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Scrutinizing the Mechanisms of West Non–Zone 3 Conditions during Tidal Ventilation

A long time ago, it was demonstrated that blood flow through arterioles, capillaries, or veins is well mediated by the Poiseuille law (the gradient between the upward and backward pressures of the vessel), provided the proper backward pressure is used, taking into account the surrounding pressure of the vessel and its closing pressure, leading to the principle of the vascular waterfall and the Starling resistor with different vessel zone conditions in which zone 3 regards the absence of any flow limitation (1). West zones are no more than the application of this principle to the pulmonary capillaries (2). Figure 1 illustrates its application to the vena cava as well as the pulmonary capillaries.

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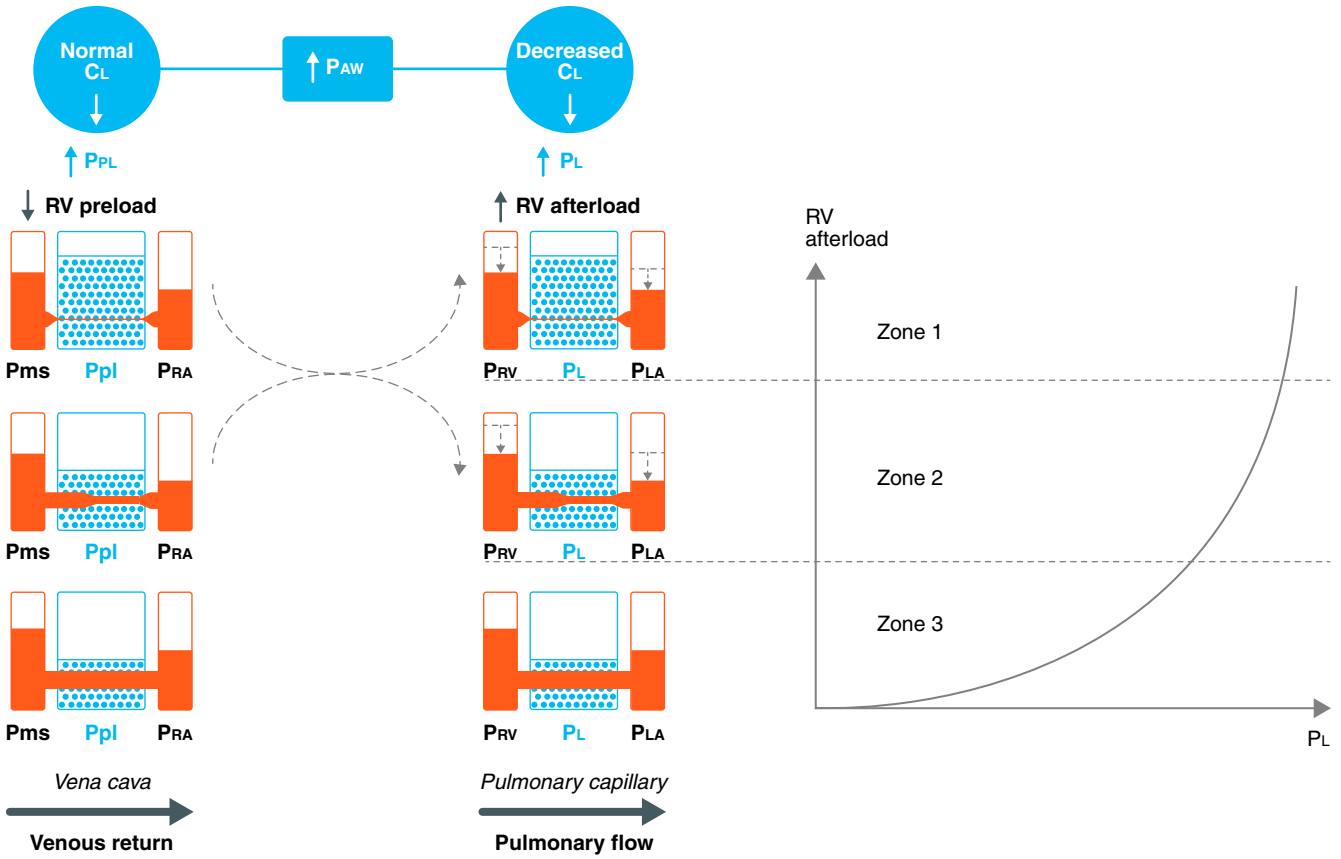

