**"Happy" hypoxia in COVID-19:**

**What we learned from CT perfusion**

Paolo Pelosi, MD, FERS

Anesthesia and Intensive Care Unit - COVID-19 Critical Care Unit - San Martino Policlinico Hospital - IRCCS for Oncology and Neurosciences – University of Genoa - Genoa – Italy; email: *ppelosi@hotmail.com*

Coronavirus disease 2019 (COVID-19) pneumonia might affect different organs and be more correctly defined as Multiple Organ Dysfunction (MODS)-CoV-2 Syndrome, associated with systemic inflammatory response. It can cause severe respiratory failure requiring mechanical ventilation and multiple organ support. In early phases, often patients with COVID-19 pneumonia show a disconnection between profound hypoxemia without proportional signs of respiratory distress, renamed as “happy hypoxemia”, and rapid worsening can occur. This is a particular challenging clinical presentation for timely referral to advanced trespiratory support and intubation. Better understanding of the pathophysiological determinants of clinical presentation may optimize therapeutic management. The abnormalities observed on chest computed tomography (CT) and the clinical presentation of COVID-19 patients are not always like those of typical acute respiratory distress syndrome (ARDS) and can change over time. We identified three different chest CT patterns in COVID-19 pneumonia: 1) multiple, focal, possibly overperfused ground-glass opacities; 2) inhomogeneously distributed atelectasis; and 3) a patchy, ARDS-like pattern. Each phenotype can benefit from different treatments and individualized ventilator settings. By using CT perfusion techniques, it was possible to show that the distribution of perfusion is altered, higher in ground-glass regions, and following a non-gravitational pattern (in supine and prone position). The amount of hypoperfused areas (i.e. thrombotic) was associated with worse outcome. Higher levels of positive end-expiratory pressure (PEEP) was not associated with greater recruitment, as well as the use prone position. COVID-19 pneumonia is like “primary ARDS”, with minor interstitial and pulmonary edema, less atelectasis and less recruitment with higher pressures. Hypoxia alterations are best explained by alterations in regional alveolar ventilation (aeration)-perfusion (V/Q) relationships and less by true pulmonary shunt, depending to the severity of hypoxia. Peripheral macro- and microemboli are common, and attention should be paid to the risk of pulmonary embolism. Microthrombosis, within certain limits, might be even protective to keep “safe” oxygenation levels, otherwise increasing shunt. The overall evaluation of pulmonary and clinical pattern is mandatory to decide the use of non invasive or invasive respiratory support. In conclusion, preserved oxygen saturation despite low partial pressure of oxygen in arterial blood samples occur, due to leftward shift of the oxyhemoglobin dissociation curve induced by hypoxemia-driven hyperventilation as well as possible direct viral interactions with hemoglobin. Ventilation-perfusion mismatch, ranging from shunts to alveolar dead space ventilation, is the central hallmark and offers various therapeutic targets. We suggest three main pillars for therapeutic management of severe (MODS)-CoV-2 Syndrome: 1) the early use of corticosteroids; 2) the early use of anticoagulants from low molecular weight heparin to heparin and thrombolytics, according to clinical evolution and laboratory patters; 3) the use of personalized mechanical ventilation strategies based on respiratory mechanics and chest CT patterns. CT perfusion should become a standard to better understand pulmonary evolution pattern and optimize ventilatory treatment in COVID-19 pneumonia.