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Early View

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COVID-19 conundrum: Clinical phenotyping based on pathophysiology as a promising approach to guide therapy in a novel illness

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Twitter: The current evidence of COVID-19 pathophysiology supports the idea of specific phenotypes, and clinical phenotyping may be valuable to guide therapy.

Dear Editor,

We read with interest the recent editorial by Bos *et al* on the perils of premature phenotyping in COVID-19[1]. The authors concluded that a normal compliance variant of ARDS does not exist, based on two small cohort studies reporting low respiratory system compliance in COVID-19 patients[2, 3]. However, this assumption may be erroneous, as first, the admission and intubation thresholds are highly variable across units, resulting in marked heterogeneity. Secondly, several studies demonstrate that a high proportion of mechanically ventilated COVID-19 patients exhibit near-normal lung compliance [4–6].

These observations, on first glance, seem incompatible with the current understanding of ARDS pathophysiology, as profound hypoxemia and normal lung compliance rarely co-exist in ARDS[7]. A heuristic approach would be to ignore these inconsistencies, attempting to 'fit' them into existing paradigms. However, initial intuitions may often be wrong, and cognitive biases must be overcome to find a solution to this conundrum. Using a deductive approach, firstly the diagnostic criteria need a relook, to exclude misclassification as a reason for the observed clinico-pathological discrepancy.

How specific is the Berlin definition for underlying pathology?

ARDS is characterized by diffuse alveolar damage (DAD), with increased pulmonary vascular permeability, loss of aerated lung tissue and low respiratory system compliance [8]. However, several unrelated pathologies such as eosinophilic pneumonia or diffuse alveolar haemorrhage may cause respiratory failure fulfilling the clinical criteria for ARDS[9]. Accordingly, these *ARDS mimics* [9] require specific treatment based on their underlying pathophysiology.

Several other conditions presenting with hypoxemia and *normal lung compliance* may additionally be misclassified as ARDS; diffuse microvascular pulmonary thrombosis being one such pathology. In a case report [10], the clinical presentation was 'ARDS-like', with profound hypoxemia and bilateral infiltrates on radiology, but with normal ventilatory parameters on spirometry. Such disorders, where perfusion impairment is the dominant mechanism for hypoxemia, cannot be considered as 'true' ARDS[6]. This lack of diagnostic specificity of the Berlin definition could be due to the omission of objective indicators of lung volume loss, such as low respiratory system compliance, in its final version[8].

Perfusion loss from in-situ thrombosis may be the dominant initial pathology in COVID-19 lung injury

The early radiological changes of ground glassing and consolidation in COVID-19 were considered to be infective or inflammatory in aetiology[11]. However, recent paired parenchymal-perfusion imaging studies demonstrate well-demarcated perfusion defects underlying these changes, implicating a thrombotic aetiology [4, 12–16]. Unmatched defects are also seen[4, 15]. Moreover, the parenchymal changes follow a peripheral 'vascular distribution' which are often wedge-shaped [11, 16]. These findings suggest that the primary insult is vaso-occlusive, as infections or inflammation are rarely confined to vascular boundaries. Additionally, proximal vascular dilatation suggests distal vessel occlusion[13, 16] Interestingly, rapid radiological resolution and clinical improvement with inhaled thrombolytics have been described in a small case series[17].

Autopsy findings of viral endotheliitis, further clarify the pathogenesis of thrombotic manifestations in COVID-19 [18, 19] with a prothrombotic cytokine response[20] that mirrors the response seen in extensive vascular injury[21]. Further, natural and iatrogenic sequelae could explain the observed phenotypic heterogeneity of COVID-19 [5, 7] (Figure 1). Of note, DAD is not universally found on autopsies[22], suggesting this as a sequela and the terminal pathology than the index event. On the other hand, diffuse pulmonary microthrombosis is consistently visible on autopsies. [18, 22, 23].