Figure 1. Impact of mechanical ventilation on systemic venous return and pulmonary blood flow, with their potential interaction. A model of a vascular waterfall and the Starling resistor. Left part: Potential impact of mechanical ventilation on systemic venous return and right ventricular (RV) preload. The venous return is normally driven by the difference between the upward mean systemic pressure (Pms) and the backward right atrial pressure (P_{RA}), with no influence of the surrounding pressure of the vena cava, which is the pleural pressure (Ppl), a situation corresponding to a zone 3 condition ($Pms > P_{RA} > Ppl$). Pms is the equilibrium pressure into the circulatory system when the heart stops beating. The cyclic rise in airway pressure (Paw) induces a predominant rise in Ppl in case of normal lung compliance (C_L) (15), impeding partially or completely the systemic venous return by inducing a zone 2 ($Pms > Ppl > P_{RA}$) or zone 1 ($Ppl > Pms > P_{RA}$) condition, respectively. Middle part: Potential impact of mechanical ventilation on pulmonary blood flow and RV afterload. The pulmonary blood flow is normally driven by the difference between the upward systolic right ventricle pressure (P_{RV}) and the backward left atrial pressure (P_{LA}), with no influence of the surrounding pressure of lung capillaries, which is the transpulmonary pressure (P_L), a situation corresponding to a West zone 3 condition ($P_{RV} > P_{LA} > P_L$). The cyclic rise in Paw induces a predominant rise in P_L in case of altered C_L (15), impeding partially or completely the pulmonary blood flow by inducing a zone 2 ($P_{RV} > P_L > P_{LA}$) or zone 1 ($P_L > P_{RV} > P_{LA}$) condition, respectively. The preload effect, by impeding venous return and RV preload, may reduce P_{RV} and P_{LA}, inducing a transition from West zone 3 to zone 2 or from zone 2 to zone 1 (gray dashed arrows). Right part: Curvilinear relationship between transpulmonary pressure and RV afterload as a consequence of West zone condition alterations.

In this issue of the *Journal*, Slobod and colleagues (pp. 1311–1319) report interesting results regarding the prevalence of lung non–zone 3 conditions during inspiration across a 2- to 12-ml/kg range of V_T in 51 postoperative passively ventilated cardiac surgery patients (3). Using detailed invasive hemodynamic phenotyping, coupled with echocardiography in a few patients, the authors found that even low V_T was associated with a cyclic inspiratory increase in markers of right ventricular (RV) afterload and a decrease in RV stroke volume. Non–zone 3 conditions were present in >50% of subjects at a $V_T \geq 6$ ml/kg, with a corresponding mean driving pressure of 11–12 cm H_2O.

In non–zone 3 conditions, the backward pressure for the pulmonary flow is no longer the pulmonary venous pressure but now the distending pressure of the alveoli (i.e., transpulmonary pressure) (2). This usually suggests a partial (zone 2) or complete (zone 1) collapse of pulmonary capillaries with a limited or interrupted flow. Slobod and colleagues found a linear relationship between transpulmonary pressure at end inspiration and the rise in RV afterload. It is interesting to note that this relationship was already reported, but as being curvilinear (4), demonstrating that above a given value of transpulmonary pressure, West zone 2 or zone 1 conditions occur, abruptly increasing RV afterload. Jardin and colleagues (5) previously reported in patients with acute respiratory distress syndrome (ARDS) that transpulmonary pressure increased when V_T or positive end-expiratory pressure was increased; this generated an increase in RV isovolumetric contraction pressure (a good surrogate of RV afterload) and a decrease in pulmonary artery

pulse pressure (a good surrogate of RV stroke volume), as reemphasized by Slobod and colleagues.

The new information in the Slobod and colleagues study is that the effect of tidal ventilation on RV afterload was also observed in patients without ARDS with a low V_T, whereas it was usually considered that such a deleterious effect of mechanical ventilation is especially pronounced in patients with ARDS, in whom transpulmonary pressure is more likely to be severely elevated. In patients without ARDS, mechanical ventilation is expected to cause a decrease in systemic venous return (preload effect) mediated by a significant change in intrathoracic pressure (pleural pressure), which may reduce the superior vena cava transmural pressure toward its critical closing pressure, inducing venous return flow limitation, according to a vascular waterfall effect and the Starling resistor principle (6, 7) (Figure 1). This is especially true in cases of central hypovolemia and fluid responsiveness status. Notably, compliance of the respiratory system, as well as that of the lung and chest wall, were far to be normal in the post–cardiac surgery patients evaluated by Slobod and colleagues. This could explain in part their results suggesting an afterload effect even in patients without ARDS with low V_T.

Other specific points in this study deserve discussion. First, the hemodynamic consequence of increased RV afterload is usually prominent when RV function was previously impaired. Slobod and colleagues report a decrease in RV stroke volume during insufflation, but, unfortunately, they do not report RV function at baseline. Second, the authors state that many critically ill patients have "RV limitation" (i.e., their right ventricle cannot increase its end-diastolic volume in response to increased afterload to maintain stroke volume). This assertion is questionable for several reasons. RV failure was defined in critically ill patients as a state in which the right ventricle is unable to meet the demands for blood flow without excessive use of the Frank-Starling mechanism (8). In many acute clinical situations, such as massive pulmonary embolism or ARDS, increased RV afterload is associated with RV dilatation and venous congestion (9). Interestingly, Slobod and colleagues not only reported an "RV limitation" during insufflation but also a decrease in transmural right atrial pressure (i.e., the distending pressure of the right atrium). This could suggest that alteration of the RV afterload parameters they observed was related to an upstream decrease in systemic venous return and RV preload mediated by mechanical ventilation, a crucial point to be well understood (Figure 1).

