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Hypermetabolism in critically ill patients with COVID-19 and the effects of hypothermia: A case series

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ABSTRACT

Background: We have observed that critically ill patients with COVID-19 are in an extreme hypermetabolic state. This may be a major contributing factor to the extraordinary ventilatory and oxygenation demands seen in these patients. We aimed to quantify the extent of the hypermetabolic state and report the clinical effect of the use of hypothermia to decrease the metabolic demand in these patients.
Methods: Mild hypothermia was applied on four critically ill patients with COVID-19 for 48 h. Metabolic rates, carbon dioxide production and oxygen consumption were measured by indirect calorimetry.
Results: The average resting energy expenditure (REE) was 299% of predicted. Mild hypothermia decreased the REE on average of 27.0% with resultant declines in CO_2 production (VCO_2) and oxygen consumption (VO_2) by 29.2% and 25.7%, respectively. This decrease in VCO_2 and VO_2 was clinically manifested as improvements in hypercapnia (average of 19.1% decrease in pCO_2 levels) and oxygenation (average of 50.4% increase in pO_2).
Conclusion: Our case series demonstrates the extent of hypermetabolism in COVID-19 critical illness and suggests that mild hypothermia reduces the metabolic rate, improves hypercapnia and hypoxia in critically ill patients with COVID-19.

1. Introduction

Critically ill patients with coronavirus disease 2019 (COVID-19) have mortality rates of 50–88% which is higher than that seen in patients with other causes of acute respiratory distress syndrome (ARDS) [1–3]. We have observed that critically ill patients with COVID-19 are in an extreme hypermetabolic state which may be a major contributing factor to the extraordinary ventilatory and oxygenation demands seen in these patients. Hypothermia is widely used in cardiac surgery and patients after cardiac arrest to decrease metabolic demand for end organ preservation [4–7]. There are also limited reports of the use of therapeutic hypothermia in patients with ARDS [8–11]. However, the use of hypothermia to reduce the basal energy expenditure on patients with COVID-19 has not been described.

We report use of hypothermia in four patients with severe respiratory compromise secondary to COVID-19 with refractory hypercapnia and/or hypoxia despite optimal ventilator support. All four patients were in an extreme hypermetabolic state. Therapeutic hypothermia with a target temperature of 34.5 °C for 48 h was achieved using the Arctic Sun (Medivance Inc., Louiville, CO). Predicted metabolic rates were calculated using the Mifflin-St. Jeor Equation. Actual metabolic rates, carbon dioxide production and oxygen consumption were measured using the CCM Express indirect calorimeter (MGC Diagnostics, Saint Paul, MN). All arterial blood gas results were measured at a temperature of 37 °C.

2. Case series

2.1. Case 1

A 69 year old male with diabetes presented with shortness of breath found to be COVID-19 positive and emergently intubated. The patient received hydroxychloroquine, anakirna, corticosteriods, and convalescent plasma with worsening hypoxia and hypercarbia. The patient was hypermetabolic with a resting energy expenditure (REE) of 4282 Kcal/day (278.8% of predicted). He underwent therapeutic hypothermia on hospital day #32 with an average 20.9% reduction in REE, 8.3% reduction in pCO_2 and

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Table 1
Changes in indirect calorimetry.

Case #				% Change in REE		% Change in VCO2		% Change in VO2	
	Temperature baseline (^{0}C)	Measured REE (Kcal/day)	Measured/predicted REE (%)	Hypothermia	Rewarm	Hypothermia	Rewarm	Hypothermia	Rewarm
1	36.7	4282	278.8%	−20.9%	−13.2%	−33.1%	0.0%	−25.2%	−15.6%
2	36.2	3728	282.6%	−15.3%	−4.2%	−12.0%	7.9%	−15.9%	−6.2%
3	37.1	4381	261.7%	−6.4%	−9.9%	−31.2%	−25.6%	0.5%	−5.5%
4	35.9	6490	374.7%	−65.3%	−43.5%	−76.9%	−59.9%	−62.3%	−39.2%

REE = Resting Energy Expenditure.

improvement of PaO_2/FiO_2 (P/F) ratio from 93 to 263. All improvements were sustained after full rewarming. As the patient had no meaningful neurological status since intubation, the family elected for withdrawal of care and the patient expired hospital day #39. Patient's arterial blood gas prior to withdrawal was 7.39/60/100 (ventilator setting: assist control, tidal volume 4 cc/kg, respiratory rate 35 breaths per minute, PEEP of 5, FIO_2 55%).

