Intrapulmonary shunt measured by bedside pulse oximetry predicts worse outcomes in severe COVID-19

To the Editor:

Hypoxaemia is a key indicator for hospital admission with coronavirus disease 2019 (COVID-19) [1, 2]. Controversy surrounds the pathophysiology underlying hypoxaemia, with intrapulmonary shunt, mismatch in ventilation-to-perfusion (V'_A/Q') ratio, endothelial injury, microvascular coagulation and host inflammatory response hypothesised to play a role [3–6]. It has recently been proposed that COVID-19 pneumonia may exist as two phenotypes dependent on the preservation of lung mechanics and the relative contribution of V'_A/Q' mismatch and intrapulmonary shunting to hypoxaemia [7]. We hypothesised that V'_A/Q' mismatch and intrapulmonary shunting are present in COVID-19 pneumonia and aimed to assess their effect on outcome. A mathematical model was used to construct oxygen–haemoglobin dissociation curves (ODC) [8] to determine the degree of shunt and V'_A/Q' mismatch in a cohort of patients with severe COVID-19. Factors contributing to shunt and mortality were identified.

All patients presenting to our hospital in March 2020 with a diagnosis of COVID-19 through real-time PCR were included [1]. The study was approved by the local patient safety and quality control committee. The Medical Research Council ethics decision tool indicates that this research does not require review by an NHS Research Ethics Committee in England. As all patient data was anonymised, informed consent was not deemed necessary for this study, in line with local guidance.

Epidemiological, clinical, laboratory and radiological characteristics were collected in addition to level of oxygen therapy required and outcome. Unless anticoagulated prior to admission, all patients received venous thromboembolism prophylaxis. The NEWS2 score was used for all patients, a validated aggregate scoring system of patient physiological observations [9].

We retrospectively collected fingertip pulse oximetry data documented by paramedics and the emergency department. Two saturations at different inspired oxygen fraction (F_{IO_2}) values taken on admission and less than 6 h apart were used to construct ODCs. In 10 patients, the model was unable to derive a curve for the calculation of V'_A/Q'. This was likely because these patients deteriorated rapidly on admission, skewing the data. However, the model was still able to calculate intrapulmonary shunt for these patients using a single data point.

The construction of ODCs has been described in detail elsewhere (figure 1) [7, 8]. The method uses a two-compartment model [10] and corrects for haemoglobin concentration. Shunting reduces arterial oxygen saturation through arteriovenous admixture which cannot be corrected by increasing F_{IO_2}. The shunt can therefore be calculated from depression of the ODC [10]. V'_A/Q' reduction decreases post-alveolar blood oxygen content, shifting the ODC rightwards [10]. This is reversible by increasing F_{IO_2}. These parameters are quantified by comparison to a reference curve.

Spearman rank correlation co-efficient was used to examine the relationship between shunt and clinical parameters.

In March 2020, 108 patients were admitted with confirmed COVID-19 [1]. 14 not requiring oxygen and seven without adequate data available were excluded. The remaining 87 were included. Mean±SD age was 68.3±1.8 years and 41% (n=36) were female. Body mass index was 28.3±0.1 kg·m^{-2}. 65 patients (75%) were white British; eight (9%) white other; eight (9%) black, Asian, or minority ethnic (BAME); and six (7%) unknown ethnicity. 46% of patients were ex- or current smokers. Cardiovascular diseases (hypertension
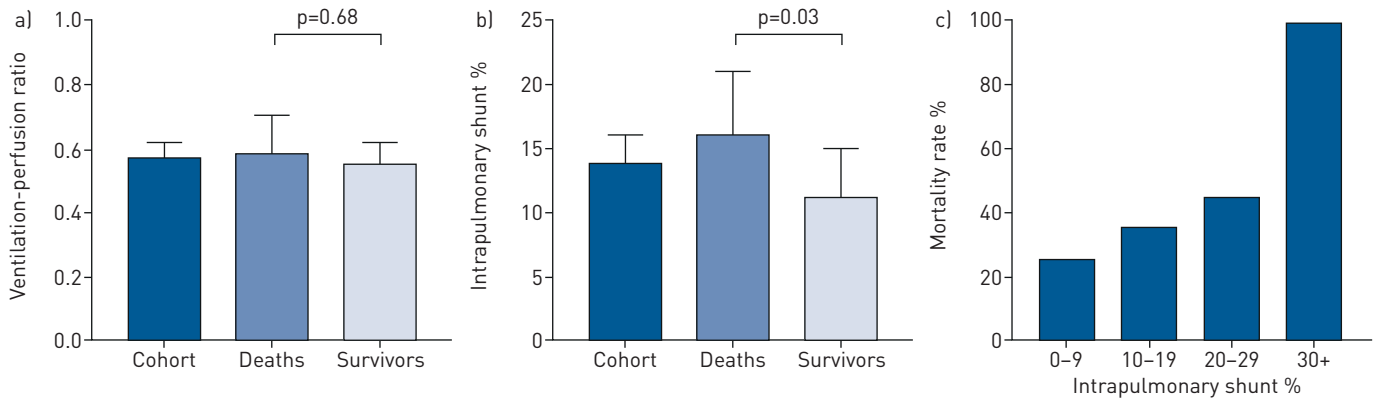
FIGURE 1 a) Ventilation-to-perfusion ratio in the death and survivor groups. b) Intrapulmonary shunt in the death and survivor groups. c) Mortality rate at increasing level of intrapulmonary shunt.

