Intrapulmonary Shunt and Alveolar Dead Space in a Cohort of Patients with Acute COVID-19 Pneumonitis and Early Recovery

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Short Title: Shunt and Dead Space in Acute COVID-19 Pneumonitis and Early Recovery

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**Author Contributions:**

The majority of the authors (PH, GKP, CEF, GH, TCA, AM, PDW, KK) met on at least a fortnightly basis remotely. The original idea and study design were conceived in these meetings (PH, GKP, CEF, GH, TCA, AM, PDW, KK). Ethics approval, subject identification, data collection, including clinical data, and data analysis occurred in Sweden (PH, RL, SH, JP). Analysis of the raw data signals was primarily performed by GKP, with discussion of signal analysis by all authors (PH, GKP, CEF, GH, TCA, AM, PDW, KK), and further data analysis, including statistical analysis in Sydney (KK, CEF, TCA). All stages of the study were discussed at fortnightly meetings, including trouble shooting of protocols, and quality control of the data. All authors contributed to the preparation of the manuscript and approved the final version.

**Conflict of Interest:**

AM has received consulting fees for medical education from Livanova, Equillum, Corvus and Jazz. PDW has received consulting fees from SMS Biotechnology and Third pole inc. PH received unconditional loan of the equipment used in this study from the Djurgården Hockey Club, Stockholm. No other author has a conflict of interest to declare.
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Take Home Message

Hypoxaemia in COVID-19 is due to a variable combination of intrapulmonary shunt and increased dead space, likely from both airspace and vascular pathology. Increased dead space present up to 2 months later suggests persistent pulmonary vascular pathology.

Word count: 3046
Abstract

**Background:** Pathological evidence suggests that COVID-19 pulmonary infection involves both alveolar damage (causing shunt) and diffuse micro-vascular thrombus formation (causing alveolar dead space). We propose that measuring respiratory gas exchange enables detection and quantification of these abnormalities. We aimed to measure shunt and alveolar deadspace in moderate COVID-19 during acute illness and recovery.

**Methods:** We studied 30 patients (22 males, age: 49.9±13.5 years) 3-15 days from symptom onset and again during recovery, 55±10 days later (n=17). Arterial blood (breathing ambient air) was collected while exhaled O2 and CO2 concentrations were measured, yielding alveolar-arterial differences for each gas (AaPO2, aAPCO2) from which shunt and alveolar dead space were computed.

**Measurements and Main Results:** For acute COVID-19 patients, group mean (range) for AaPO2 was 41.4 (-3.5 to 69.3) mmHg; aAPCO2 was 6.0 (-2.3 to 13.4) mmHg. Both shunt (% cardiac output) at 10.4 (0 to 22.0)% and alveolar dead space (% tidal volume) at 14.9 (0 to 32.3)% were elevated (normal: <5% and <10%, respectively), but not correlated (P=0.27). At recovery, shunt was 2.4 (0 to 6.1)% and alveolar dead space was 8.5 (0 to 22.4)% (both P<0.05 versus acute); shunt was marginally elevated for 2 patients, however, 5 (30%) had elevated alveolar dead space.

**Conclusions:** We speculate impaired pulmonary gas exchange in early COVID-19 pneumonitis arises from two concurrent, independent and variable processes (alveolar filling and pulmonary vascular obstruction). For most patients these resolve within weeks, however, high alveolar dead space in ~30% of recovered patients suggests persistent pulmonary vascular pathology.
**Introduction**

Since the beginning of 2020, over half a billion people have been diagnosed with COVID-19, a disease caused by infection with the novel corona virus SARS-CoV-2. Many have required hospitalisation, with 10-20% of those requiring intensive care, mainly due to respiratory compromise [1]. World-wide there have been more than 6 million deaths.

Patients with early COVID-19 respiratory failure present with hypoxemia and hyperventilation [2] [3-6]. The hypoxaemia is likely related to ventilation/perfusion $V_A/\dot{Q}$ mismatch, and in particular to increased intrapulmonary shunt arising from alveolar filling with fluid or cellular debris. However, pathology reports from COVID-19 infected lungs also frequently demonstrate pulmonary vasculature involvement, including severe endothelial injury, widespread thrombosis with microangiopathy, and new vessel growth [7] [8] [9]. Pulmonary vessel micro-embolism reduces capillary blood flow, thus generating areas of high $V_A/\dot{Q}$ and promoting increased alveolar dead space.

