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Cheap and simple, could it get even cooler? Mild hypothermia and COVID-19

1. Introduction

Theories regarding the pathophysiology of COVID-19 seem to attach the injury of target organs to faulty immune responses [1]. The early onset symptoms would allegedly result from an individual's impaired interferon (IFN) response, allowing viral replication, viral spread, and direct viral aggression. In contrast, and comparable to SARS-CoV infection, during COVID-19's most severe phase, viral titers are paradoxically diminished. Inflammatory status, with occasionally overwhelmed cytokine production and leucocyte infiltration, then becomes a relevant mechanism in the late stage [1].

Despite not being as substantial as originally envisioned, the role of interleukin (IL)-6 in COVID-19 appears to retain importance, as circulating levels positively relate to disease severity [2], and its suppression could eventually decrease mortality (as shown in animal models). The IL-1 family emerge within inflammatory mechanisms and pathways as well, further inducing the expression of IL-6 and tumor necrosis factor (TNF)-α, among other hypercytokinemia catalyzing effects [1]. Moreover, IL-1 inhibition showed significant survival benefit in an explanatory analysis [2]. Additionally, another immunological deviation of COVID-19 is lower absolute numbers of lymphocytes, which is linked to a worse prognosis. These lymphocytes are negatively correlated with serum rises in IL-6 and TNF-α, which are in part due to TNF-α's effect of inducing T cell apoptosis [1]. Moreover, abrupt systemic TNF-α hikes are a recounted etiology of diffuse mitochondrial dysfunction resulting in multiple organ failure [3]. TNF-α neutralization might then be a major point too, since it provides protection against SARS-CoV infection in animal models [1].

In the light of the complexity of the COVID-19 disease mechanisms, it makes sense to resort to a therapy that could provide an equally multifaceted approach, but without prohibitive risks. Ultimately, we believe that mild therapeutic hypothermia (TH) is a suitable candidate for this role. A paramount distinction is between intrinsic, accidental, and therapeutic hypothermia. The first (intrinsic) is an independent main predictor of poor prognosis [4]; and the second (accidental) relates to increases in the infection risk and morbid cardiac events [5]. The distinguishing aspects of TH are the predefined setpoint, the tightly restricted variations, and the consciousness suppressed by sufficient sedation, diminishing the risk of unfavorable responses (e.g., shivering and tachycardia), thereby avoiding harmful increases in myocardial oxygen consumption and the work of breathing [5,6].

2. Inflammation

Suppression of inflammatory phenomena is the backbone of the application of TH. The release of IL-1, IL-6, and TNF-α is abated in serum and at the tissue level, while IL-10 concentrations are locally uplifted [7-9]. Also, the generation of free radicals is weakened, ensuring more harmonious balance with endogenous antioxidative mechanisms, which mitigates aggression, leading to sub-lethal injury instead of permanent damage and cell death. Also, hypothermia can sometimes directly stunt the apoptotic pathway [5].

3. Respiratory

On account of the ensuing drop in metabolic rate, CO_2 partial pressure ($PaCO_2$) and acidosis restrictions are loosened, favoring lung protective ventilation. Moreover, the lower oxygen-extraction rate could potentially result in greater arterial oxygenation [10]. Noteworthy is the evidence proposing that $PaCO_2$ reduction, along with arterial O_2 partial pressure (PaO_2)/fractional inspired oxygen (FiO_2) ratio increase, could last even after completion of hypothermia and rewarming [11,12]. Proposed mechanisms rely broadly on intrapulmonary shunt improvement [13], uplifting mixed venous, venous admixture, and arterial oxygen tensions. The inhibition of neutrophil aggregation and lung infiltration, the amelioration of alveolar epithelial damage, and the optimization of the reactions of the pulmonary vasculature are the contended explanations [7,9]. Additionally, the pathogenesis of microthrombi development in the capillary system could potentially be addressed [4], providing dead-space reduction. At the same time, hypothermia mitigates ventilator-induced lung injury [9], as it supposedly does with infectious lung injury [12]. As a reflection, enhancements in ventilation perfusion (V/Q) mismatch and transalveolar diffusion capacity may become achievable. Although most gains have been described on a theoretical or experimental basis, there are studies undergirding their validity in clinical practice [12,13].

