

Management Strategy of Hyperthermic State in Critically Ill Patient.

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Abstract

Pyrexia is a protective physiologic response of the body against external and internal aggression. Temperature control is safe in and effective in septic shock but remain controversial in sepsis. Treating pyrexia to reduce oxygen consumption appears to have beneficial in cardiac arrest, low cardiac output and acute brain injury. Multiple therapeutic options are available for managing pyrexia, with precise targeted temperature management. Notably, the use of pharmacotherapy versus surface cooling has not been shown to be advantageous. When these two-therapy failed to control the extra-corporal method of cooling should be started. Renal replacement therapies are not typically indicated for temperature control but, in patients requiring renal support, they contribute to heat loss and participate in pyrexia control. Renal replacement therapies may represent a confounding factor in comparative trials on temperature control.

Keywords: Pyrexia. CRRT. SIRS. Aortic dissection.

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Background

Pyrexia is a common problem in ICU patients. The presence of pyrexia frequently results in the performance of diagnostic tests and procedures that significantly increase medical costs and expose the patient to unnecessary invasive diagnostic procedures and the inappropriate use of antibiotics. The main diagnostic dilemma is to exclude noninfectious causes of pyrexia and then to determine the site and likely pathogens of those with infections. ICU patients frequently have multiple infectious and noninfectious causes of fever [1] necessitating a systematic and comprehensive diagnostic approach. Around 35 % of in-hospital patients will develop pyrexia [2], increasing up to 70 % amongst the critically unwell [3]. Pyrexia has long been thought of as a protective physiological response to help host defenses, although this is now being challenged. Despite recent advances, it remains unclear whether pyrexia or the physiological response to pyrexia causes morbidity and mortality and whether management of pyrexia with pharmacological agents or physical cooling actually confers benefit.

Pathophysiology

The process of tightly regulating body temperature within a specified range (± 0.2 °C), or thermoregulation, is an essential homeostatic mechanism. Thermoregulation consists of afferent signaling via warm and cold thermoreceptors, central processing within the hypothalamus and efferent response. These responses include regulation of peripheral blood flow, diaphoresis and shivering. Whilst there is strict control there is also rhythmic temperature variability over a 24-h period [4]. This circadian rhythm is altered in critically ill patients with both temporal shifts and a larger

magnitude of variation, both increasing with disease severity [5]. Pyrexia secondary to the systemic inflammatory response should be distinguished from hyperthermia resulting from excessive heat production, as observed in heatstroke and malignant syndromes, or from ineffective heat loss. Here we will present two cases of life threatening hyperpyrexia in severe ill patient. Case **one**; Ventricular septal defect (VSD) is a rare but lethal complication of myocardial infarction (MI). The event occurs 2-8 days after an infarction and often precipitates cardiogenic shock. Male patient 62 years old was diagnosed with interventricular septal defect after anteroapical myocardial infarction. Hemodynamic situation was very bad, in cardiogenic shock because of low cardiac output with low EF 30%. After coronary angiography, Intra-Aortic Ballon Pump (IABP) was inserted (Arrow set 40 cc balloon) via left femoral artery for circulatory support. After preparation the patient was immediately put in operation room. The operation consisted in closure of VSD with synthetic patch Dacron, left ventricular aneurism repair and two aorto-coronary bypass. Weaning from heart lung machine was easy with little hemodynamic support from vasoactive drugs. Urine output during whole operation and early hours was normal. Hours later after operation the temperature arrived till 39.9° C associated with elevated heart rate, low blood pressure, elevated vasoactive drugs and no urine output (septic shock). Four hours after installation of acute kidney injury Continuous veno-venous hemofiltration (CVVHF) was started via left femoral vein (12 FR double lumen Arrow catheter was inserted). Hemofiltration was performed with Prismaflex -Gambro machine and M-100 AN-69 Filter membrane and with effluent dose 25 ml/kg/hour. After renal recovery, 48 hours later, hemofiltration was stopped and patient continued to have good urine output and

good hemodynamic performance. Amiodarone iv was started also due to paroxysmal atrial fibrillation with high frequency, initially 300 mg loading dose, and after 1000 mg for first 24 hour. In third postoperative day, after termination of hemofiltration, the temperature reached again high value 40° C associated initially with high heart rate, rhythm disorder till life threatening arrhythmia ventricular fibrillation multiple times (4 times in hour), converted with electric cardioversion. Physical method of cooling and antipyretic medication was started but without success, meanwhile patient continued to develop ventricular fibrillation. So, we decided to start again CRRT, without warming lines, to cool down the patient. After restarting the hemofiltration, the temperature slowly went down and heart rate was stabilized in normal sinus rhythm with no more life threatening arrhythmia. After three days of hemofiltration, IABP was removed and hemofiltration was stopped and patient was disconnected from ventilator. The patient was discharged from ICU in normal hemodynamic situation, good urine output and without fever.

