In their analysis, Jensen and colleagues point out that respiratory support variables alone are as good (or better) than oxygen variables. Keller and colleagues’ report indicates that antenatal variables are also comparable (7). Conceptually, we like the physiologic approach of Svedenkrans and colleagues (13). An optimal research definition might include measurements of oxygenation, CO₂ elimination, and magnetic resonance imaging for the structural abnormalities that contribute to gas exchange abnormalities. For epidemiologic purposes, the definition does not seem to make much difference if it is consistently applied. For therapeutic studies, perhaps the outcome should be linked to the target of the therapy, such as parenchymal inflammation, airway injury, or pulmonary hypertension.

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Loss of Microbial Topography Precedes Infection in Infants

Studies demonstrating that breastfeeding protected infants from respiratory infections began in the early 20th century. At the time, it was presumed that this was a result of nutritional deficiencies in formula (1). In the mid-20th century, it became apparent that breast milk was more than a source of calories, but also a vehicle for the transmission of antibodies, immune cells, and oligosaccharides meant for microbial, rather than infant, nutrition (2). As a consequence, infant formulas now include substances meant to promote a healthy microbiome, yet formulated infants are still more susceptible to respiratory infections (3). Despite more than a century of data on the role of breast milk in protection from respiratory infections, we still do not know whether or how maternal antibodies help shape the composition of the upper respiratory tract microbiome, whether breast milk directly promotes the growth of some respiratory microbes over others, or whether protection from respiratory infections is primarily a consequence of immune maturation.
Mode of delivery also alters the oral and nasopharyngeal microbiota, and ultimately affects susceptibility to infection. Infants born by vaginal birth are quicker to acquire species such as Corynebacterium spp., Moraxella spp., and Dolosigranulum spp., which are associated with reduced colonization of respiratory pathogens, than their Caesarian-born counterparts (4). How colonization of the nasopharynx by microbes that are not major components of the vaginal microbiota occurs is not clear, but may be a result of immune development as opposed to direct seeding of microbes (5). Although the mechanisms of microbiome development are not fully elucidated, in this issue of the Journal, Man and colleagues (pp. 760–770) provide provocative evidence that both the composition of the infant microbiome and the ability to maintain the topography of the nasopharyngeal community are important for protection from respiratory infections early in life (6).

Expanding a previous study of the nasopharyngeal microbiome from birth to 6 months (7), Man and colleagues examined the oral microbiome in the same cohort and investigated whether changes in oral and nasopharyngeal communities were associated with respiratory tract infections in early life. They previously had confirmed findings that breastfeeding and mode of birth influences these microbial communities (5, 8), and identified that the presence of certain microbes such as Neisseria spp. and Prevotella spp. in the first month of life are predictive of future respiratory infection. These data might lead one to conclude that the presence of some microbes enriched by birth mode or breastfeeding protect against infections. Indeed, this is consistent with decades of carriage studies that demonstrate that carriage of some pathobionts will protect against colonization by others (9). The surprising element of this study is that changes in the nasopharyngeal microbiome occurred up to a month before the occurrence of a respiratory infection and were characterized by an increase in primarily oral taxa (e.g., Neisseria lactamica, Prevotella nanceiensis, Fusobacterium spp.) in the nasopharyngeal microbiota. It is well documented, and Man and colleagues confirm, that the nasopharyngeal microbiome changes during a respiratory infection. These changes may be a result of direct microbial competition, leukocyte recruitment and concomitant changes in the oxidative environment (10), and/or changes in mucus production (11). It is possible, but not proven, that the infant nasopharyngeal microbiome becomes supportive of oral species, which include many anaerobic species, before infection as a result of changes in oxidative tension resulting from subclinical inflammation or immune involvement.

Limitations of the study include the fact that respiratory tract infections were confirmed by symptoms rather than definitive virologic testing. Timing of childhood vaccinations was also not recorded. The majority of the children in the study would have been vaccinated with the pneumococcal conjugate vaccine at 6–9 weeks, and again at 4 months (12). Pneumococcal vaccination alters the composition of the respiratory tract microbiota, and could conceivably contribute to observed changes in the microbiota that precede infection (13). In general, 16s RNA sequencing does not provide sufficient resolution of Streptococcus spp. to determine whether acquisition of S. pneumoniae was one of the events that triggered a loss of topography.

Another counterintuitive finding was the role of daycare in microbial dysbiosis. As many parents will attest, having a child enter daycare can be the start of several months of fevers and runny noses. Five of the children in the study developed respiratory tract infections in their first month of daycare, but the loss of nasopharyngeal topography was apparent a month earlier. This implies that the loss of topography may predispose children to infections once there is a second insult, such as exposure to new microbes or the stress of beginning daycare.