We hypothesized that in early COVID-19 pneumonitis, hypoxaemia is associated with both increased intrapulmonary shunt and increased alveolar dead space. Using bed-side measurement of exhaled PO$_2$ and PCO$_2$, combined with arterial blood gas measurements, we measured alveolar-arterial partial pressure differences for both O$_2$ (AaPO$_2$) and CO$_2$, (aAPCO$_2$), from which both intrapulmonary shunt and alveolar dead space values were then determined using a novel computational model [10].
Methods

Subjects

Thirty patients admitted to Danderyd Hospital in Stockholm, Sweden who were ≥18 years old and PCR positive for SARS-CoV-2 were recruited between November and December 2020. Patients were excluded if they were in immediate need of intubation or mechanical ventilation, had advanced pulmonary or cardiac disease, current malignancy, previous thromboembolic disease, current pregnancy, or were unable to tolerate the study protocol, which required spontaneous breathing of ambient air for several minutes. Data were collected within 24 hours of presentation to hospital and again 55 ± 10 days after discharge in early recovery (n=17). 13 patients did not return for follow up. A subset of the acute data has been reported previously [6].

Thirteen healthy volunteers, negative for SARS-CoV-2 on PCR testing, and with normal pulmonary function (Vyaire-Vyntus Spiro PC-spirometer with SentrySuite Software, Vyaire, Mettawa, Illinois) were recruited from hospital staff as methodological controls.

All participants gave written informed consent, and the study protocol was approved by the Swedish Ethical Review Authority, diary number 2020-02966.

Clinical Data

Anthropometric and demographic data were collected, along with body temperature for the acutely ill. Pathology test results, pharmacological interventions, respiratory support (including oxygen therapy), and duration of hospitalization data were also collected.

Study Protocol
Subjects were studied in a semi-recumbent position, wearing a noseclip and breathing ambient air via a mouthpiece with antivirus filter (MicroGard II, Vyaire Medical GmbH, Hoechberg, Germany, apparatus dead space 75ml) attached to an inspired/expired gas measurement system (Vyaire Oxycon Pro, Hoechberg, Germany). Collected data included PO$_2$, PCO$_2$ and respiratory gas flow at high sampling frequency (100 Hz). After a few minutes of adaptation, participants maintained steady state breathing (end-tidal PCO$_2$ within ±2 mmHg across several breaths) at a (metronome facilitated) frequency and tidal volume of their choice. Data were recorded over a steady-state 3-5 minute period, during which radial arterial blood was collected over several breaths and then processed immediately (Radiometer ABL800 Flex Plus, Radiometer Medical ApS, Bronshoj, Denmark) to obtain values for arterial PO$_2$ ($P_aO_2$) and PCO$_2$ ($P_aCO_2$). For the acute patient studies, arterial blood gas values were expressed at body temperature [11]. Recovered patients and healthy subjects were assumed to have a body temperature of 37ºC.

*Exhaled Gas Analysis.*

Three separate breaths, preceding the arterial blood sample by 35 ± 10 seconds, were selected, independently analyzed, and resulting parameters averaged. Following alignment of gas and volume signals, PO$_2$ and PCO$_2$ values for each breath were plotted as a function of expired volume, and a linear least-squares fit applied to the alveolar plateau (Phase III, see Figure 1). Mean alveolar gas values, $P_{alv}O_2$ and $P_{alv}CO_2$ [10] at the mid-point (by volume) of the expired breath were determined from the fitted lines. Exhaled gas measurements in the acute patient studies were corrected for water vapour pressure at body temperature using Antoine’s formula [12]. Alveolar-arterial partial pressure differences for both O$_2$ and CO$_2$ were then calculated as $P_{alv}O_2 - P_aO_2$ (AaPO$_2$) and $P_aCO_2 - P_{alv}CO_2$ (aAPCO$_2$).
Computational Analysis

