genetic and environmental factors that affect gene regulation affect disease risk, remains a major challenge. The discovery that a regulatory variant affecting *MUC5B* expression in distal airways is associated with a very large increase in risk of developing pulmonary fibrosis is a compelling early step toward this goal (12). It will also be critical to identify disease-associated changes in mucin gene expression in different regions of the lung and to understand how these affect mucus function. Recent studies show that differences in mucus composition are associated with dramatic differences in mucus organization and function. For example, MUC5B and MUC5AC are found within distinct domains of mucus plugs in fatal asthma, and the MUC5AC-rich domains play a unique role in mucostasis by tethering to the epithelium (13). In pigs, MUC5B from submucosal gland ducts formed strands composed of multiple MUC5B filaments, whereas MUC5AC emerged from superficial secretory cells as wispy threads or sheets, and it seems likely that these distinct structures contribute differently to mucociliary transport (14). Understanding how regional and disease-associated differences in mucins and other mucus components affect host defense and lung function is likely to be a long but rewarding journey. Okuda and colleagues have provided a map that will help us find our way. ■

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Can a Physiologic Insight "Resuscitate" Research in Cardiopulmonary Resuscitation?

Anyone who has ever performed successful cardiopulmonary resuscitation (CPR) knows instantly that they have done something truly incredible. The significance of the act and the elemental feeling of usefulness is the same for all members of the extended healthcare team or the public who have just saved a life. CPR is also unique in that its core principles are well understood by many, or at least that's what we think. It consists of clearing a patient's airway, rhythmically pumping the thorax to circulate blood around the body, providing some ventilation to replace spontaneous breathing, and if a shockable arrhythmia is present, performing defibrillation.

Initial research into CPR yielded major gains. Campaigns to convert bystanders into competent responders have been success stories of major proportions, leading to marked improvements in rates of survival with good neurological outcome (1–3). However, recent clinical research into CPR has not improved its effectiveness. Large randomized controlled trials have tested the optimal types

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and doses of inotropic agents, bicarbonate, or anti-arrhythmic agents without identifying beneficial treatments (4–6). Perhaps the most striking (and highly powered) recent randomized controlled trial was the CCC (Continuous Chest Compression) study, which roughly translates into: ventilation is not sufficiently important to warrant interruption of CPR (7).

A novel insight in this issue of the *Journal* by Grieco and colleagues (pp. 728–737) has the potential to move beyond this impasse (8). The investigators began with careful observations of end-tidal CO_2 ($ETCO_2$) tracings during CPR in victims of cardiac arrest. Because exhaled CO_2 reflects delivery of venous blood to the lungs, $ETCO_2$ tracings are recommended to monitor the effectiveness of CPR. But during CPR, the $ETCO_2$ tracing is characterized by oscillations; this is assumed to represent variable ventilation and exhalation of CO_2. However, in many patients, these CPR-related oscillations were inconsistent or absent, presumably reflecting obstruction to airflow that prevented passage of the CPR-related CO_2 oscillations to the $ETCO_2$ monitor at the end of the endotracheal tube.

Because large airways were patent in each patient (endotracheal tubes were present in all), the investigators hypothesized that the airflow obstruction occurred in small airways. To quantify the degree of airway closure, they developed an Airway Opening Index, representing the changing $ETCO_2$ values during CPR compared with the maximal $ETCO_2$. Thus, a higher index reflects greater transmission of CO_2 and greater airway patency.

Two sets of experiments confirmed that small airway closure could explain this phenomenon. Using a bench lung model, they reproduced the $ETCO_2$ waveforms observed in the real patients by simulating airway closure, and demonstrated that incremental levels of positive end-expiratory pressure (PEEP) increased transmission of the oscillations, as well as elevating inspiratory flow and minute ventilation. In addition, the highest $ETCO_2$ value during CPR represented the closest estimate of the actual alveolar CO_2. Each of these findings was recapitulated in human cadavers (Thiel model), where the alveoli were loaded with CO_2 before CPR; although PEEP improved transmission of oscillations, elevating the airway index, it did not compromise the effect of chest compressions on intrathoracic pressure.

If upheld, these findings could have immense application to the conduct of CPR in several direct ways. First, although perfusion with poorly oxygenated blood is preferable to no perfusion, without at least some ventilation, the perfusing blood will ultimately contain very little oxygen. Given that oxygenating tissues is the primary function of circulating blood, how could it be that ventilation during CPR seems not to be important? The idea that small airways close during CPR and prevent alveolar delivery of the applied breath could explain this paradox, because if the airways could be opened by titrated PEEP, the importance of ventilation during CPR could be properly evaluated. Second, it is possible that many trials reporting failure of carefully considered therapies (e.g., inotropic agents, antiarrhythmic medications, and even advanced airway techniques [9]) may represent false-negative results because ventilation was inadequate in so many patients. This is because if return of circulation does not occur rapidly, then ongoing CPR with inadequate ventilation would render any cointervention ineffective. Third, measuring the Airway Opening Index (or a version of it) should be easy, given that $ETCO_2$ monitors are now widely available, including in ambulances. Thus, small airway closure during CPR could be detected and eliminated with small levels of PEEP.

