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EDITORIAL

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Sildenafil for pulmonary hypertension in ARDS: a new *pleasant* effect?

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Acute lung injury (ALI) as well as its more severe form, acute respiratory distress syndrome (ARDS), is a complication of several severe diseases characterized by alveolar spaces filled with exudates, loss of lung volume, acute severe hypoxemia, and pulmonary hypertension. The pathogenesis of ALI/ARDS also involves vasoconstriction leading to alterations in pulmonary blood flow and injury to lung microcirculation. Normal fibrinolytic mechanisms are impaired, causing procoagulant and thrombotic events in the pulmonary capillaries, and these events further impair the oxygenation of blood and excretion of carbon dioxide, progressively increasing pulmonary vascular resistance and worsening pulmonary hypertension [1]. In patients with ARDS, all the aforementioned pathophysiologic events are associated with an increased risk of death [2–4]. Pulmonary hypertension might be further aggravated because of hypoxic pulmonary vasoconstriction, which preserves gas exchange, and/or protective mechanical ventilation with low tidal volume and moderate/high positive end-expiratory pressure (PEEP), which causes a variable degree of hypercapnia and subsequently vasoconstriction of the pulmonary vascular bed [5, 6]. The negative effect of pulmonary hypertension is particularly important in the performance of the right ventricle (RV). Acute cor pulmonale, described as RV dilation with septal dyskinesia, impairment of left ventricle diastolic filling, and compensatory tachycardia to preserve cardiac output, occurs in 25% of patients with ALI/ARDS receiving protective mechanical ventilation [6]. In this scenario, systemic vasodilators are not usually recommended because their benefit on pulmonary circulation is achieved at the cost of further aggravation of ventilation/perfusion mismatch due to increases in intrapulmonary shunt and hypoxemia induced by the simultaneous dilation of systemic and pulmonary vessels, and might favor systemic hypotension [5, 7].

Selective modulation of pulmonary perfusion in ARDS became feasible with the introduction of nitric oxide (NO). Inhaled NO not only reduced pulmonary hypertension, thus decreasing the RV load, but also improved matching of ventilation and perfusion, thus ameliorating hypoxemia [5, 7, 8]. Similar findings were reported in physiologic investigations using aerosolized prostacyclin [7]. Interestingly, combining inhaled NO with other interventions such us PEEP and prone positioning yielded additive results on oxygenation [9]. However, a recent systematic review and meta-analysis found no survival advantage, and possible increased mortality and renal dysfunction with NO, precluding its routine use in ALI/ARDS [10].

In this issue of Intensive Care Medicine, Cornet et al. [11] investigate the physiologic effect of a single 50-mg dose of sildenafil, a phosphodiesterase-5 inhibitor with non-urologic effects on right ventricular myocardium and

in pulmonary artery smooth-muscle cells [12], in ten patients with ARDS. Interestingly, they found that sildenafil modestly but significantly decreased pulmonary arterial pressure and pulmonary artery occlusion pressure without improving oxygenation at the same time the shunt fraction increased. The authors correctly conclude that selective pulmonary vasodilation was not achieved since the ratio of pulmonary to systemic vascular resistance and the ratio of pulmonary to systemic arterial pressure remain unchanged, which can explain the deterioration in shunt fraction and oxygenation. However, the results of the Cornet et al.'s study [11] deserve further comment and must be interpreted with caution. First, the number of patients included is rather low, and the effects, although significant, are small in magnitude. Moreover, most of the patients had sepsis requiring treatment with vasoactive drugs. In sepsis, NO-induced vasodilation probably increases the effect of sildenafil in the systemic circulation [5]. Second, patients initially presenting with bilateral infiltrates suggestive of bilateral pneumonia were excluded from the study. One a priori argument could attribute the failure to achieve selective pulmonary vasodilation to the lack of responsiveness of sildenafil on vessels in consolidated regions; however, this argument is speculative and severely restricts the number of patients that can be treated. Third, in Cornet et al.'s study [11], the right ventricular stroke work index improved even at moderate values of pulmonary hypertension. Recent data showed that a decreased cardiac index, lower RV stroke index, and left ventricle deformation are common in ARDS, even during protective mechanical ventilation with moderate PEEP [13]. In this context, vasodilators could decrease RV systolic overload and increase both right and left ventricle performance [13, 14]. Fourth, the effects of vasodilators on gas exchange must be individualized in each case. When positive pressure ventilation or prone positioning improves functional lung recruitment, selective lung vasodilators improve oxygenation [9]. However, this is not the case in most patients with ARDS [15, 16]. Therefore, the effect of aerosolized and/or systemic vasodilators must be weighed against their net effect on heart, lung, and whole-body oxygenation. In other words, if a vasodilator moderately worsens oxygenation and shunt fraction but improves RV performance without marked effects on oxygen delivery to peripheral tissues in a patient with ARDS and severe pulmonary artery hypertension, it is probably safe to continue treatment under strict monitoring and clinical control.

Nowadays, sildenafil is recommended to improve pulmonary hemodynamics at rest and during exercise in COPD and to reduce pulmonary vascular resistance in severe forms of pulmonary arterial hypertension, where it has shown survival benefits [12, 17]. Cornet et al.'s study [11] adds valuable physiologic information about the effects of a new and more specific vasodilator, sildenafil, in selected patients with ARDS. However, a literature search [5] reveals that a pulmonary vasodilator that is selective to lung vessels, does not cause impairment in hypoxic pulmonary vasoconstriction, and has no adverse effects is yet to be found. Until one is found, sildenafil should be considered experimental in the general ARDS population until well-designed clinical trials determine whether the benefits outweigh the risks, but it should also be considered potentially useful in patients with life-threatening acute cor pulmonale and stable systemic hemodynamics.

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