We employed the 7-decade old, 3-compartment lung model of Riley and Courand [13] to calculate shunt and alveolar dead space from AaPO$_2$ and aAPCO$_2$. In this model, the lung is considered to have an intrapulmonary shunt compartment with a $V_A/Q$ of 0, also encompassing regions of very low $V_A/Q$, and an alveolar dead space compartment with $V_A/Q$ of infinity, also encompassing regions of very high $V_A/Q$. The remainder of the lung is assumed to be normal, with a $V_A/Q$ ratio given by non dead space ventilation divided by non-shunt blood flow. A critical difference exists between the Riley and Courand model and the current approach: Riley and Courand used the venous admixture equation for O$_2$ to calculate shunt and the Bohr equation for CO$_2$ to calculate dead space. However, shunt may increase arterial PCO$_2$ and contribute to calculated alveolar dead space, while deadspace (without compensatory hyperventilation) lowers arterial PO$_2$ and contributes to calculated shunt. Our approach [10] recognizes this complexity and resolves it, still within the three-compartment framework, by determining the values of shunt and dead space that, present together, predict the measured arterial and expired alveolar PO$_2$ and PCO$_2$ values and hence their partial pressure differences. In addition, the Bohr equation usually includes anatomic dead space which commonly dominates total dead space numbers. Our approach eliminates anatomic dead space by using mean alveolar partial pressures as in Figure 1, and not those of mixed exhaled gas.

Using the measured $VCO_2$ (respiratory frequency x volume CO$_2$ per breath), $P_{ah}O_2$, fractional alveolar oxygen concentration ($F_{A}O_2$), $P_{ah}CO_2$, and fractional alveolar carbon dioxide concentration ($F_{A}CO_2$), we calculated:

1. total expired alveolar ventilation $V_A = V CO_2 / F_{A}CO_2$
2. inspired alveolar ventilation \( \dot{V}_t = \dot{V}_A \frac{1-F_A O_2 - F_A CO_2}{1-F_I O_2} \)

3. \( \dot{V} O_2 = \dot{V}_1 x F_I O_2 - \dot{V}_A x F_A O_2 \)

Cardiac output \((\dot{Q}_T)\) was then estimated as \( \dot{Q}_T = 5 \dot{V} O_2 + 5 \) with both \( \dot{Q}_T \) and \( \dot{V} O_2 \) expressed in L/min [14, 15]. The oxygen tension at which hemoglobin is 50% saturated (HbP\(_{50}\)) was assumed to be 26.8 mmHg. Using these values and each patient’s own data for \( \dot{V} O_2 \), \( \dot{V} CO_2 \), \( \dot{V}_A \), \( \dot{Q}_T \), base excess, hemoglobin concentration and body temperature, we applied the algorithm first published by West in 1969 [16] to estimate the values of intrapulmonary shunt and alveolar dead space that would result in the measured \( P_a O_2 \) and \( P_a CO_2 \) in each individual to within 0.2 mmHg.

Intrapulmonary shunt was expressed as the percentage of pulmonary blood flow perfusing unventilated regions (shunt %), while alveolar dead space was expressed as the percentage of alveolar ventilation associated with unperfused regions (alveolar dead space %). Based on published measurements using the multiple inert gas elimination technique in normal subjects [17], the 95% upper confidence limit for physiological shunt is 5% and for alveolar dead space is 10%. Further methodological details can be found elsewhere[10].

**Statistical Analysis**

This was an observational study and a sample size was not calculated. Individual data were pooled and reported as group mean \( \pm \) standard deviation or inter quartile range (IQR). Comparisons were made using paired t-tests. Relationships between variables were examined using Spearman’s rank correlation coefficients. P<0.05 was considered significant.

**Results**
Subject Characteristics

See Table 1.

Acute COVID-19 Patient Data

All patients had moderate disease and were studied at hospital presentation and within 3-15 days of symptom onset. Twenty four were admitted (mean stay 4.0±2.8 days, range 1-12), of these 18 required supplemental oxygen, and one was subsequently admitted to ICU. There were no deaths.

Pharmacological Interventions

Twenty two patients received prophylactic low molecular weight heparin, 12 less than 24 hours before the study (LMWH) (Tinzaparin, 4500E/d s.c), while therapeutic LMWH (Tinzaparin 175 U/kg bd/d s.c.) was administered to one patient. Post study, 14 patients received corticosteroids (Betamethasone 6 mg orally), 3 received Remdesivir, and convalescent plasma was administered to 2 patients.

Pathology Findings

C Reactive Protein levels were elevated in all patients, while almost 40% had elevated levels for D-Dimer (Table 2).