Case two; Aortic dissection remains a devastating vascular catastrophe with a high mortality rate if not diagnosed and managed promptly. However, its signs and symptoms are unpredictable. As the dissection progresses, other organs can be affected and can obscure the inciting diagnosis. Acute aortic syndromes have a mortality as high as 1% per hour for acute type A aortic dissections. A 67-year-old male with no significant past medical history presented to the emergency room with the chief complaint of sudden onset of substernal chest pain radiating to his back. Acute aortic dissection was suspected and then confirmed with contrast CT. After diagnosis, patient was transferred in cardiac surgery department and was prepared for emergency surgery.

Blood test and creatinemia was normal before CT. Urine output, blood pressure, blood gas and electrolytes were normal before surgery. Extra-corporal circulation was instituted in retrograde way via right femoral artery and right atrium. Cooling down in 25°C rectal temperature aortic arc was inspected releasing the aortic clamp, to find the entry intimal point. After 22 minutes circulatory arrest, hemi-arc aortic replacement was performed and 5 minutes retrograde perfusion via superior vena cava. After rewarming the patient was disconnected from heart lung machine with no circulatory support. Due to massive bleeding, a large quantitative blood and fresh frozen plasma was transfused in immediately postoperative period. High doses of noradrenalin e dopamine were used to maintain normal blood pressure and urine output. 48 hours after operation, the fever was installed with elevated temperature till 40,5° C. Decreasing temperature with physic and pharmacologic failed and the temperature remained elevated. In this situation CRRT was started via left femoral artery with no warming blood lines. The temperature gradually decreased, in normal value. During this period, we didn't use antipyretic drugs and the temperature was maintained in normal values. During the hemofiltration, urine output was normal and vasoactive drugs dose were minimal. Hemofiltration was stopped four days later when the patient didn't had any more fever. After ten days of mandatory ventilation the patient was disconnected from ventilator in good situation but with motoric neurologic sequel. The patient was transferred in the ward for physiotherapy treatment.

Discussion

Should we treat pyrexia?

The cost of pyrexia

The cost of pyrexia should be considered in several ways. Pyrexia has a metabolic cost such that cooling febrile ICU patients will reduce oxygen consumption by 10 % per °C [6], Small studies in sedated patients demonstrated a significant reduction in V_{O2} (the rate of oxygen consumption) and V_{C O2} (the rate of carbon dioxide elimination) during cooling [6, 7], In septic shock, temperature lowering by ibuprofen was associated with increased lactate clearance [8]. In patients with acute brain injury, pyrexia may increase intracranial pressure and worsen secondary ischemic damage [9], These suggest the possibility of therapeutically offloading the cardiorespiratory system and preserving brain function at times of stress. Whether the cost of pyrexia translates to unfavorable outcomes remains unknown. The incidence of pyrexia is decreasing over time with an absolute reduction of 35 % found in Canadian ICUs [10]. This did not coincide with an appreciable decrease in mortality, suggesting that important outcomes may not be affected by the incidence of pyrexia. Perhaps the question should not be “should we treat pyrexia?” but “in what conditions is it beneficial to treat pyrexia?”. This is highlighted in a large observational study where fever within the first 24 h of ICU admission was significantly associated with decreased mortality in patients with infection while peak fever >40 °C was associated with increased mortality in patients without infection [11], An observational study on 1400 non-neurological critically ill patients also revealed different associations between the maximal peak temperature and mortality according to the presence of sepsis or not [12]. Fever >39.5 °C was associated with increased mortality in non-

septic patients while moderate fever (37.5-38.4 °C) was associated with decrease mortality in septic patients. Moreover, this study highlights different impacts of fever treatment. Physical cooling did not alter the mortality risk and the use of antipyretic agents did not alter mortality in the non-septic group but did increase 28- day mortality in the septic group (adjusted odds ratio 2.61 (P = 0.028) for nonsteroidal anti-inflammatory drugs (NSAIDs) and 2.05 (P = 0.01) for paracetamol [12].