4. Cardiovascular

TH tends to decrease cardiac output along with the heart rate, and mild diastolic dysfunction may occur. However, myocardial contractility, systolic function, and blood pressure typically improve [5,13]. In unstable septic patients, cooling previously decreased vasopressor requirements and achieved a mortality advantage [14]. Microhemodynamics are modulated too, with animal experiments and small clinical studies suggesting that the imbalance of the local secretion of vasoactive substances in various organs could be corrected [5]. With regional blood flow redistribution, alongside a hypothermia-mediated elevation in oxygen's solubility [12], increments in O_2 extraction and tissue diffusion could be expected [12,13]. In contrast, the decline of O_2 consumption and CO_2 production is parallel with the metabolism reduction [5,15]. Additionally, hypothermia heightened ischemia-tolerance in different animal models [5]. These various

adaptations are also seen in the coronary bed, lifting myocardial perfusion, which has attracted the interest around the application of TH in acute infarction [5]. A pooled analysis of trials investigating hypothermia in early ST-elevation myocardial infarction patients has shown a trend towards a reduction of infarct size and heart failure incidence [16]. Putting all of these components together, the supply and demand equation remains constant or improves [10]. Lastly, mild cooling, different from profounder hypothermia, not only does not increase the risk for arrhythmias, but also actually reduces the odds, and makes defibrillation more likely to succeed if arrhythmias do occur [5].

5. Renal

TH might be capable of attenuating kidney histopathological injury in systemic inflammation or ischemia-reperfusion environments [7]. Also, fluid balance targets could be aided by the "cold diuresis effect" [5].

6. Hemostasis

The prothrombotic state of COVID-19 is another target that needs to be addressed. Mild hypothermia affects the kinetics of coagulation, plus thromboxane A2-induced platelet aggregation and leukocyte adhesion —all of which are associated with microthrombi formation [4]. Also, but to a lesser extent, the synthesis and concentrations of coagulation factors may diminish, especially in moderate or more profound hypothermia [4]. There has long been sufficient evidence to address a theoretical antithrombotic effect to hypothermia. A healthy-volunteers-based study has since demonstrated (in vivo) the progressive attenuation of the blood coagulation system while facing decreasing temperatures [17]. However, it was the work of Johansen et al. [4] that really shed a light on the effect of TH in acute blood dyscrasia. The randomized controlled trial comprised sepsis patients, and the outcome was the degree of functional coagulopathy. Improvement was elicited in both hypo-and hypercoagulability patterns, asserting a tendency towards the normalization of blood clotting. Moreover, the effect seemed to be sustained afterwards, under normothermia. Therefore, it is a plausible thesis that the actual effect of TH reduces deviations from hemostasis throughout the whole spectrum of coagulopathy instead of simply inhibiting coagulation [4]. Reinforcing this proposition, and reassuring the method's safety, mild hypothermia does not appear to aggravate intracranial bleeding in subarachnoid hemorrhage or traumatic brain injury [6], nor hemorrhagic complications in acute liver failure [18].

7. Infections

It is fair to consider the possibility of TH prompting SARS-CoV-2 virus replication. IL-6 interaction with viral behavior has already been studied, and overexpression facilitates the viral persistence, relapse, and exacerbated clinical outcomes of HIV, hepatitis C virus, herpes simplex virus, Chikungunya, and influenza [19]. Incrementally, animal in vivo blockage of IL-6 during acute infection with the murine leukemia virus resulted in a reduced viral load and increased production of IFN-γ [20]. TNF-α has the potential of reactivating latent HIV-1 infections, but bench research around an in vitro model suggests that cooling could foster virus latency and dampen responsiveness to the reactivation-stimuli of TNF-α [21]. Further, TH has been successfully applied in the management of viral meningoencephalitis [22], and even of viral-infection-related acute respiratory distress syndrome (ARDS) [8].