Arterial Blood Gas, Oxyhemoglobin Saturation and Exhaled Alveolar Gas Data

Arterial blood gas data reflected an acute respiratory alkalosis with hypoxemia (Table 3). \( P_{\text{alv}}O_2 \) values were all >102 mmHg, \( P_{\text{alv}}CO_2 \) values were all <38 mmHg and SaO2 were >89%.

Alveolar-Arterial Differences
There was wide inter-patient variance in AaPO$_2$ and aAPCO$_2$ (see Table 3 and Figure 2A). Any negative values (expected from experimental noise), were considered to be zero when calculating shunt and dead space.

**Intrapulmonary Shunt and Alveolar Dead Space**

Values for intrapulmonary shunt and alveolar dead space varied considerably between patients (Table 4, Figure 2B) but, importantly, there was no significant correlation between the shunt and dead space values (P=0.27). Significant positive correlations were detected between shunt and both D-Dimer (r=0.36, P=0.03) and CRP (r=0.42, P=0.01) but not for alveolar dead space (P>0.15).

Overall, 23 patients had an elevated shunt (defined as >5%), while 22 patients had elevated alveolar dead space (defined as >10%). Simultaneously increased shunt and dead space were present in 19 patients, 4 patients had elevated shunt but normal alveolar dead space and 3 had an elevated alveolar dead space but normal shunt (Figure 2B).

**Healthy Subject Data**

Healthy subjects were all normoxemic with normal acid-base status (see Table 3). No healthy subject had a shunt value >5% (Table 4, Figure 2B); two had slightly elevated values for dead space (Table 4, Figure 2B). Overall, shunt and dead space values from the healthy subjects conformed to the previously established upper limits of normal [17].

**Transition from Acute Illness to Recovery**
Shunt and alveolar dead space fell significantly following recovery (Figures 3 and 4). However, shunt was slightly elevated in 2 patients, while 5 (29.4%) had an elevated dead space. There was no correlation with duration after recovery (both p>0.15).

Discussion

Using simultaneous measurements of arterial and exhaled oxygen and carbon dioxide tensions, interpreted using a three-compartment computational lung model, we developed a bedside methodology for quantifying as if there is both intra-pulmonary shunt and alveolar dead space [10] and then applied it here in the highly infectious disease setting of COVID-19 pneumonitis. Measurements in a healthy subject cohort (technical controls) conformed to historical normal limits previously established by more sophisticated techniques [17].

Pulmonary Gas Exchange in Early COVID-19 Pneumonitis

The main finding from the present study is that in early acute COVID-19 pneumonitis intrapulmonary shunt is elevated for most patients, however, many also have an elevated alveolar dead-space. Furthermore, intrapulmonary shunt and dead space values were not correlated in moderate COVID-19 pneumonitis. Hence, dead space cannot be predicted from the magnitude of shunt and vice versa. This suggests that in early SARS CoV-2 pulmonary infection two pathophysiologically distinct process, either separately or together are in play: 1) patchy alveolar filling/edema/atelectasis (pneumonia) resulting in lung regions with low or zero $V_A/Q$ (ie shunt), and 2) patchy pulmonary vascular occlusion (emboli) resulting in high $V_A/Q$ regions (ie alveolar dead space). However, the relative contribution of these two processes is highly variable from patient to patient. This is similar to findings in intubated patients with severe ARDS, where
hypoxaemia is due to increased intrapulmonary shunt and increased dead space [18]. This is the first time that this has been demonstrated physiologically in mild/moderate COVID pneumonitis. While intrapulmonary shunt is perhaps an expected contributor to hypoxemia in a pulmonary viral infection [18], previous authors have suggested that for COVID-19 patients shunt values can be so elevated as to be considered “excessive” for the degree of lung injury present (2). This observation has led to the suggestion that SARS CoV-2 may specifically impair hypoxic pulmonary vasoconstriction (HPV), thus preventing HPV driven restriction of pulmonary capillary blood flow to lung regions with poor or no ventilation, increasing shunt [2, 19]. Whether intrapulmonary shunt values detected in the present study are “excessive” remains undetermined.

A major feature of our results was the high dead space values occurring in 73% of patients, with 63% having both elevated intrapulmonary shunt and dead space, and 10% having elevated dead space with no evidence of shunt. Increased alveolar dead space is a consequence of ventilation of under-perfused alveoli, and we speculate is consistent with reported diffuse and widespread small pulmonary arterial obstruction from thrombus formation, as detected in pulmonary pathological specimens [7, 20] from deceased COVID-19 patients. This interpretation is further supported by the absence of large vessel emboli on contrast CT imaging (performed for clinical purposes) in a sub-group (n=18) of the present patient cohort, although there was no correlation between dead space and d-dimer.

