"different" BPD from a pathobiological point of view, as some of these patients may have been invasively ventilated, whereas some others may have experienced an impaired lung development without the ventilation-induced inflammatory trigger (11). Each of these subclassifications can then be managed more precisely to match their physiology, and data on outcomes can be more accurately portrayed and compared. In the commented study, MRI was performed when severe BPD was already established; however, the aforementioned diagnostic tools might be used much earlier in infants with chronic pulmonary insufficiency of prematurity to direct them toward a particular therapeutic approach or a more tailored ventilation rather than just give snapshots of the patients' situation (Figure 1). This would match with the main issues identified by the International Neonatal Consortium statement (6).

We believe that innovative diagnostic tools and a new mindset are critically necessary to provide precision medicine to our most vulnerable patients and improve our ability to care for and learn from them. ■

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Bubble Trouble in COVID-19

In training, we learn that there are five causes of hypoxemia: $\dot{V}/Q$ mismatch, right-to-left shunt, diffusion impairment, hypoventilation, and low $F_{I_{O_2}}$. Right-to-left shunts may be intracardiac or intrapulmonary and are characterized by a reduced or absent response to supplemental oxygen. Frontline healthcare workers witness this shunt physiology on a regular basis while caring for hospitalized patients with coronavirus disease (COVID-19). Gattinoni and colleagues initially described this unique phenomenon of large shunt fractions and severe hypoxemia in patients with COVID-19 as compared with "typical" acute respiratory distress syndrome (ARDS) (1). Hypoxemia in COVID-19 can also be disproportionate to the degree of symptoms and impairment in lung mechanics. In a study by Guan and colleagues, only 18.7% of 1,099 hospitalized patients with COVID-19 reported dyspnea despite the majority having abnormal chest imaging (2). Although both intrapulmonary and

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intracardiac shunting have been described in classical ARDS, they are generally present in a minority of patients and are not a predominant feature (3).

In this issue of the *Journal*, Reynolds and colleagues (pp. 1037–1039), in a pilot study, used automated transcranial Doppler (TCD) ultrasound to define the prevalence of intracardiac or intrapulmonary shunting in patients with COVID-19 (4). With this method, agitated saline microbubbles are injected into a central or peripheral venous catheter and TCD is used to detect and quantify microbubbles that appear in the cerebral circulation. Normally, the microbubbles, whose diameter exceeds the pulmonary capillaries, are trapped in the pulmonary circulation. In patients with intracardiac shunting or intrapulmonary vasodilatation, however, the bubbles transit through the pulmonary circulation and can be visualized downstream in the left heart (as detected by contrast-enhanced transthoracic echocardiography [CE-TTE]) or middle cerebral artery (as detected by TCD). Compared with CE-TTE, TCD is more sensitive but less specific and unfortunately cannot distinguish intracardiac from intrapulmonary shunting (5).

Reynolds and colleagues found that the majority (15/18, 83%) of patients with COVID-19 had detectable microbubbles in the cerebral circulation by TCD (4). Although this is a small pilot study, this prevalence is much higher than that reported in prior studies of patients with ARDS (3). Notably, these prior studies also used the less sensitive method of CE-TTE for microbubble detection. Although more information regarding ventilator settings, pulmonary hemodynamics, and the presence or absence of patent foramen ovale would have been helpful to characterize the patients, these findings suggest that intrapulmonary vasodilatation could play an important role in the pathogenesis of hypoxemia associated with COVID-19. To further support this hypothesis, pulmonary vascular dilatation and altered perfusion has also recently been identified as a radiographic finding in COVID-19 pneumonia (6). Reynolds and colleagues also found that the number of microbubbles was inversely correlated with oxygenation (Pa_{O_2}:$F_{I_{O_2}}$ ratio) and lung compliance, suggesting that microbubbles may be a marker of disease severity from both a gas exchange and lung mechanics perspective (4).

This study describes a high prevalence of intrapulmonary vasodilatation (or intracardiac shunting) in patients with COVID-19 that leads to detection of microbubbles in the cerebral circulation (4). Could this finding provide therapeutic insight into the management of COVID-19 pneumonia and associated hypoxemia? Archer and colleagues hypothesized that hypoxemia in COVID-19 is due to impaired hypoxic vasoconstriction and have suggested trials of medications that promote hypoxic vasoconstriction, such as almitrine, or medications that inhibit endogenous vasodilator pathways, such as indomethacin or methylene blue (7). These medications could potentially counteract hypoxemia related to intrapulmonary vasodilatation and impaired hypoxic vasoconstriction but have not yet been studied in COVID-19 pneumonia.

Hepatopulmonary syndrome (HPS), a pulmonary complication of liver disease, is characterized by intrapulmonary vasodilatation and impaired hypoxic pulmonary vasoconstriction with resultant hypoxemia (8). Interestingly, despite severe hypoxemia in HPS due to intrapulmonary vascular dilatation, the response to 100% inspired oxygen can sometimes result in remarkably high Pa_{O_2} values (500–600 mm Hg), no doubt reflecting the lack of associated alveolar damage as seen in ARDS or COVID-19 pneumonia. There are no approved medical therapies for HPS, but prior studies could potentially provide insight into novel therapeutic options for COVID-19. In HPS, medications that target hypoxic pulmonary vasoconstriction, such as almitrine, have been studied without consistent benefit (9, 10). Other therapies, such as methylene blue, garlic, and inhaled pulmonary vasodilators, such as inhaled nitric oxide, have been associated with improved oxygenation in small studies or case series of patients with HPS (10, 11). Inhaled nitric oxide is postulated to improve oxygenation in HPS by redistribution of pulmonary blood flow and improved $\dot{V}/Q$ matching and is actively being studied as a treatment for COVID-19.