In patients with acute brain injury, pyrexia has been identified as an independent risk factor for increased mortality and poorer neurological outcome [10, 13-14].

Results are, however, inconsistent as fever could be a marker of brain injury severity [15]. The presence or not of infection may also alter the relationship between body temperature and outcome [16, 17]. In more than 100,000 patients, a negative association between early peak fever above 39 °C and hospital mortality was found in patients with traumatic brain injury and stroke but not in patients with central nervous system infection [17].

Pharmacological methods of cooling

Nonspecific medication used to reduce heat production in the critically ill patient includes sedative agents and neuromuscular blocking agents. More specific antipyretic medications include paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). Paracetamol acts by selective inhibition of the cyclooxygenase-3 enzyme (COX-3); this results in reduced production of fever generating prostaglandins. With a relatively limited side-effect profile in most patients, paracetamol is widely used in critical care patients with fever. The other major group of antipyretics are NSAIDs—the risks of exacerbation of renal impairment and gastric ulceration with the use of these drugs mean

that they are often relatively contraindicated in the critically ill population.

Physical methods of cooling

Initially simple methods can be instituted, such as uncovering the patient whilst preserving their dignity and using cold towels placed across the patient or in the axillae. If ice packs are used, care must be taken to ensure that the ice does not come into direct contact with the patient's skin and cause subsequent thermal injury. Cooling blanket systems utilize circulated cold water and a feedback control system monitoring the patient's core temperature to achieve and maintain normothermia. In refractory cases of hyperthermia, more invasive methods of cooling may need to be implemented. This begins with rapid infusion of cooled i.v. fluids. Other invasive methods of cooling include the installation of cold fluid into body cavities such as the stomach, pleura, bladder, and peritoneum. Continuous renal replacement therapy (CRRT) is often regarded as one of the more important advances in intensive care medicine in recent years. The use of CRRT in critically ill patients with acute renal failure, combined with cardiovascular instability, severe fluid overload, cerebral edema or hyper catabolism and high fluid requirements, is widely accepted. CRRT is also used in some non-renal indications, and these are less well established. These non-renal indications are based on the (presumed) elimination of inflammatory mediators [such as systemic inflammatory response syndrome (SIRS) and sepsis, acute respiratory distress syndrome (ARDS), and cardiopulmonary bypass (CPB)], on the removal of fluid (ARDS, CPB, chronic heart failure), or on the elimination of other endogenous toxic solutes (inborn errors of metabolism, lactic acidosis, crush injury, tumor lysis syndrome).

In our cases there was no indication to start again CRRT for acute kidney injury, because the patient had good urine output and little bit alteration of renal markers. Because we failed to decrease the elevated temperature with pharmacological and physical method, only CRRT had wonderful result non-only in temperature control but also in hemodynamic and rhythm stability.

Pharmacological versus non-pharmacological methods.

A meta-analysis of 11 trials, from 48 reviewed, considered pharmacological versus non-pharmacological antipyretic treatments with outcome measures being targeted temperature and haemodynamic effects [20]. It found that intravascular as opposed to surface cooling had better target temperature results, although there was a non-significant trend towards higher mortality. Only three small studies consisted of a head-to-head comparison of pharmacologic and non-pharmacologic methods, for which the analysis was inconclusive [20]. In sepsis, the three largest RCTs compared ibuprofen [8], paracetamol [19] and surface cooling [18] against placebo or no treatment. The maximal between-group differences in temperatures reported were 0.6 °C on day 1, 0.9 °C at 10 h and 1.6 °C at 12 h, respectively. Although inconclusive, these data may suggest that controlling fever by surface cooling is more efficient than by antipyretic agents.

Summary

Temperature is not only an important clinical marker of severity of illness but also an independent predictor of morbidity and mortality in critically ill patients. Close monitoring and regulation to avoid extremes of body temperature

is particularly important in the critically ill patient. This will prevent the uncontrolled disruption of homeostasis and associated subsequent organ dysfunction and failure. Additional studies are needed to explore and clarify the role of antipyretic treatments in febrile critically ill adult patients (pharmacological vs non-pharmacological treatment)

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