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## Hypermetabolism and Coronavirus Disease 2019

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<PE-AT>Hypermetabolism and COVID-19

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**Abstract**

Background: Hypermetabolism has been described in stress states such as trauma, sepsis, ARDS, and severe burn injuries. We hypothesize that patients with COVID-19 may develop a hypermetabolic state which may be a major contributing factor to the extraordinary ventilatory and oxygenation demands in patients with COVID-19.

Method: Resting energy expenditure (REE), carbon dioxide production (VCO<sub>2</sub>) and oxygen consumption (VO<sub>2</sub>) were measured by indirect calorimetry on seven critically ill patients with COVID-19.

Results: The median measured REE was 4044 Kcal/day which was  $235.7\% \pm 51.7\%$  of predicted. The median VCO<sub>2</sub> was 452 mL/min (range 295-582 mL/min) and the median VO<sub>2</sub> was 585 mL/min (range 416-798 mL/min).

Conclusion: Critically ill patients with COVID-19 are in an extreme hypermetabolic state. This may explain the high failure rates for mechanical ventilation for these patients and highlights the potential need for increased nutritional requirements for such patients. <PE-FRONTEND>

## **Clinical Relevancy Statement**

We describe our findings that critically ill patients with COVID-19 are in an extreme hypermetabolic state with extraordinary oxygen consumption and carbon dioxide production. This may explain the high failure rates for mechanical ventilation for patients with severe COVID-19, may help direct nutritional requirements for such patients, and may also suggest targets for therapeutic interventions which have not been explored to date.

## **Introduction**

Many patients with Coronavirus disease 2019 (COVID-19) remain hypoxic and hypercarbic despite being on maximal ventilator settings. A dissociation between the degree of lung injury and the severity of hypoxia and hypercapnia has been observed in patients with COVID-19.<sup>1</sup> This suggests that the severity of acute respiratory failure of patients with COVID-19 may not be solely attributable to pulmonary compromise. As Acute Respiratory Distress Syndrome (ARDS) is associated with production of pro-inflammatory cytokines and induction of a hypermetabolic state,<sup>2</sup> we hypothesize that patients with COVID-19 may develop a hypermetabolic state which may be a major contributing factor to the extraordinary ventilatory and oxygenation demands in patients with COVID-19.

## **Methods and Results**

This retrospective case series included seven adults with confirmed COVID-19 requiring mechanical ventilation with continued hypercapnia and/or hypoxia. Resting energy expenditure (REE) was predicted using the Penn State equation and measured using CCM Express indirect calorimeter (MGC Diagnostics, Saint Paul, MN). All patients were on  $\text{FiO}_2$

≤ 60% and did not require renal replacement therapy and/or thoracostomy tubes to ensure the accuracy of the indirect calorimetry measurements.

All patients were on intravenous sedation infusions. Median age was 62 years (range 55-74 years), 5 (71.4%) patients were male, median length of intubation was 19 days (range 3-39 days). Median pCO<sub>2</sub> and pO<sub>2</sub> were 60 mmHg (range 53-72mmHg) and 75 mmHg (range 61-95mmHg), respectively. Indirect calorimetry results are shown in Table 1. The median measured REE was 4044 Kcal/day which was 235.7% ± 51.7% of predicted. The median VCO<sub>2</sub> was 452 mL/min (range 295-582 mL/min) and the median VO<sub>2</sub> was 585 mL/min (range 416-798 mL/min). Levels of inflammatory markers are shown in Table 2. There were no strong positive correlation between C-reactive protein and D-Dimer to both measured REE and measured REE/predicted REE (Pearson correlation coefficient < 0.5).

## Discussion

This case series demonstrates the significant metabolic demands of critically ill patients with COVID-19. Hypermetabolism has been described in stress states such as trauma, sepsis, ARDS, and severe burn injuries.<sup>2,3</sup> However, the measured resting energy expenditure seen in our case series of patients with COVID-19 far exceeds that described for other disease states.<sup>2,3</sup> The profoundly increased oxygen consumption and carbon dioxide production seen in our patient cohort as a result of their hypermetabolism may help explain the high failure rates for mechanical ventilation for patients with severe COVID-19. Some of these patients may be considered for extracorporeal membrane oxygenator support (ECMO), however, the oxygen consumption and carbon dioxide production in all seven patients in our

cohort would have exceeded the O<sub>2</sub> and CO<sub>2</sub> transfer capacity of typical adult oxygenators used in ECMO circuits.

These observations may suggest the need for increased feeding beyond the 15-20 kcal/kg actual body weight/day that is currently recommend for critically ill patients with COVID-19.<sup>4</sup> While patients with ARDS have energy expenditures that is approximately 30% above REE<sup>2</sup>, we found most patients with COVID-19 have energy expenditures of greater than 200% of REE. Adequate nutritional support is vital for preservation of respiratory muscle function, promotion of immune response to infection and mitigation of oxidative cellular injury.<sup>5</sup> However, given the extraordinarily high REE seen in patients with COVID-19, purely using REE measurements as targeted goal for nutritional calories in these patients may result in overfeeding and increased CO<sub>2</sub> production.<sup>6</sup> We are currently involved in studies looking at the ideal target calories relative to the REE measured from indirect calorimetry in critically ill patients with COVID-19.

In additional to having implications for the management of nutritional support in patients with COVID-19, our observations of extreme hypermetabolism in critically ill patients with COVID-19 suggest possible targets for therapeutic interventions which have not been explored to date. We are currently embarking on interventional studies aiming to decrease the metabolic demand of patients with COVID-19 and reconfiguring ECMO circuits to meet the increased need for gas exchange.

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TABLE 1: Indirect Calorimetry Results

Patient #	Age	Body Mass Index	Measured REE (Kcal/day)	Predicted REE (Kcal/day)	VCO2 (mL/min)	VO2 (mL/min)
1	62	26.6	5186	1733	582	750
2	74	24.6	2845	1296	303	416
3	70	37.5	3052	1865	295	455
4	57	28.1	4044	2108	452	585
5	57	27.4	3952	1955	468	565
6	69	25.1	4282	1617	401	642
7	55	25.2	5414	1753	555	798

REE = Resting Energy Expenditure

Table 2: Inflammatory Markers

Patient #	Hospital Day (#)	Measured REE (Kcal/day)	Measured REE/Predicted REE (% Predicted)	C-Reactive Protein (mg/dL)	D-Dimer (ng/mL)
1	8	5186	299	7.11	13862
2	8	2845	219	0.5	2894
3	22	3052	164	13.36	1160
4	23	4044	192	3.94	980
5	30	3952	202	13.38	2019
6	32	4282	265	14.5	560
7	55	5414	309	12.6	1393

REE = Resting Energy Expenditure