Perfusion loss is the primary mechanism of hypoxemia in early COVID-19 respiratory failure

The early COVID-19 respiratory failure phenotype, with hypoxemia in the presence of preserved lung mechanics[4–6] suggests perfusion impairments as the main pathophysiology. Although the ground glass changes signify ventilatory impairments, owing to perfusion loss, the affected alveoli act as dead spaces rather than shunts. In this situation, hypoxemia occurs primarily due to flow redistribution and overperfusion involving a significantly reduced vascular bed resulting in ventilation/perfusion mismatch [24, 25]. This typically requires loss of 40 to 50 percent of pulmonary vascular bed before clinically significant hypoxemia could occur, indicating a large reserve. Reduced mixed venous saturation could further exacerbate hypoxemia. Also, during extensive obstruction, available time for red cell oxygenation within the alveolar capillaries may be reduced, due to insufficient microcirculatory recruitment and increased flow velocities. Diffusion limitation may result, further aggravating hypoxemia [24, 25]. These insights are key to understanding the clinical phenotypes of COVID-19 lung injury.

Clinical phenotype of perfusion loss differs markedly from that of primary alveolar disease

While hypoxemia can result either from ventilatory impairments or from disorders of alveolar perfusion, there are stark differences in their clinical features. In alveolar diseases such as pneumonia, shunt perfusion results in early hypoxemia, with clinically proportionate dyspnea due to abnormal lung compliance. However, in progressive perfusion loss, hypoxemia manifests late due to the large lung perfusion reserve, initial ventilatory compensation that mitigates ventilation/perfusion mismatch from overperfusion, and adequate initial right ventricular compensation to acute pressure overload. Further, unlike ventilatory disorders, the initial hypoxemia in this situation may be ‘silent’ owing to minimal parenchymal injury and normal lung compliance, at this stage. However, once dyspnea sets in, there would be rapid clinical progression whereby minor changes in mixed venous saturations or transit time could result in major changes in systemic oxygen saturation. Correspondingly, as the perfusion reserve continues to decline, physiological stress and exertion would be poorly tolerated.

Eventually, right heart compromise would result in cardio-respiratory collapse and rapidly progressing multi-organ failure.

Summary and conclusions

Although COVID-19 respiratory failure may fulfil the Berlin criteria, it would be inappropriate to describe the early lung pathology of progressive pulmonary in-situ thrombosis as ARDS. Evidence-based therapies for ARDS may not be applicable at this stage of illness as the lung mechanics and hemodynamics mirror that of a large pulmonary embolism. Moreover, a protocol-based 'one size fits all' approach could potentially be catastrophic, as employing a high positive end-expiratory pressure strategy in a normally compliant lung would result in significant barotrauma and deterioration of right heart dysfunction. As lung pathology appears grossly different at various stages of illness, a tailored phenotypic approach to management, guided by pathophysiology, would be more appropriate than a syndromic approach.