There is extensive pathological evidence of pulmonary micro-vascular involvement in COVID-19 pneumonia [20]. Histopathology of patients who died from COVID-19, compared with those who died from influenza, showed microvascular changes present in COVID-19 infected lungs
that were not present with influenza, including endothelial injury, alveolar capillary microthrombi, and new vessel growth [7]. In a study which correlated radiological findings with histopathological inflammation in 8 patients who died of COVID-19, there was evidence of vascular damage and thrombosis in regions without concurrent airspace involvement [21]. It has been proposed that the vascular injury may precede the development of frank pneumonia and alveolar filling [22].

High $V_A/Q$ regions (dead space) may also be a consequence of redistribution of ventilation from unventilated alveoli (shunt) resulting in relative over-ventilation of normally perfused alveoli. Our analysis adjusts for any effect of intrapulmonary shunt on aAPCO$_2$, so that redistribution of ventilation from obstructed ventilation zones is unlikely to contribute significantly to our measured dead space values.

**Pulmonary Gas Exchange in Early Recovery from COVID-19 Pneumonitis**

In recovery, intrapulmonary shunt decreased in all patients and values were within normal expected limits for all but two patients (see Figures 3 and 4). Consequently, ventilation was restored to lung zones previously identified as having no or very low alveolar ventilation. Dead space also decreased in most patients to within, or close to, normal expected limits (see Figures 3 and 4). However, in 5 patients, dead space was $>10\%$, ranging from 10.7\% to 22.4\%. Consequently, for most patients perfusion was restored to lung zones previously identified as having no or very low perfusion. However, for $\sim 30\%$ of those studied in recovery (see Figures 3D and 4), persistent, or even increasing, dead space values suggests persistent or evolving damage to the pulmonary vasculature. This may be a consequence of pre-morbid disease (eg COPD or interstitial lung disease). However, if a consequence of COVID-19 infection, this
finding is of particular interest, since recently published data [23] suggests that COVID-19 infection poses increased risk for deep vein thrombosis, pulmonary embolism, and bleeding episodes, at three, six, and two months (respectively) after an acute infection.

**Clinical Implications**

The finding that there is likely both acute and chronic pulmonary micro-vascular disease in COVID-19 pneumonitis has implications for the clinical management of patients, both in the acute and recovery phases of the disease process. For example, anti-coagulation with low molecular weight heparin has had mixed outcomes, with benefit in moderate disease, but no real improvement found in severe disease [24, 25]. Perhaps a clearer picture might emerge if outcomes were stratified by presence or absence of high $V_\theta/Q_\theta$ regions. Targeted therapeutic approaches may then be deployed for patients with increased dead space, who may need anticoagulation, versus those with shunt but low dead space, where anticoagulants may, in theory, have risk without major benefits. Application of this methodology could be used in patients with persistent COVID-19 symptoms to better delineate pulmonary pathology.

**Limitations**

This study was performed in a small sample of patients with early and mild/moderate disease, early in the pandemic, when few therapeutic interventions were available, and was restricted to those able to tolerate breathing room air. Also, recovery data were collected at only one time point, and we do not have follow up data on all patients. Consequently, it may not be generalizable to more severe disease. Other (pre-existing) co-morbidities such as anaemia may have impacted on our findings although there was no clinical evidence of these abnormalities.
The logistical limitations imposed by an acute airborne infection meant that we were unable to use more sophisticated techniques such as multiple inert gas elimination [26] or imaging tools [27].

We estimated cardiac output and Hb P50, required for the calculation of intrapulmonary shunt and deadspace. Cardiac output was determined from its well-documented relationship to $\dot{V}O_2$ [14, 15], which was measured; Hb P50 was taken to be 26.8 mmHg for all participants. Sensitivity analysis for these two uncertain variables shows a minor effect over a wide range of determined intrapulmonary shunt values, with no effect on dead space[10].