2.2. Case 2

A 73 year old male with coronary artery disease and hypertension admitted with fevers and shortness of breath found to be COVID-19 positive with an acute pulmonary embolism. The patient was placed on systemic anticoagulation with progressive respiratory failure requiring intubation hospital day #3. The patient received hydroxychloroquine, corticosteriods, convalescent plasma, tocilizumab, and remdesivir with worsening hypoxia and hypercarbia. He was found to be hypermetabolic with an REE of 3728 Kcal/day (282.6% of predicted). He underwent therapeutic hypothermia on hospital day #12 with an average 15.3% reduction in REE, and 18.9% reduction in pCO_2. There was also an improvement in oxygenation, the PEEP was able to be reduced from 9 cm H_2O to 7 cm H_2O to maintain similar P/F ratios. The improvement in oxygenation was sustained after rewarming which allowed for the PEEP to be further reduced to 5 cm H_2O. Although the initial improvements in pCO_2 were sustained after full rewarming which allowed for the pressure support to be reduced from 40 cm H_2O to 33 cm H_2O, the patient became increasingly hypercarbic day #6 after full rewarming (hospital day #18). Patient's family requested palliative care and expired hospital day #32.

2.3. Case 3

A 57 year old obese male with no significant past medical history admitted for shortness of breath found to be COVID-19 positive, intubated on hospital day #8. The patient received hydroxychloroquine, corticosteriods, anakinra, and convalescent plasma with worsening hypoxia and respiratory acidosis (pH 7.1, pCO_2 >104 mmHg). He was found to be hypermetabolic with an REE of 4381 Kcal/day (261.7% of predicted). He underwent therapeutic hypothermia on hospital day #23 with an average 6.4% reduction in REE and 13.9% reduction in pCO_2. The P/F ratio improved from 160 to 319. These improvements were sustained after full rewarming. The patient is currently on CPAP trials.

2.4. Case 4

A 62 year old obese female with history of asthma admitted for fevers and shortness of breath found to be COVID-19 positive, intubated on hospital day #10. The patient received hydroxychloroquine, corticosteroids, and anakinra with worsening respiratory acidosis (pH 7.0, pCO_2 > 104 mmHg) with associated oliguric renal failure and hypotension requiring levophed, vasopressin and phenylephrine drips. She was found to be hypermetabolic with an REE of 6490 Kcal/day (374.7% of predicted) and underwent therapeutic hypothermia on hospital day #48 with an average 65.3% reduction in REE and 35.1% reduction in pCO_2. The patient's vasopressor requirements and renal function improved during hypothermia. These improvements were sustained after full rewarming. The patient was weaned off all vasopressors hospital day #53 and had full renal recovery. The patient is currently on CPAP trials.

3. Discussion

We report 4 cases of the application of hypothermia in hypermetabolic patients with COVID-19 with refractory hypercapnia and/or hypoxia with resultant decrease in metabolic demand and clinical improvement in respiratory status.

Hypermetabolism is seen in stress states such as trauma, sepsis, ARDS, and severe burn injuries [12,13]. Metabolic demand has been shown to be increased by around 19% in patients with trauma and/or sepsis and 30% in patients with ARDS [13,14]. With an average REE of 299% of predicted, patients with COVID-19 in our case series exhibited an extreme level of hypermetabolism that has not been previously described in other disease states. As none of our patients in our case series were febrile at the time of the indirect calorimetry measurement, we postulate that the observed hypermetabolic state may be secondary to the hyper-inflammatory response and cytokine storm that is seen in critically ill patients with COVID-19. This degree of hypermetabolism, with resultant increases in CO_2 production and oxygen demand, may contribute to the severe hypercarbia and hypoxia that is frequently seen in critically ill patients with COVID-19. This may also account for the dissociation between the degree of lung injury on radiological studies and the severity of hypercapnia and hypoxia that has been observed in these patients

Table 2
Changes in arterial blood gas.

