Editorial

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SARS-CoV-2 related right ventricular dysfunction

Disfunción del ventrículo derecho por SARS-CoV-2

Disfunção ventricular direita devido a SARS-CoV-2

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As the SARS-CoV-2 pandemic continues and spreads, new variants of the virus appear, associated with greater contagiousness, which together with social fatigue after more than a year of confinement of various kinds that has led to the relaxation of social distancing measures, we understand more about this complex new disease and we realize the complexity of vaccinating all of humanity in the short term.

Although the lung is generally the shock organ, COVID-19 is a complex systemic disease affecting all the economy and in about 5% of cases it can course with such a hard and erratic evolution, reaching the definition of a critical illness whose full impact is not yet completely understood. ARDS a serious complication in these circumstances usually requires intelligent and tailored mechanical ventilation and all the ongoing multi-systemic support that only an intensive care unit can offer.

In addition to the basic pathophysiological mechanisms of multi-organ injury produced by SARS-CoV-2, there are different pathophysiological mechanisms through which the heart can be damaged in this disease, that include a hypercoagulable state, vascular inflammation and endothelial damage as well as thrombosis, accompanied by hypoxemia, severe alveolar injury, abnormalities in the pulmonary circulation and pulmonary arterial hypertension, which require the use of mechanical ventilation, as well as B-cells activation related immune damage with the release of vasoactive mediators, phenomena of vasoconstriction with increased load on the right heart and pulmonary hypertension, and an over activation of monocytes and macrophages by T-cells that induces a cytokine storm, particularly IL-6, IL-10 and TNFa.

To date, the reported cardiovascular consequences of COVID-19 include ST elevation myocardial infarction, myocarditis, heart failure, pulmonary embolism (PE), arrhythmias, sudden death, pulmonary hypertension and right ventricular dysfunction (RVD). Right ventricle (RV) damage is quiet common in patients with COVID-19, which is associated with more severe symptoms, a higher frequency of kidney failure and worse clinical outcomes.

The lung's heart, the RV, suffers like this, serious attacks in critically ill patients due to SARS-CoV-2. RV afterload is usually increased by the effect of pulmonary hypertension as well as other factors that affect pulmonary circulation such as mechanical compression due to interstitial edema, microvascular thrombosis, hypoxic or mediator-induced pulmonary vasoconstriction, and remodeling of the pulmonary vascular musculature, and RV enlargement is not uncommon during mechanical ventilation, a form of life support that can contribute through increased intrathoracic pressure to hemodynamic collapse with significant deleterious effects on RV, especially through the effect of PEEP, mode of mechanical ventilation and the volume status. A frequency of RVD between 22 and 50% has been reported in cases of severe ARDS in the past.

As expected, there is also a high burden of RVD in critically ill patients with COVID-19 and this is associated with a high mortality; RV damage may be an association between myocardial damage and lung injury in COVID-19. RV pressure overload increases wall tension, increases myocardial oxygen consumption, and decreases RV oxygen supply during systole in an unusual state of systemic, persistent and severe hypoxemia. This further leads to myocardial ischaemia and reduces RV contractility. RV dilatation may precede development of acute *cor pulmonale*.

As we know, the RV is of a different architecture to the LV and has a complex 3D geometry, it is designed to deliver equivalent stroke volume to the lungs under lower pressure conditions to avoid overwhelming the low resistance pulmonary capillary bed, so that at the same degree of change in afterload, the decrease in stroke volume is much greater on the right side of the heart than on the left. The transverse section of the RV is crescent-shaped compared with the thick wall of the left ventricle, and its relative surface area is higher and the volume is lower. The thin RV free wall has greater compliance than the left ventricle. These anatomical features allow acute dilatation of the RV when there is a sharp increase in afterload. RV systolic function is sensitive to increased pressure, and a slight rise in pulmonary circulation resistance causes RV overload and impaired systolic function.

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Although the main mechanisms of damage to RV in COVID-19 through an increase in afterload and decrease in its contractility are ARDS per se and PE, direct viral injury, hypoxemia, inflammation and immune response may also contribute.

Although the conventional echocardiographic parameters are not sensitive to early RV systolic dysfunction and the limitation of not obtaining a good window with the presence of PEEP, the method of choice for making the diagnosis of dilatation and RVD is the transthoracic echocardiogram, many times with elevated cardiac biomarker concentrations which has allowed the identification of between 20 and 28% of acute myocardial injury in hospitalized patients during the pandemic.

RVD is present when the following parameters used to quantify RV function are less than low values in the normal range: pulsed Doppler systolic myocardial velocity < 9.5 cm/s, tricuspid annular plane systolic excursion (TAPSE) < 17 mm, RV ejection fraction < 45%, and RV fractional area change < 35%. RV dilatation is usually observed early in the pressure-overloaded right ventricle. Typically, in the RV-focused view, a basal diameter > 41 mm and an intermediate horizontal diameter > 35 mm indicate RV dilatation. Most inpatients with COVID-19 have RV dilatation or dysfunction, being LV dysfunction less common.