Collectively, these data imply that the upper respiratory tract microbiome is modified by factors we do not yet understand. Despite the physiologic differences between the nasopharynx and oral cavity, the distinction between these topographies is blurred at times of immunological or possibly physiological stress. Older adults are also highly susceptible to respiratory infections and also lose topographical distinctions between the naso- and oropharynx (14). Although the processes of immune development and immunosenescence are quite different, perhaps the end result, loss of topography preceding respiratory infections, is the same.

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Myocardial Fibrosis as a Potential Maladaptive Feature of Right Ventricle Remodeling in Pulmonary Hypertension

The ability of the right ventricle (RV) to adapt to increased pulmonary pressures is the main determinant of clinical outcomes in patients with pulmonary hypertension (PH). The RV and the pulmonary vasculature behave as a single interrelated cardiopulmonary unit, and an improved understanding of the nature and range of RV responses to increased afterload is needed. Some RV responses to elevated pulmonary pressures are clearly adaptive, whereas others are thought to be maladaptive. Early recognition of features of maladaptive change may enable timely interventions to prevent deterioration of RV function (1).

Myofibroblast activation is a cellular response to increased RV afterload, which leads to myocardial fibrosis and an altered extracellular matrix. Precisely where RV fibrosis falls on the continuum of adaptive to maladaptive RV change is a topic of ongoing debate (2). Histologic studies support RV fibrosis as a consistent feature of PH; however, these studies have mostly examined myocardial biopsies and explants from patients with end-stage PH. Noninvasive imaging methods that indirectly assess fibrosis enable examination of patients in earlier stages of the disease course and offer insights into physiologic consequences of RV changes. Most previous magnetic resonance imaging (MRI) studies in PH have measured late gadolinium enhancement as a surrogate of fibrosis (3). Recently, T1 mapping with myocardial extracellular volume (ECV) assessment has emerged as a more useful technique for assessing diffuse interstitial fibrosis and for following changes in the extent of fibrosis over time (4, 5).

In this issue of the Journal, Jankowich and colleagues (pp. 776–779) use myocardial ECV assessment in patients with PH to investigate the relationship between diffuse interstitial fibrosis in the RV free wall and pulmonary artery (PA) stiffness, as measured by PA pulse wave velocity and PA relative area change (6). The authors found a strong positive correlation between RV ECV and PA pulse wave velocity (0.73; P = 0.001) and a strong negative correlation between RV ECV and PA relative area change (−0.69; P = 0.003), supporting a relationship between RV fibrosis and PA stiffness in this cohort. Univariable linear regression models demonstrated significant associations between RV ECV and these surrogates of PA stiffness, and associations remained significant after adjustment for biological variables and MRI metrics of RV function in bivariable models. No significant relationships existed between RV ECV and measures of RV function, such as RV ejection fraction (RVEF), in this cohort.

The authors should be commended for their use of a new, and perhaps more sensitive, MRI technique to investigate a relatively unexplored issue: the nature and clinical significance of RV fibrosis in PH. Their study offers unique insight into a cohort of patients with early disease and relatively preserved RV function, with a mean RVEF of 46% (SD, 12%). In addition, this is one of only a few MRI studies that have examined changes in the RV free wall, rather than limiting observations to the septum and ventricular insertion points. Given previously reported associations between measures of PA stiffness and poor clinical outcomes in PH, the authors suggest that RV fibrosis may be an early marker of deleterious RV remodeling, observed in this cohort before deterioration in any functional metric, such as RVEF.

Although it is provocative to speculate that RV fibrosis may be an early maladaptive response to PA stiffness, Jankowich’s study has several limitations that should lead to cautious interpretation of its results. As a cross-sectional study, these results do not give any hints to temporality. That is, these findings do not support a conclusion that PA stiffness causes, or even necessarily precedes, RV fibrosis. Several additional issues limit the generalizability of the results. This is a rather small cohort (n = 16) with a sex distribution atypical for PH cohorts (94% male). Further, the cohort comprises patients across multiple different World Symposium on Pulmonary Hypertension (WSPH) classifications of PH, with the majority of patients classified as group 2 (n = 6) and group 3 (n = 6). Different WSPH groups are known to have different pathobiologic features, and variations in pathophysiology are therefore to be expected. Indeed, there is evidence that even within the group 1 classification of PH, patterns of fibrosis differ across disease subtypes. Hsu and colleagues found that patients with scleroderma-related pulmonary arterial hypertension have significantly more fibrosis on endomyocardial biopsies of the RV...