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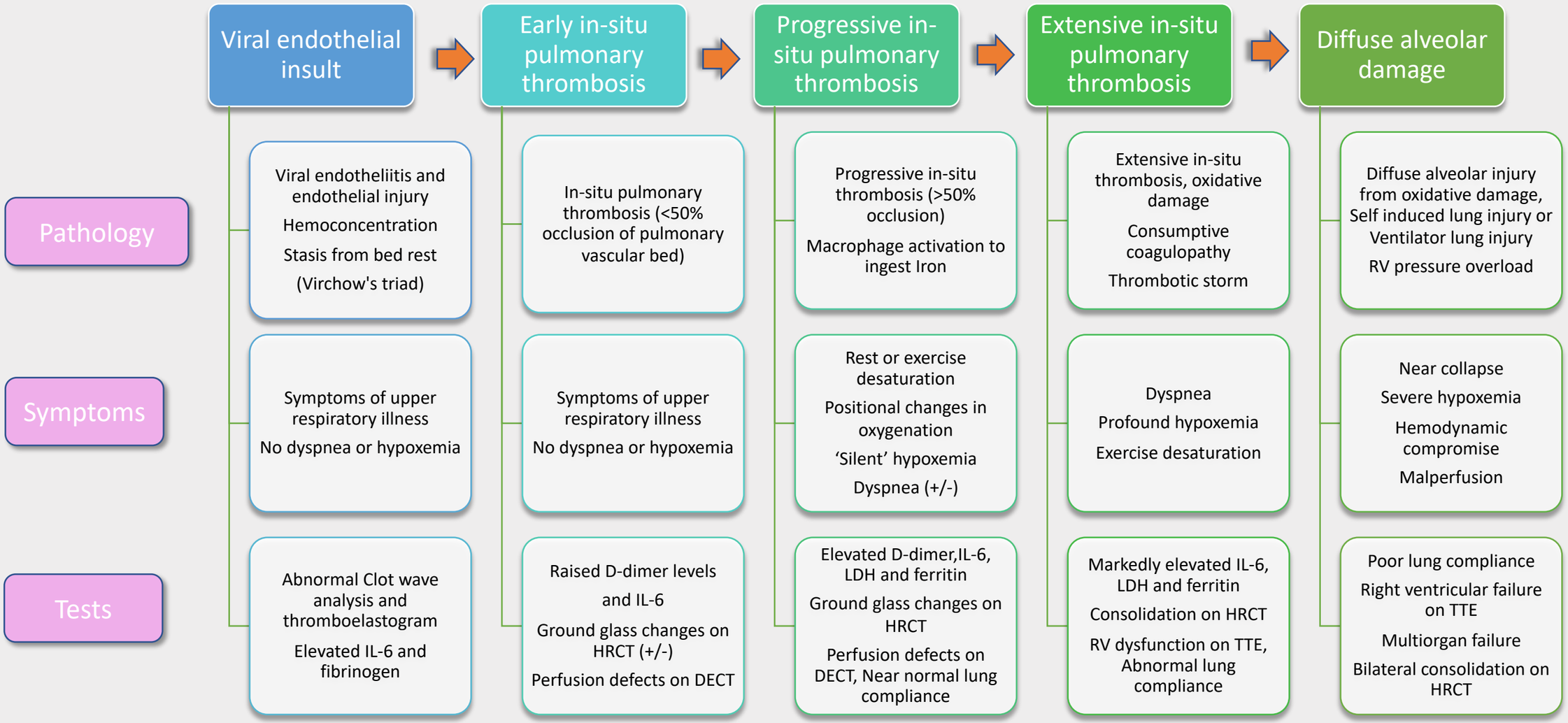

Figure 1: Progression of COVID-19 related lung injury and respiratory failure

Caption : *Viremia with viral endotheliitis fuels an inflammatory response appropriate for vascular injury, resulting in a prothrombotic state. Interleukin-6 upregulates fibrinogen gene expression. Pulmonary in-situ thrombosis is facilitated by Virchow's triad. Early disease is subclinical due to lung perfusion reserve. Progression may be aborted in young individuals with rapid endothelial turnover and robust intrinsic thrombolysis. Progressive in-situ microvascular thrombosis eventually leads to hypoxemia when reserves are exhausted. Initial hypoxemia may be silent (no dyspnea) as lung compliance is normal. Oxidative damage from iron and heme in the presence of unextracted alveolar oxygen after perfusion loss, may be a major determinant of parenchymal injury. Additionally, self-induced lung injury, ventilator lung injury and secondary infections result in diffuse alveolar damage. D-dimer, Lactate dehydrogenase and ferritin are elevated sequentially. Pulmonary in-situ thrombosis as the initial insult and major determinant of COVID-19 related lung injury explains the observed clinical phenotypes and disease spectrum. Early risk stratification and anticoagulation may avert thrombotic storm.*

Abbreviations: *IL-6 : Interleukin-6, HRCT: high resolution computed tomography; DECT: Dual energy perfusion computed tomography; TTE: Transthoracic echocardiogram; ARDS: acute respiratory distress syndrome; RV: right ventricle ; LDH: lactate dehydrogenase*