Indeed, lung West zones are supported by a potential competition between alveolar distending pressure and pulmonary capillary flow. This competition was reported by Zapol and colleagues many years ago to occur only in patients with acute lung injury and not in patients with normal lung compliance (10). A decrease in pulmonary blood flow, as a consequence of a preload effect of mechanical ventilation, may potentiate West non–zone 3 conditions, especially when lung compliance is depressed. This competition is corrected by fluid loading, especially when the patient is hypovolemic (11).

When the increase in RV afterload is really the *primum movens*, non–zone 3 conditions are usually related to lung overinflation (an abnormal and absolute increase in alveolar distending pressure) (Figure 1), and the decrease in RV stroke volume is associated with RV dilatation, as previously reported using echocardiography in patients with ARDS during tidal ventilation (12). The decrease in systemic venous return is then the consequence (transmural right atrial pressure is increased) and not the cause (transmural right atrial pressure is decreased) of the afterload effect (12). In this case, RV function may be worsened by fluid loading (13, 14) and requires adjustment of ventilator settings and strategies to relieve pulmonary vascular dysfunction.

In conclusion, the study of Slobod and colleagues is definitely interesting to analyze. Its main value is to allow intensivists to better understand heart–lung interactions and their respective mechanisms. Although some data on RV size and RV function are missing, we may assume that changes in RV afterload observed in their patients without ARDS were at least in part primarily related to a decrease in systemic venous return and RV preload. A "pure" RV afterload effect, as observed in patients with ARDS, is associated with RV dilatation and venous congestion. In clinical practice, echocardiography is therefore essential in depicting these respective effects because fluid management in these 2 conditions is opposite. ■

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Another Study Shows Electronic Cigarettes Harm Lungs: It Is Time for Researchers to Move from the Tobacco Playbook to a Tobacco Endgame

Electronic cigarette (e-cigarette) use is common among adolescents and young adults. An entry to nicotine addiction, e-cigarettes are casually associated with future combustible cigarette and dual-use among young people and with significant harm to cardiovascular and respiratory health in adults. In this issue of the *Journal*, Xie and colleagues (pp. 1320–1329) report on the association of electronic cigarette use with respiratory symptom development among young adults in the United States using data from the PATH (Population Assessment of Tobacco and Health) study (1). They present longitudinal data from PATH Waves two through five, reflecting survey data from 2014 to 2019, demonstrating that both former and current e-cigarette use is associated with the development of respiratory symptoms and wheezing in 18- to 24-year-old young adults who otherwise had no respiratory disease or symptoms at baseline. The associations were seen whether or not subjects reported ever smoking combustible cigarettes.

As the authors note, "e-cigarettes have gained immense popularity," including high rates of current e-cigarette use among youth who have never smoked combustible cigarettes. This state of affairs has come about through deliberate and effective targeting of youth through investments in marketing and promotion by the tobacco industry. Abundant evidence shows that e-cigarettes contain toxic chemicals with inflammatory and carcinogenic effects; while concentrations are often lower than those found in combustible cigarettes, this is relevant to their potential harm-reduction benefit and not to addiction of new users.

This paper reports important and significant findings contributing to our understanding of the harms of e-cigarette products. The analysis uses all available PATH data and appropriately excludes participants with preexisting respiratory disease. Young people with asthma, for example, are likely to have very different patterns of use and exposure and to have been nonusers of any nicotine products because of potential symptom exacerbation. Xie and colleagues cite two other longitudinal studies using PATH data to explore the association between e-cigarettes and wheezing. One, using longitudinal data, reported similar odds of wheezing in 12- to 17-year-old adolescents who used e-cigarettes (2). The other, using the same data and similar design, found dual use of e-cigarettes and combustible cigarettes, but not e-cigarettes alone, associated with more respiratory symptoms in those aged 12 or older (3). Another research group is constructing summary measures to define "'functionally important respiratory symptoms" with regard to self-reported health status, using PATH data (4).

The important underlying questions, however, are not whether symptoms are casually proven if one includes the few 12- to 14-year-olds who vape in samples or whether young people develop wheezing, cough, or both symptoms from e-cigarette exposure. Nor is it appropriate to conclude that more research is needed to understand what damage these products might cause. Rather, the question that must be asked is whether these competing analyses continue to undermine and delay effective action to protect the public's health. Throughout its history, the tobacco industry has used multipronged efforts to distort and promote disagreement over the scientific evidence, and uses these controversies to delay effective regulatory action (5). The "tobacco playbook" is increasingly recognized in other industries, and its effects are clearly seen in the

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