It seems that severe COVID-19 ARDS is associated with a specific phenotype of RV radial impairment with sparing of longitudinal function, so it is important to avoid interpretation of RV proficiency based only on echocardiographic long-axis parameters in these patients. RV-PA coupling potentially provides important additional information above standard measures of RV performance in this type of patients. RV FAC correlates with markers of cardiac stress (hs-TnI and NTpro-BNP) and pulmonary vascular resistance (PVR).

Magnetic resonance image (MRI) can be used to quantitatively assess myocardial fibrosis and edema. This technique is currently the gold standard for evaluating cardiac morphology and function, although its role cannot be fully deployed in times of pandemic, due to various inconveniences such as mobilizing infectious critical patients outside the ICU, mechanical ventilators with metal components, limited availability, speed of image acquisition and costs between others. It includes analysis of conventional sequences and quantitative mapping sequences, to quantitatively assess diffuse fibrosis and quantificate the severity of edema, a very common post-COVID finding (54 to 60% of cases). Post-contrast T1 mapping can better obtain extracellular volume fraction, which can be used as the most sensitive biomarker of myocardial fibrosis and is highly consistent with histopathological findings. Some of these changes of sustained cardiac involvement, including edema, fibrosis, and impaired RV contractile function, may remain in patients who recover from COVID-19, aspect that requires careful study.

The therapeutic approach of RVD includes appropriate fluid replacement usually reducing volume load, enhancing RV contractility, and reducing pulmonary arterial pressure. Diuretics and ultrafiltration techniques can reduce intravascular volume. The RV Starling curve is flat, and improvement in RV function can only be observed with a large negative fluid balance. Normally, the RV filling pressure needs to be maintained at a slightly increased level (8-12 mmHg). Central venous pressure, mixed venous oxygen saturation, ultrasonography and echocardiography help determining the volume status, RV filling and O_2 supply.

Some pharmacological interventions in RVD deserve to be highlighted, since they can be indicated in its management, always in an individualized fashion.

If the therapeutic strategy includes increasing contractility, levosimendan a calcium sensitizer that stabilizes the spatial configuration of myocardial fibrin increasing myocardial contractility needs to be considered. This calcium sensitizer has the advantages of no effect on diastolic function or arrhythmia, and does not increase myocardial oxygen consumption. Levosimendan improves RV myocardial contractility and reduces RV afterload. Norepinephrine might improve RV function by restoring RV perfusion pressure as suggested experimentally in models of massive PE. Intravenous epoprostenol can improve symptoms, hemodynamics, and the survival rate, and enhance RV systolic function. Bosentan is a specific endothelin receptor antagonist, which reduces mean pulmonary arterial pressure and increases the cardiac index. Inhaled iloprost can also be useful under circumstances of pulmonary hypertension.

Milrinone a phosphodiesterase-3 inhibitor with a prominent vasodilator component can be wisely used in a critical closely monitored patient with RVD with infusions no longer than 48 hours because of arrhythmias, sometimes on top of other inotropes or pressor agents.

Special attention deserves the inhaled nitric oxide (iNO) a gaseous selective pulmonary vasodilator that reaches only ventilated regions of the lung, producing relaxation of the accompanying pulmonary capillaries, this specific vasodilator effect in well-ventilated alveolar units added to the pulmonary blood flow redistribution effect from unventilated to ventilated regions of the lung, explain the improvement in the ventilation-perfusion mismatch and oxygenation, as well as the decrease of the pulmonary vascular resistance and pulmonary artery pressure (PAP) that reduces the right ventricular afterload with almost no systemic side effects. There is enough experience with its use in ARDS since the

90's, enhancing the beneficial effects of protective ventilatory strategies that recruit and keep the lung open at the same time that significantly improve different pathophysiologic variables, although without showing a clear survival effect in small series of cases; so it is indicated in a dose-response fashion in patients who are in front of a severe acute RVD or in a phase of severely impaired gas exchange that is unresponsive to maximal medical therapy, and if successful this rescue treatment can help prevent multisystemic distant hypoxic organ damage and failure.

It may also be indicated in cases of heart disease, pulmonary arterial hypertension, thromboembolism, right ventricular failure, major lung resections and lung transplantation between others. Very low doses of only 10 ppm of iNO are able to enhance PaO_2, higher concentrations are necessary to decrease the elevated PAP. Its use as rescue therapy was reported during the 2009 AH1N1 influenza pandemic in different countries and since then it has been considered that ICU's treating severe influenza pneumonic cases should provide advanced ventilatory support and rescue therapies including iNO, very likely the same will happen now as more experience with severe cases of COVID-19 be achieved in the world, a more frequently related condition to venous thromboembolic disease and RVD than other viral pulmonary diseases.

Finally, it is worth mentioning the possibility of reducing afterload through the use of specific forms of mechanical ventilation, ECMO, ECCO2R and IABP, not forgetting the evidence of the protective role of prophylactic doses of low molecular weight or standard heparin.

We do not know the possible effect of systemic steroids and other anti-inflammatory and antifibrosing drugs on myocardial lesions associated with COVID-19, so we are sure of the need to generate new scientific knowledge on this delicate issue, the adverse effect that RVD has on COVID-19 mortality cannot be a coincidence and we must prepare to understand and combat it in a better way.

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