**Conclusions**

Our study shows that in early mild to moderate COVID-19 pneumonitis, there is both increased intrapulmonary shunt and increased alveolar dead space, with marked inter-patient variability and lack of correlation. These findings suggest that alveolar filling resulting in little or no ventilation to some alveoli, and pulmonary microvascular compromise, resulting in little or no blood flow to other alveoli, are both present to varying, but separate, degrees in the early phases of mild to moderate COVID-19 pneumonitis. For essentially all patients, shunt resolved in early recovery, however, for ~30% of patients, elevated dead space persisted, at least in the early recovery phase. Characterizing individual patient pulmonary pathophysiological responses may help inform more personalized approaches to effective treatments in both the acute and recovery phases of infection with SARS-CoV-2.
References


**Figure 1.** Expired gas tracings from one patient; PO$_2$ (top black line, red symbols and lines) and PCO$_2$ (bottom black line, blue symbols and lines). Dashed line indicates the beginning of alveolar emptying (Phase III), sloping dashed lines indicate the linear regression fits to Phase III. $P_A$CO$_2$ and $P_A$O$_2$ were measured from the mid-volume of the linear regression fit to Phase III (approximately 225 ml in this example). Filled symbols indicate mean alveolar values; open symbols indicate contemporaneous arterial values, arterial-alveolar differences are indicated by the solid vertical lines connecting them.

**Figure 2.** AaPO$_2$ and aAPCO$_2$ (A); intrapulmonary shunt and alveolar dead space (B). Acute COVID-19 patients (red symbols, n=30) and healthy subjects (green symbols, n=13). Dotted lines show 95% upper limits for normal (21).

**Figure 3:** Individual (symbols and lines), and grouped data (box plots: horizontal line=mean, box=IQR,whiskers=range) for 17 patients during acute COVID-19 infection and again in early recovery, together with 13 healthy individuals: (A) AaPO$_2$; (B) aAPCO$_2$; (C) Shunt; (D) Alveolar dead space. Dotted lines show the 95% upper confidence intervals for normal; **P<0.0001, *p<0.05.

**Figure 4.** Shunt and dead space trajectories from acute COVID-19 illness (red symbols) to recovery (blue symbols). Dashed lines connect paired acute and recovery data (n=17); dotted lines show the 95% upper confidence limits of normal.
Table 1: Anthropometric, demographic and body temperature data for acutely ill COVID-19 patients, recovered COVID-19 patients and healthy subjects.

