* production was similar during tidal breathing, cough, and FVC. Although cough and FVC both generated more particles than tidal breathing, the number of viable bacilli per particle was lower, such that 1 minute of tidal breathing generated more viable aerosolized bacilli than one cough or FVC maneuver. These findings are consistent with ongoing expulsion of viable bacilli from infectious patients, regardless of whether they are actively coughing or breathing regularly.

Although the sample size of this study was small, the results, if replicated in other patient populations, could have important implications for both TB diagnosis and our understanding of TB pathophysiology. From a diagnostic perspective, the presence of viable *M. tuberculosis* in exhaled tidal-breath air suggests that we need not limit TB testing to specimens (e.g., sputum) that require forced coughing. Further research into validating diagnostic modalities such as face-mask sampling (11) and other breath test modalities (12) is therefore warranted. Regarding pathophysiology, generation of presumably infectious aerosols in this study occurred without coughing, supporting the hypothesis that viable bacilli can be aerosolized without forceful maneuvers to expel them into the respiratory tract.

The authors estimated that, among these 38 individuals, more than 90% of the *M. tuberculosis* aerosolized in an average day could have been generated during tidal breathing. It is important, however, not to overinterpret this result as indicating that most transmission necessarily occurs from individuals with subclinical TB. All of the individuals in this study were Xpert positive and highly symptomatic. Indeed, the mean rate of spontaneous coughing during tidal breathing was about one cough every 3 minutes (though there was no correlation between these spontaneous coughs and detection of *M. tuberculosis*). Thus, it may still be true that symptomatic individuals generate the majority of transmission, even if those symptoms are not necessary for transmission itself. It is notable, however, that a sizeable proportion of people identified with subclinical TB in national prevalence surveys have smear-positive disease (13). Given this evidence that tidal breathing can generate presumably infectious aerosols, it seems likely (though is not proven) that such asymptomatic-but-smear-positive individuals contribute substantially to transmission.

Another key finding of this study was that variability in production of aerosolized *M. tuberculosis* varied much more by individual than by type of respiratory maneuver. More than half of the participants in this study generated 0–2 detectable bacilli during 15 minutes of breathing and coughing, whereas three participants generated more than one bacillus per minute (and one participant, who did not cough spontaneously during tidal breathing, generated a viable aerosolized bacillus every 25 s). Thus, in terms of curbing the spread of TB, it may be more productive to characterize the individuals who generate large numbers of aerosolized bacilli than the events (e.g., coughing) during which those bacilli are generated. But certainly, for individuals diagnosed with smear- or Xpert-positive pulmonary TB, we should not promote a strategy of just "covering one's cough" to slow transmission.

In summary, this study elegantly demonstrates that, among untreated Xpert-positive individuals, viable *M. tuberculosis* is aerosolized not just through coughing, but also through tidal breathing. This work complements recent research on respiratory viruses, in which influenza virus and rhinovirus (14), as well as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (15), were detected in subsets of infected individuals during tidal breathing without cough. After more than a century of research, it is becoming clear that transmission of airborne pathogens like *M. tuberculosis* does not require a cough. All it takes is a simple breath. ■

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Pneumothorax: Clearing the Air on the Pressure-Dependent Airleak Hypothesis

Pneumothorax research, a long-neglected subject, has recently attracted unprecedented, and much overdue, interest sparked by several landmark randomized clinical trials (1, 2). Debates on optimal management of pneumothorax consistently lead to the fundamental gaps in our understanding of the disease pathophysiology (3, 4). For example, through endobronchial valve studies, we now understand the conventional concept that one airway leading to one leak site is over-simplistic (5). Most patient do not have an obvious site of leak on CT or even when surgeons submerge the lung underwater intraoperatively, rekindling arguments about how air passes through visceral pleura (e.g., hypothesis of pleural pores) (6).

In this issue of the *Journal*, Walker and colleagues (pp. 145–149) proposed a new hypothesis that chest tubes inserted for pneumothorax drainage create a negative pressure outlet, exacerbating the pressure gradient across the visceral pleural defect, and cause prolonged airleak (7). They stated that "ongoing visceral airleak is largely dependent on an induced pressure gradient." This hypothesis is thought-provoking and has merits. However, it is difficult (if not impossible) to test and lacks empiric evidence, and, most importantly, its clinical application can potentially cause harm.

Confirming the hypothesis is difficult because measurement of pleural pressure gradient requires intrapleural placement of a catheter with a pressure-measuring device (e.g., manometer), which inevitably provides an escape route and disturbs the pressure gradient. Corroborative evidence is also lacking. The majority of pneumothoraces treated with tube drainage do heal with time despite this potential pressure gradient. All clinicians have encountered patients whose pneumothorax enlarges without drainage; conversely, removing the pressure gradient (e.g., when chest tubes dislodge or are prematurely removed) does not stop the leak but generates surgical emphysema or recurrence of pneumothorax. These observations argue against tube drainage being the key driving force for ongoing airleaks. Interestingly, Walker and colleagues have published data showing that a sizeable number of traumatic pneumothoraces did not enlarge even when patients were subjected to positive pressure ventilation (which would induce a much larger pressure gradient across visceral pleural defects than chest tube insertion in patients breathing spontaneously [8]).

The authors provided three "rationales" to support their hypothesis. All evidence was indirect and the interpretation contestable. First, the result of the PSP (Primary Spontaneous Pneumothorax) trial (1) was used to support this hypothesis. The PSP study was a randomized clinical trial that investigated the noninferiority of conservative management (no drainage) of pneumothorax against conventional smallbore tube drainage. The trial found that 85% of patients were successfully managed without drainage. Radiographic lung reexpansion was, as expected, slower with conservative management, although by 8 weeks, there were no significant intergroup differences. However, the study did not (and could not) measure if airleak resolves faster with or without a chest tube and should not be used as evidence of such. Not draining the pneumothorax allows the lung to remain deflated and brings the edges of any defect to closest proximity and enhances healing—an alternative explanation (to the pressure gradient hypothesis) for the benefits of conservative management.

In their second rationale, the authors interpreted that patients with an ongoing airleak (shown by tracer gas) whose pneumothorax air was aspirated but had a "recurrence" the next day as a consequence of exacerbation/reopening the airleak from the negative pressure gradient generated during evacuation (9). A more plausible explanation would be that those airleaks never stopped. Aspiration temporarily cleared the air, and sufficient air accumulated over the following hours to become appreciable radiologically. The third rationale centered on a study of post–lung-resection patients (10) whose pleural pressure changes (including possible trapped lung space) would be very different from spontaneous pneumothorax.

If the authors' hypothesis is accepted, patients with a chest tube and ongoing leak should have their tubes clamped/removed—an

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