(46%), stroke (16%), ischaemic heart disease (13%)), diabetes (25%) and respiratory diseases (asthma (15%), COPD (15%)) were the most common comorbidities. 24% of patients had previous or current cancer.

Baseline blood tests showed an activated inflammatory response (median C-reactive protein (CRP) 82, interquartile range (IQR) 49–156; lactate dehydrogenase (LDH) 628, 528–807; ferritin 926, 357–1620) and coagulation cascade (median D-dimer 1100, 663–1550). One patient had a possible pulmonary embolus on computed tomography pulmonary angiogram in addition to severe COVID-19 changes. 31 patients (36%) died.

The median shunt was 14% (IQR 4–21%) and V'_A/Q' was 0.58 (IQR 0.50–0.68) (figure 1). Shunt was 45% higher (p=0.03) in patients that died (16%, IQR 6–23%) than in those who survived (11%, IQR 1–17%) (figure 1). There was no difference (p=0.69) between the median V'_A/Q' ratio of patients that died (0.59, IQR 0.49–0.70) and those that survived (0.50, IQR 0.56–0.68). Mortality rate increased with shunt severity (figure 1). All five patients with a shunt greater than 30% died.

Shunt was related to admission NEWS2 score (Spearman correlation coefficient 0.33, p=0.0002), CRP (0.38, p=0.001), LDH (0.45, p=0.002) and urea (0.29, p=0.007), as well as duration of continuous positive airway pressure (CPAP) therapy (0.40, p=0.001) and length of hospital stay (0.25, p=0.02). V'_A/Q' mismatch was not related to any measured parameters.

The pathophysiology underlying hypoxaemia in COVID-19 is controversial [3–5]. This study identifies intrapulmonary shunt as a major pathophysiological mechanism. Shunt severity was predictive of worse outcome: longer length of stay; longer CPAP duration; and higher mortality. Furthermore, shunt correlated with CRP and LDH, but not D-dimer. V'_A/Q' mismatch, although present, was not prognostic.

Micro- and macrovascular thromboses within the pulmonary architecture [5] have been implicated in the pathogenesis of COVID-19 hypoxaemia. Dual-energy computed tomography scans identified profound perfusion abnormalities with shunting of blood to areas of lung with impaired gas exchange [6]. Our study confirms that pulmonary vascular shunting may play a significant role in the development of hypoxaemia in COVID-19. From a pathophysiological perspective, the strong correlation of CRP with intrapulmonary shunt and outcomes such as length of CPAP and death implies that a more profound inflammatory response correlates with more severe shunting, which in turn is related to worse clinical outcomes.

It has been hypothesised that COVID-19 pneumonia may exist on a spectrum between two phenotypes [7]. The less severe form ("type L") may be associated with preserved lung mechanics with hypoxia proposed to be secondary to localised pulmonary vascular inflammation impairing hypoxic pulmonary vasoconstriction and physiological V'_A/Q' matching. The more severe form ("type H") may be associated with a more "typical" acute respiratory distress syndrome picture: reduced lung compliance, enhanced inflammation and shunting. This theoretical model was derived from clinician observation and, to date, has not been formally confirmed. Our study provides evidence in favour of this hypothesis by confirming that more severe shunting is associated with worse outcomes, whilst V'_A/Q' mismatching does not correlate with severity of disease. The pathophysiology underlying a shunt means hypoxaemia cannot be completely reversed by increasing F_{IO_2}. This may provide an explanation for why these patients have worse outcomes. Further research may also provide insight into the underlying mechanisms responsible for "silent hypoxia" described in COVID-19 and the role of intrapulmonary shunting.

This study also demonstrates that oxygen saturations at two different F_{IO_2} values can be used to construct ODCs useful for predicting outcome. A simple computer-based algorithm was used that can be performed

at the bedside on admission and may help prioritise treatment pathways. The strength of this method is that the ODC is a predictable physical property of haemoglobin, which even in fluctuating clinical situations allows the objective and accurate measurement of shunting and V'_A/Q' mismatch. It performs well against more complex methods [11].

This study is limited by the small sample size. However, numbers are in excess of studies using this technique in other clinical conditions (E. Russell-Jones and co-workers, unpublished results). Furthermore, the retrospective design means that oxygen saturations were taken up to 6 h apart. Future prospective studies will be able to collect oxygen saturations at different F_{IO_2} in a shorter time period, reducing the risk of patient deterioration in the interval period.

This study highlights the utility of simple clinical measurements to construct an ODC quantifying shunt and V'_A/Q' mismatch in patients with COVID-19. We also show that the degree of shunt appears to predict outcome. Furthermore, these observations add to our understanding of the pathophysiological mechanisms responsible for hypoxaemia in COVID-19. Our study has significant clinical applicability. Our noninvasive method of early calculation of shunt could assist decisions on triaging and risk stratifying. Given, though, the limited number of subjects and retrospective nature of our study, the next phase of our research will aim to validate these results in a larger, prospective cohort.

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