Do critical care patients hibernate? Theoretical support for less is more

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Energy balance is key to life. Organisms are confronted with trade-offs in their use of energy and have evolved mechanisms to cope with states of energy limitation. Given the central role that energy deficits play in critical illness, understanding these adaptations might improve our knowledge of disease, facilitate novel therapeutic strategies, and avoid injurious interventions.

Torpor and hibernation represent extreme forms of adaptation based on a suppression of metabolism to assist survival during periods of environmental stress. Torpor identifies a short-term hypometabolic state while hibernation defines a seasonal phenomenon characterized by multiple successive bouts of torpor [1].

Torpor, a coordinated behavioural, physiological and molecular phenomenon, is characterized by decreases in heart, respiratory and metabolic rates, lowering of the body thermostat and hypothermia. Torpor is widespread but not ubiquitous among mammals; humans do not spontaneously enter torpor and no known interventions induce it. This is not due to phylogenetic distance from torpor species as it is described in primates, nor size as torpor can be present in bears but absent in rats [2].

To date, no unique traits of torpor have been identified. Genes governing torpor are present in non-hibernating species, suggesting the potential for torpor is present in most mammalian species, including humans [1]. Along with decreased metabolism, torpor is characterised by a switch towards preferential fatty acid metabolism, boosted antioxidant defences and suppression of apoptosis, coagulation and immunity. These adaptations confer organ protection with increased tolerance to cold, hypoxia and ischaemia-reperfusion [3].

Some of these organ-protective effects could be partially replicated in non-hibernating species by transfusing blood components collected from hibernators (suggesting non-species-specific circulating mediators), or through pharmacological stimuli. Of note, outcome benefits could not be consistently replicated in clinically-relevant models [4].

Therapeutic hypothermia is another existing hibernation-like strategy aimed at decreasing metabolic demands. This has been tested in various clinical conditions, but results are inconsistent, with a signal towards harm in sepsis [5]. These conflicting results partly relate to challenges in cooling patients both effectively and promptly, and to adverse effects of hypothermia. Another fundamental difference is that therapeutic hypothermia causes a passive decrease in metabolic rate while, in torpor, metabolism is actively reduced first, making the latter a more efficient and clinically desirable way to induce hypometabolism. In summary, despite encouraging preclinical data, we still lack an easily applicable, effective therapy to induce torpor in humans.

Despite the lack of spontaneous torpor in humans, numerous analogies are found in clinically relevant physiological and pathological responses. Myocardial hibernation is an adaptive, reversible down-regulation of cardiac metabolism and contractility [6]. Originally described as an energy-preserving strategy during periods of hypoperfusion, it has also been reported in sepsis [7]. Hibernating myocardium is characterized by modifications that recapitulate features of torpor albeit with a major difference: in myocardial hibernation glucose is the preferred energetic substrate, whereas fatty acid metabolism is up-regulated in torpor [3, 8]. This divergence in substrate use during stress is commonly found between hibernating and non-hibernating species, and is not unique to the heart [3, 9]. It may be crucial in understanding differences between adaptive and maladaptive responses to acute illness.

Sepsis-related organ dysfunction offers an intriguing parallel with torpor. Substantial dysfunction exists despite minimal cell death, reduced cellular oxygen consumption and normal/elevated tissue oxygen levels [10]. Moreover, in survivors, organs usually recover functionality within days-to-weeks. These features were originally attributed to cytopathic mechanisms and, in particular, mitochondrial damage [11]. Alternatively, these changes could represent an adaptive shutdown aimed at reducing cellular energy requirements, with a trade-off between organ function and cellular viability [10]. This hypothesis is supported by the extensive transcriptomic reprogramming seen in sepsis [12, 13], associated with metabolic modulation and downregulation of mitochondrial genes. This is similar to torpor where mitochondrial suppression is an important driver of hypometabolism [14].

The overlap between torpor and acute illnesses suggests the presence of a protective genomic response, conserved throughout evolution in both hibernating and non-hibernating species, that modulates the host response to improve survival [15].

Oxygen delivery insufficient to meet metabolic needs can result in life-threatening shock. Although this is often the case in early pre-resuscitative critical illness, post-resuscitation oxygen delivery is usually more than adequate due to a relative suppression of cellular oxygen use [16, 17]. This transition from energy deficit to hypometabolism again shows similarities between critical illness and torpor. It is reasonable to consider that certain features of critical illness may be adaptive rather than pathological, and, similarly to torpor, have evolved to enhance survival.

If this hypothesis is correct, it could provide the biological rationale to explain why the last 30 years of clinical research have consistently shown benefit from a “less is more” approach to the critically ill, as we suggested 15 years ago [18]. Indeed, the merciless pursuit of “healthy normal” physiological targets as part of clinical management may induce deleterious modifications of this adaptive allostasis. For example, Cooper and colleagues showed how decompressive craniectomy in traumatic brain injury is associated with worse outcomes, despite decreased intracranial pressures [19]. Future therapeutic efforts should perhaps shift from driving energy supply to reducing demands. Comparative study of hibernating species may allow us to understand how this hypometabolic state could be achieved safely and effectively, and how it could be reversed, at the appropriate time, to promote recovery of normal function, akin to arousal from torpor seen in animals.

Further research may lead to a clinical paradigm shift towards “permissive organ dysfunction”. A research priority is to improve our understanding of critical illness biology to tease out adaptive from maladaptive responses, and to identify how these could be exploited clinically. If and when the adaptive response becomes maladaptive, clinicians must intervene to prevent irreversible organ damage and death. Effective torpor triggers and mitochondrially-targeted therapies that modulate metabolism [20] might soon become available for testing in humans. In the interim, clinicians need to consider how the response to critical illness may represent, at least in part, a complex protective phenomenon that should be taken into account in future clinical trials, and not compromised by clinical interventions.

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Figure Legend

Figure 1. Schematic representation of the similarities between hibernation, torpor and critical illness, with examples of sources of energy stress and consequent adaptatory mechanisms.