Another aspect worth considering is the impingement on the risk of secondary infections. Pathophysiologically, it is reasonable to expect the individual to be rendered prone to new infections, as the very mechanisms that provide tissue protection could impair the capacity of thwarting invading microorganisms. However, current data do not support an increased overall infection rate [23,24] or differences in infection-related mortality [25,26]. The possible exception is severe bacterial meningitis, in which a trend towards higher mortality led to the

premature discontinuation of the trial [23]. However, evidence does indicate higher incidences of pneumonia and bacteremia [15]. Nevertheless, this trend is blurred by confounders. Most hypothermia studies contemplated instances post arrest or severe trauma, which, by themselves, are independent risk factors for pneumonia [15]. Moreover, many TH protocols include daily blood cultures; therefore the relative increase in bacteremia could be partially due to active searching. However, outcomes did not appear to be adversely affected even when infections occurred [5].

8. Testing

While far more consolidated in the post-cardiac-arrest scenario, TH has already shown signs of eventual utility in alternate extreme conditions, such as severe traumatic brain injury, viral encephalitis [22], acute liver failure [18], sepsis, and varied respiratory insufficiencies [8], as summarized in Table 1. Concerning these latter two situations, the success of hypothermia in the treatment of severe septic ARDS has already been reported, with survival benefit suggested [13,27]. However, ideal target temperature and duration of maintenance remains undefined. Regarding mild hypothermia (34 °C–35.9 °C), lower temperatures might outperform shallower reductions, at least in terms of neurological outcomes. On the other hand, it seems logical that—even within the same temperature range—bolder decreases could potentiate the inherent risks of the method; however, confirmation is lacking [24]. Optimal runtime is also controversial. Although there is evidence suggesting that the risk of infections may increase after 12 h [5,8,24], previous series have already used more extensive strategies—apparently without compromising safety—and 48 h is the most commonly used time frame [23]. Therefore, the target of 34 °C, with fluctuations held under ±0.2 °C–0.5 °C, sustained for 48 h, seems reasonable. Similar uncertainty surrounds the best technique of cooling [23,24]. Nevertheless, Polderman [5] proposed the cornerstones of safe TH, which we favor in this article. The induction phase should be the fastest possible in reaching the core-temperature target; in the maintenance phase, fluctuations ought to be minimal; and rewarming must conform to a rate around 0.1 °C/h.

Expeditious induction intends to minimize the side effects of the proceedings, including (inter alia) hypovolemia, electrolyte disorders, and hyperglycemia [5,6]. All patients need significant suppression of consciousness before the protocol is started, to avoid unnecessary discomfort and hazardous hypothermia-induced stress responses. During the induction phase, neuromuscular blockade should, preferably, also be instituted; however, prolonged paralysis is usually unnecessary [5]. If needed, anti-shivering agents—such as fentanyl, propofol, clonidine, hand warming, facial warming [28], and magnesium—can be applied as auxiliary measures. Experimental studies point out that neglect of this detail may result in the loss of the protective effects of hypothermia [5]. Therefore, proper sedation is one of the mainstays that differs TH from accidental hypothermia, both conceptually and in terms of expected harm. Thus, its importance cannot be emphasized enough. Jump-start cooling, by means of a loading dose of 4 °C–6 °C cold saline [23], if pertinent, coupled with surface cooling (ideally through a cooling mattress, plus cooling air and/or ice packs), could rapidly accomplish a reduction in core body temperature. Nonetheless, it is noteworthy that no preferred method has been established, or superseded the outcomes achieved by others [23,24]. One can argue that normothermia could be the best target when controlling the temperature of a critically ill COVID-19 patient. This is a difficult decision to make without clinical or experimental studies; however, from the pathophysiological point of view, there are potential benefits (to be clinically proven) of the use of TH.

The rewarming phase is perhaps the most critical of all. A careless rise in the patient's temperature can precipitate hyperkalemia, hypoglycemia, and infections by bacterial gastrointestinal translocation [3]. Moreover, rapid rewarming could also forfeit the protective effects of