Although this study, and another promising to increase perfusion during CPR using inhaled nitric oxide (10), are grounds for optimism, there are important reasons to be cautious. Several steps are required to corroborate this theory of small airway closure. The results need to be reproduced by others, and the nature and locus of the airway closure need to be better understood, perhaps using novel imaging. Although the cadaver studies were reassuring about the lack of adverse effects of PEEP, the optimal level of PEEP, balancing airway patency against perfusion, needs to be understood in individual patients. Finally, clinical trialists in the field will need all of their accumulated insight and experience to guard against a false-negative (or, far less likely, a false-positive) controlled trial.

In conclusion, CPR is a very special gift. Research in the field made early gains, but more recently progress has been slow. The physiologic insight by Grieco and colleagues has the potential to make a major positive difference to the field: If treating small airway closure works, survival after CPR might increase, and more important, so too might the quality of life among survivors. ■

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When the Fetus Is Exposed to Smoke, the Developing Lung Is Burned

Some have questioned why the *Journal* has published so many papers on the health effects of household air pollution (HAP) from domestic cooking in recent years. There are compelling reasons to do so. Approximately 3 billion people, or 40% of the world's population, still cook using open fires or simple stoves fueled by kerosene, biomass (wood, animal dung, and crop waste), or coal that generate considerable HAP (1). The Global Burden of Disease project attributes multiple noncommunicable diseases, including chronic obstructive pulmonary disease (COPD) and lung cancer, to HAP (2). In low- and middle-income countries (LMICs) where most women do not smoke tobacco, HAP may be the major cause of COPD and lung cancer in women. The World Health Organization estimates that HAP causes close to 3 million deaths per year, including 500,000 deaths of young children due to pneumonia or nearly half of all deaths due to pneumonia in children under 5 (1). Simply put, HAP has a huge public health impact that is theoretically preventable.

A major criticism of the evidence base used to estimate the health impacts of HAP is the relative paucity of both measured exposure data and objectively measured outcome data, evidence gaps that are understandable given the difficulty of obtaining such data in the low-resource environments of countries where cooking with dirty fuels is common (3). The paper by Lee and colleagues (pp. 738–746) published in this edition of the *Journal* provides data that help fill both of these gaps (4). These investigators used 48-hour personal monitoring of carbon monoxide (CO) exposures four times over the course of pregnancy to assess prenatal exposure to HAP among rural participants in a cluster-randomized intervention trial of cleaner-burning cookstoves (GRAPHS [Ghana Randomized Air Pollution and Health Study]), an impressive exposure assessment effort. They then measured lung function parameters (i.e., the ratio of the time to peak tidal expiratory flow to expiratory time, tidal volume, respiratory rate, and minute ventilation with flow–volume loops, as well as passive respiratory system compliance with the single-occlusion technique) on the infant offspring of the monitored mothers at 1 month of age. This again is an impressive effort, and the first to obtain high-quality infant lung function measurements in such a low-resource setting.

The primary finding of this elegant study is that maternal CO exposure during gestation was associated with lower infant lung function. This effect of HAP exposure was greater in girls than in boys. Moreover, infant lung function measured at 1 month of age was associated with an increased risk of pneumonia before age 1 as assessed by active weekly surveillance by fieldworkers, followed by physician evaluation of suspected cases using the World Health Organization's Integrated Management of Childhood Illness guidelines. Physician-assessed severe pneumonia was also associated with infant lung function.

Although the authors acknowledge some limitations of their study, including the relatively small sample size, lack of dietary data, and inability to confirm a diagnosis of pneumonia with chest imaging, the implications of their findings are profound. The fetal programming hypothesis, which proposes that prenatal environmental conditions are important determinants of disease in adulthood, is supported by both epidemiological and animal experimental data (5). Advances in epigenetic research also provide a plausible mechanism for such programming. Considerable evidence exists to suggest that maternal exposure to ambient air pollution and environmental tobacco smoke during gestation can lead to reduced lung function in offspring, which in turn can lead to a low lung function trajectory in adulthood associated with an increased risk of COPD (6–8). In addition to the lower infant lung function associated with maternal prenatal CO exposure, Lee and colleagues found that lower infant lung function increased the risk of early-childhood pneumonia. These findings now add exposure to HAP as another prenatal environmental risk factor for poor respiratory health later in life. The greater effect of prenatal exposure to HAP on girls in the current study is notable given that the greatest burden of HAP-related respiratory disease in LMICs is for adult women.

What can be done to prevent the harmful effects of *in utero* exposure to HAP on respiratory health during the subsequent life course? The published results from randomized control trials of "cleaner" biomass cookstoves are mixed with regard to the efficacy of such interventions for the prevention of early-childhood pneumonia (9, 10), and the results of a multicountry trial of liquefied-petroleum gas stoves are not likely to be published for several years. Moreover, widespread distribution of liquefied-petroleum gas stoves may not be available in many low-income countries for a number of years. That said, reduction of prenatal and infant exposures to HAP through behavioral changes, such as not burning rubbish near the home and keeping young children away from open biomass fires, may be of some

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