Lastly, this particular method of detection of microbubbles in the bilateral middle cerebral arteries raises the question of whether increased neurologic complications of COVID-19 could be related to the high prevalence of intrapulmonary or intracardiac shunting. Patients with COVID-19 have an increased risk of ischemic stroke compared with patients with influenza (12). According to one study, cardioembolism was the second most common cause of stroke in COVID-19 (13). Others have suggested that paradoxical embolism is an important source of increased stroke risk, particularly in young people without traditional stroke risk factors (14). Because stroke is a major cause of morbidity and mortality, studies like this that could provide insights into the mechanisms of stroke in COVID-19 are critical to improved understanding of extrapulmonary disease manifestations of COVID-19.

In summary, Reynolds and colleagues describe a high prevalence of findings suggestive of intrapulmonary vasodilatation in hospitalized patients with COVID-19 (4). Microbubbles were detected in the cerebral circulation in 83% of patients and were associated with more severe hypoxemia and reduced lung compliance. The study raises the important question of whether intrapulmonary vasodilatation could represent a novel therapeutic target in the management of hypoxemia associated with COVID-19. ■

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Pulmonary Arterial Hypertension and Sex in the Right Ventricle: It Is an Interesting Picture!

Right ventricle (RV) function determines clinical course and long-term prognosis in patients with pulmonary arterial hypertension (PAH) (1). Though PAH is common in females, it has been established that RV function is inferior in male patients with PAH when compared with female patients with PAH. On cardiac magnetic resonance imaging, despite having a similar degree of pulmonary vascular disease, male patients with PAH have lower RV ejection fraction than age-matched female patients with PAH (2, 3). In addition, the improvement in RV function after pulmonary vasodilator therapies is less in male versus female patients with PAH (3). The difference in RV function response to pulmonary vasodilator therapies partially explains the survival disadvantage in male PAH patients (3). In fact, similar sex differences in RV function have also been documented in healthy individuals (4), patients with pulmonary hypertension because of left heart disease (5), and patients with pulmonary hypertension secondary to chronic lung disease (6). However, all prior studies assessing sex differences in RV function are based on load-dependent measures, which are not a true measure of RV contractility (i.e., when the RV afterload is high, the load-dependent measures can be lower despite normal RV contractile function) (7).

There is growing recognition of the importance of the interaction between the RV and the pulmonary arterial system in PAH, which is referred to as RV–pulmonary artery (RV-PA) coupling (8). RV-PA coupling represents efficient delivery of the power generated by the RV contractility into the pulmonary arterial system. In other words, it is a measure of RV adaptation to the increased afterload. During the early stages of PAH, the RV undergoes concentric hypertrophy and increases its contractile function to match the increase in afterload. This RV adaptation maintains a normal RV-PA coupling (9). However, with progression of PAH, the RV can no longer undergo hypertrophy or increase its contractile function to match the afterload. This leads to RV-PA uncoupling, RV failure, and eventually death (9).

The best measure of RV-PA coupling is the relationship between end-systolic elastance (Ees), a load-independent measure of intrinsic RV contractility, and effective arterial elastance (Ea), a measure of RV afterload (9). These measures are calculated from invasive RV pressure–volume loop analysis obtained using high-fidelity micromanometer catheters. An ideal RV-PA coupling (Ees/Ea) is 1.5–2, and an Ees/Ea ratio <0.8 defines RV-PA uncoupling (10). In addition to RV-PA coupling, pressure–volume loop analysis can assess RV diastolic function by measuring Tau and RV end-diastolic elastance (Eed) (9). Eed is a load-independent measure of RV diastolic function. It is calculated from the relationship of change in pressure and volume at end-diastole (9). Tau is a load-dependent measure of RV diastolic function. It is calculated from the reciprocal of the natural logarithm of the early maximal fall in ventricular pressure during the isovolumetric phase of diastole (9). Though load-dependent measures of RV systolic function are lower in male patients with PAH, it is unknown whether there are similar sex differences in load-independent measures of intrinsic RV contractility, RV-PA coupling, and RV diastolic function in patients with PAH.

In this issue of the *Journal*, Tello and colleagues (pp. 1042–1046) dig deeper to better understand sex differences in RV function in patients with PAH using pressure–volume loop analysis (11). They prospectively studied 57 patients with PAH, of whom 33 (58%) were females. The pressure–volume relationships were assessed using the single-beat method (12) in all 57 patients and the multibeat technique (8) with inferior vena cava occlusion in 37 patients. All patients except two also had a cardiac magnetic resonance imaging. Despite similar RV afterload (Ea), female patients had higher RV contractile function (Ees) and better RV-PA coupling (Ees/Ea) than male patients. Tau was lower in females than in males, indicating better RV diastolic function; however,

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