Table 1
COOLING INTERVENTIONAL STUDIES

Main Author (Year)	Studied population	Context	Hard Outcomes	REPORTED POTENTIAL BENEFITS Organ System					
				Inflammatory / Immune	Respiratory	Cardiovascular	Renal	Coagulatory	Neurological
[21]	In vitro model	HIV-1 bench-research		Latency-fostering effect; Decrement in responsiveness to latency-reversing agents.					
[9]	Animals (dogs)	Oleic acid-induced ARDS model		Increase of anti-inflammatory cytokines (IL-10) in BALF; Decrement of TNF-α and IL-6 in serum and BALF.	Increase in PaO2 values; Attenuation of lung's pathological injury and infiltration by PMNs.				
[7]	Animals (dogs)	Oleic acid-induced ARDS model		Increase of anti-inflammatory cytokines (IL-10) in serum.	Lung elastance and pulmonary circulation resistance improval.		Histopathological renal injury attenuation.		
[10]	Animals (dogs)	Oleic acid-induced ARDS model				Improval in oxygen delivery/consumption ratio; Decrement in HR.			
[27]	Humans	Pulmonary sepsis-related ARDS	Decrement in mortality rate.		Increase in P/F ratio; Decrement in ventilator days.				
[8]	Humans	Viral infection-related ARDS			Increase in P/F ratio; Decrement in PaCO2.				
[16]	Humans	Acute STEMI				Reduction in myocardial IS and HF's incidence.			
[4]	Humans	Sepsis						Sepsis-related coagulopathy improval (both hypo- and hypercoagulability).	
[12]	Humans	Post cardiac arrest			Increase in P/F ratio; Decrement in PaCO2, tidal volume, PIP, and ventilator days.				
[14]	Humans	Septic shock	Decrement in mortality rate.			Increase in shock-reversal rate; Decrement in vasopressor's requirements.			
[17]	Humans	Healthy volunteers						Progressive attenuation of coagulation.	
[21]	Humans	Severe viral meningoencephalitis							Cerebral perfusion improvement.
[11]	Humans	Post cardiac arrest			Increase in P/F ratio; Decrement in PaCO2.				
[3]	Humans	Influenza virus encephalitis (pediatric)							Attenuation of brain edema.
[13]	Humans	Sepsis-related ARDS	Decrement in mortality rate.		Increase in P/F ratio and O2 extraction; Decrement in intrapulmonary shunt and A-aO2.	Decrement in vasopressor's requirements and HR.			

REPORTED POTENTIAL HARMS

Ref	Subject	Condition	Reported potential harms
[10]	Animals (dogs)	Oleic acid-induced ARDS model	Decrement in blood pressure and cardiac output.
[8]	Humans	Viral infection-related ARDS	Bacteremia increased risk?
[12]	Humans	Post cardiac arrest	Increased number of positive urine and sputum cultures.
[23]	Humans	Severe bacterial meningitis	Increased mortality rate?
[14]	Humans	Septic shock	Increased nosocomial infections?
[25]	Humans	Post cardiac arrest	Increased infectious complications?
[13]	Humans	Sepsis-related ARDS	Cardiac index decrement.

hypothermia [5] and even increase IL-6, with an IL-10 decrease, thereby possibly worsening inflammation and outcomes [8].

Finally, it can be presumed that the accurate timing of intervention is decisive, which is highly likely to be related to its effectiveness. Bearing in mind the participation of the aforementioned inflammation-driven theory in the natural history of severe COVID-19, the verge of the late (after 7–10 days) clinical course downturn seems to be the best fitting moment [1]. Development or re-emergence of tachypnea, tachycardia, and fever may flag this timepoint, signaling the subset of patients that could benefit the most. Despite its overlapping effects on immunity, dexamethasone prescription should not hinder TH, provided attentive surveillance of the patient is ensured to detect early signs of infection.

9. Conclusion

According to evidence derived from previous hypothermia applications, its benefits might be seen from the perspective of inflammatory response and organic damage, particularly concerning the aforementioned systems. Thus—from extrapolations of supporting literature—the proposed TH approach appears to be pathophysiologically underpinned. However, experimental research is still needed in order to assess if the theoretical rationale translates into actual clinical benefit. Apart from the upsides depicted, it is vital to underscore the low cost and great availability of TH, which, in times of global health ordeals, ascends as a feature of major importance.

Author contributions

RRU was responsible for the conceptualization of the project, the literature review, and the writing of the manuscript. MP mentored the conduction of the study, supervised the progress, edited the drafts, and approved the final version for submission.

Declaration of interests

None.

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