<table>
<thead>
<tr>
<th></th>
<th>Acute (n=30)</th>
<th>Recovered (n=17)</th>
<th>Healthy (n=13)</th>
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</thead>
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<tr>
<td>Age (years)</td>
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<td>50.6±12.0</td>
<td>51.1±17.0</td>
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<td>Range:</td>
<td>23-78</td>
<td>51-78</td>
<td>34-68</td>
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<tr>
<td>Sex (F/M)</td>
<td>8/22</td>
<td>6/11</td>
<td>5/8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>87.5±17.0</td>
<td>87.5±18.2</td>
<td>80.2±26.1</td>
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<tr>
<td>Range:</td>
<td>46-113</td>
<td>46-110</td>
<td>58-110</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177.0±11.3</td>
<td>176.8±13.2</td>
<td>177.2±19.5</td>
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<tr>
<td>Range:</td>
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<td>150-195</td>
<td>159-198</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>27.8±4.3</td>
<td>27.9±4.7</td>
<td>25.5±6.0</td>
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<tr>
<td>Range:</td>
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<td>20.4-38.5</td>
<td>19.6-31.5</td>
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<tr>
<td>Body Temperature (ºC)</td>
<td>38.0±1.0</td>
<td>37.0 (assumed)</td>
<td>37.0 (assumed)</td>
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<tr>
<td>Range:</td>
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Data are mean ± SD, and range.
**Table 2:** Pathology data at the time of acute COVID-19 infection.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Mean±SD</th>
<th>Range</th>
<th>Number Abnormal n (%)</th>
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<tr>
<td>Hemoglobin (g/L) (n=29)</td>
<td>139.5±11.7</td>
<td>110-165</td>
<td>2 (6.8)</td>
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<tr>
<td>(117-153 for female, 134-170 for male)</td>
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<tr>
<td>D-Dimer (mg/L) (n=28)</td>
<td>0.8±0.6</td>
<td>0.3-3.2</td>
<td>11 (39.2)</td>
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<tr>
<td>(&lt;0.54 for female, &lt;0.50 for male)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C Reactive Protein (mg/L) (n=30)</td>
<td>79.1±65.7</td>
<td>3-256</td>
<td>30 (100)</td>
</tr>
<tr>
<td>(&lt;3)</td>
<td></td>
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Table 3: Arterial Blood Gases and Exhaled Alveolar Gas Measurements.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Acute (n=30)</th>
<th>Recovered (n=17)</th>
<th>Healthy (n=13)</th>
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<tr>
<td>pH Range</td>
<td>7.48±0.04</td>
<td>7.44±0.03</td>
<td>7.43±0.02</td>
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<tr>
<td>PaCO₂ (mm Hg) Range</td>
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<td>7.39 - 7.51</td>
<td>7.41 - 7.49</td>
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<tr>
<td>PaCO₂ (mm Hg)</td>
<td>34.8±4.2</td>
<td>34.4±3.7</td>
<td>37.0±2.8</td>
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<tr>
<td>Range</td>
<td>26.5 - 43.0</td>
<td>26.7 - 40.6</td>
<td>31.4 - 40.8</td>
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<tr>
<td>PaO₂ (mm Hg) Range</td>
<td>68.3±12.6</td>
<td>100.6±13.6</td>
<td>105.0±8.3</td>
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<tr>
<td>PaO₂ (mm Hg)</td>
<td>52.3 - 105.8</td>
<td>84.0 - 131.3</td>
<td>94.5 - 120.0</td>
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<tr>
<td>PalvO₂ (mm Hg) Range</td>
<td>113.3±5.7</td>
<td>113.6±6.3</td>
<td>119.5±5.1</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>30.3±4.0</td>
<td>31.4±3.1</td>
<td>35.2±2.9</td>
</tr>
<tr>
<td>Range</td>
<td>23.4 - 37.3</td>
<td>24.9 - 38.7</td>
<td>29.1 – 39.9</td>
</tr>
<tr>
<td>AaPO₂ (mm Hg) Range</td>
<td>41.4±16.3</td>
<td>13.0±9.7</td>
<td>6.5±6.9</td>
</tr>
<tr>
<td>Range</td>
<td>-3.5 - 69.3</td>
<td>-6.0 - 30.2</td>
<td>-5.8 - 21.4</td>
</tr>
<tr>
<td>aAPCO₂ (mm Hg) Range</td>
<td>6.0±4.2</td>
<td>3.0±2.3</td>
<td>1.8±1.9</td>
</tr>
<tr>
<td>Range</td>
<td>-2.3 - 13.4</td>
<td>-2.2 - 8.9</td>
<td>-1.4 - 6.0</td>
</tr>
<tr>
<td>SaO₂ (%) Range</td>
<td>94.3±0.2</td>
<td>98.7±0.5</td>
<td>98.9±0.2</td>
</tr>
<tr>
<td>Range</td>
<td>89.4 - 98.7</td>
<td>97.7 - 99.5</td>
<td>98.4 - 99.3</td>
</tr>
</tbody>
</table>

Note: All acute patient gas partial pressures are expressed at body temperature.
Table 4: Shunt and alveolar dead space in acute COVID-19 patients (including the subgroup of 17 studied later in recovery), recovered patients, and healthy subjects.

<table>
<thead>
<tr>
<th></th>
<th>Acute (n=30)</th>
<th>Acute (n=17)</th>
<th>Recovered (n=17)</th>
<th>Healthy (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shunt (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>10.4±5.4</td>
<td>11.7±5.1</td>
<td>2.4±1.9**</td>
<td>1.2±1.1</td>
</tr>
<tr>
<td></td>
<td>(0-22.0)</td>
<td>(4.1-22.0)</td>
<td>(0-6.1)</td>
<td>(0-4.1)</td>
</tr>
<tr>
<td><strong>Alveolar Dead Space (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>14.9±9.6</td>
<td>14.4±9.7</td>
<td>8.6±5.5*</td>
<td>4.7±4.3</td>
</tr>
<tr>
<td></td>
<td>(0-32.3)</td>
<td>(0-29.7)</td>
<td>(0-22.4)</td>
<td>(0-11.8)</td>
</tr>
</tbody>
</table>

**p<0.0001, p*<0.05 compared with acute subgroup,
A

AaPO$_2$ (mmHg)

aAPC$_2$ (mmHg)

B

Deadspace only

Shunt and Deadspace

Shunt only

Alveolar Dead Space (%)