Case #	% Change in pCO2		% Change in pO2		PaO2/FiO2		
	Hypothermia	Rewarm	Hypothermia	Rewarm	baseline	Hypothermia	rewarm
1	−8.3%	−10.0%	123.8%	47.7%	93	263	160
2	−18.9%	−16.7%	−2.5%	3.7%	108	102	120
3	−13.9%	−21.2%	80.6%	82.5%	160	319	365
4	−35.1%	−46.2%	−0.4%	−32.0%	250	285	223

[15].

The use of hypothermia has been widely adopted in cardiac surgery [4,5] and patients after cardiac arrest [6,7] to decrease the metabolic demand of vulnerable end organs such as the heart and the brain. Metabolic demand decreases by 8% for every degree Celsius drop in core body temperature [16]. Although limited, case reports of the use of hypothermia in patients with ARDS secondary to various etiologies including trauma, lung transplantation, pneumonia, sepsis, and H1N1 influenza has been described [8–11,17]. The correlation between hypermetabolism and the effect of hypothermia in patients with ARDS has not been described.

Our case series is the first to correlate the clinical effect of hypothermia to changes in metabolic demand in patients with ARDS and to describe the application of hypothermia in critically ill patients with COVID-19. We found that mild hypothermia decreased the REE on average of 27.0% with resultant declines in CO_2 production (VCO_2) and oxygen consumption (VO_2) by 29.2% and 25.7%, respectively (Table 1). This decrease in VCO_2 and VO_2 was clinically manifested as improvements in hypercapnia (average of 19.1% decrease in pCO_2 levels) and oxygenation (average of 50.4% increase in pO_2) (Table 2). Improvements in oxygenation may be secondary to decreased oxygen consumption resulting in a higher venous oxygen saturation. As venous admixture is an important cause of hypoxemia in patients with underlying lung injury, such as that seen in patients with COVID-19, improvements in venous oxygen saturation through the use of hypothermia may result in the improvements in arterial oxygenation as seen in our patient series. The improvement in metabolic rate were sustained with full rewarming and the clinical improvements in carbon dioxide and oxygen levels appeared to be sustained past the period of hypothermia.

Known complications for therapeutic hypothermia include arrhythmias, shivering, bleeding, and increased infections and are correlated with the degree and duration of hypothermia [16]. To decrease the risk of hypothermia, we elected to use mild hypothermia of 34.5 °C for 48 h. None of the patients in our case series experienced any adverse events during hypothermia.

4. Conclusion

Our case series demonstrate that COVID-19 critical illness induces an extreme hypermetabolic state and that mild hypothermia may be used to attenuate the hypermetabolic response seen in critically ill patients with COVID-19. It further suggests that the attenuation of hypermetabolic response may lead to improved carbon dioxide and oxygen levels in COVID-19 patients with refractory hypercapnia and/or hypoxia despite optimal medical management. Further prospective studies, including the CHILL-pilot study and one from our own institution, will need to be performed to substantiate the findings of this case series and to determine the optimal timing and duration of hypothermia [18,19].

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CRediT authorship contribution statement

Pey-Jen Yu: Conceptualization, Investigation, Writing - original draft, Writing - review & editing, Supervision. **Hugh Cassiere:** Conceptualization, Writing - review & editing. **Karl Bocchieri:** Conceptualization, Writing - review & editing. **Sarah DeRosa:** Investigation, Writing - review & editing. **Shiraz Yar:** Investigation. **Alan Hartman:** Writing - review & editing, Supervision.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.metop.2020.100046.

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