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Review

Therapeutic hypothermia in the management of acute liver failure

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ABSTRACT

A large body of experimental data and preliminary clinical studies point to the induction of mild hypothermia (32–35 °C) as a valuable approach to control the development of brain edema and intracranial hypertension in acute liver failure (ALF). The ability of hypothermia to affect multiple processes probably explains its efficacy to prevent these cerebral complications. Remarkably, mild hypothermia has been shown to prevent or attenuate most of the major alterations involved in the pathogenesis of the cerebral complications of ALF, including the accumulation of ammonia in the brain and the circulation, the alterations of brain glucose metabolism, the brain osmotic disturbances, the accumulation of glutamate and lactate in brain extracellular space, the development of inflammation and oxidative/nitrosative stress, and others. Limited information suggests that the systemic effects of hypothermia may also be beneficial for some peripheral complications of ALF. Translation of the beneficial effects of therapeutic hypothermia into standard clinical practice, however, needs to be confirmed in adequately designed clinical trials. Such trials will be important to determine the safety of therapeutic hypothermia, to identify which patients might benefit from it, and to provide the optimal guidelines for its use in patients with ALF.

1. Introduction

The development of brain edema and high intracranial pressure (ICP) are unique complications of patients with acute liver failure (ALF) developing severe hepatic encephalopathy (Blei, 2007). Traditionally considered the major cause of death in ALF, the relevance of intracranial hypertension and brain herniation may have decreased in developed countries relative to other mortality causes such as sepsis or multi-organ failure, due to improvements in critical care and the use of liver transplantation (LT) (Larsen and Wendon, 2008). Episodes of high ICP, however, may be detected during the course of ALF in between 80% and 95% of patients with stage III–IV hepatic encephalopathy undergoing ICP monitoring (Jalan, 2003; Raschke et al., 2008). High ICP remains responsible for substantial mortality (~25–50%) and for neurocognitive sequalae in patients surviving ALF (Bernal et al., 2007; Bhatia et al., 2006; Jalan, 2003; Tofteng et al., 2002), justifying the need for more effective therapies.

Induction of mild hypothermia (32–35 °C) effectively prevents brain edema and intracranial hypertension in experimental models of ALF (Vaquero et al., 2005b). Encouraged also by promising clinical experience (Jalan, 2005), several centers are progressively incorporating therapeutic hypothermia into the management of patients with ALF, particularly to bridge patients to LT when they present high ICP that cannot be controlled by conventional therapies (Jalan et al., 1999a; Raschke et al., 2008; Tofteng et al., 2002). The optimal guidelines for its use and the subgroups of patients with ALF that might benefit from therapeutic hypothermia, however, need to be refined. Clinical experiences in non-ALF conditions (traumatic brain injury, cardiac arrest) suggest that the success of this therapy critically depends on how it is implemented and on adequate patient selection (Clifton et al., 2001a; Polderman, 2009; Polderman et al., 2002; Shann, 2003). Hypothermia has profound effects at molecular, cellular, and systemic levels and, therefore, awareness of the physiology of hypothermia is essential for taking full advantage of this therapy.

2. Hypothermia research in ALF: aiming for a successful translational story

Body temperature is one of the most tightly regulated physiological parameters in humans. The deleterious effects of unintentional hypothermia are well known (Danzl and Pozos, 1994), and the inability to maintain a normal body temperature in patients with critical illnesses has been associated with a poor prognosis (Brun-Buisson et al., 1995; Margolis, 1979; Wang et al., 2005). The modern concept of therapeutic hypothermia originates in 1950 from the work of Bigelow and associates (Fig. 1), who challenged the prevailing observations that induction of hypothermia resulted in increased metabolic demands and O_2 consumption (Bigelow et al., 1950a,b). In contrast, they showed that metabolism

Abbreviations: ALF, acute liver failure; CBF, cerebral blood flow; ICP, intracranial pressure; LT, liver transplantation; RCT, randomized-controlled clinical trial.

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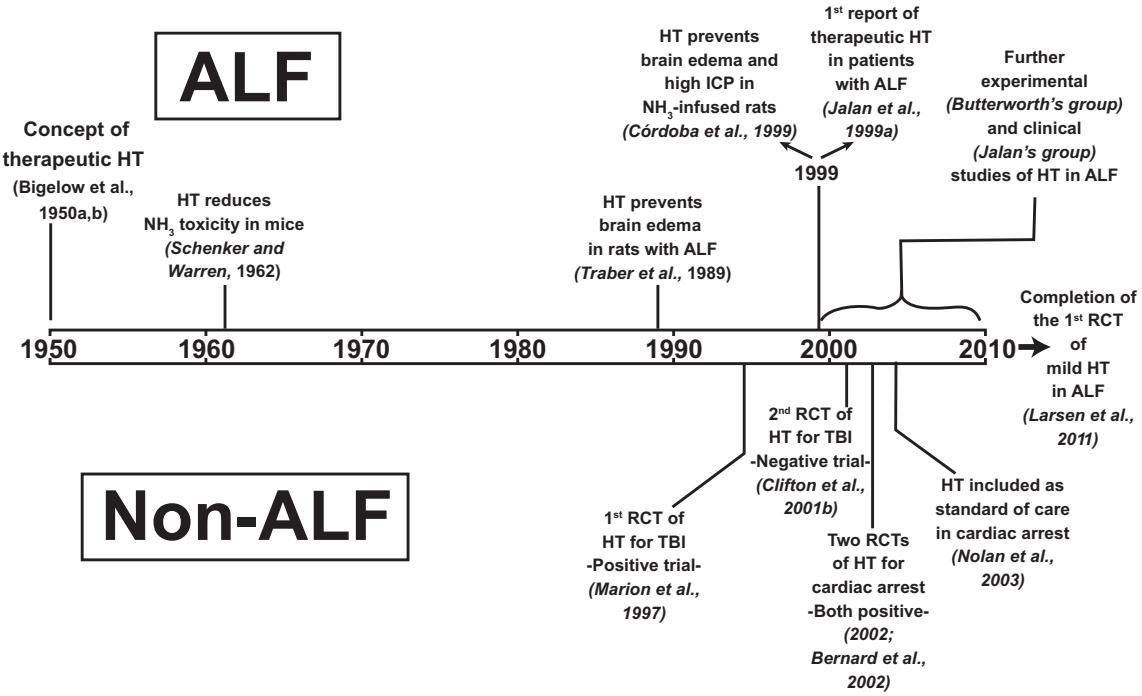

Fig. 1. Schematic showing some major events in the development of research of therapeutic hypothermia in acute liver failure (ALF) and non-ALF conditions. Abbreviations: ALF, acute liver failure; HT, hypothermia; ICP, intracranial pressure; NH_3, ammonia; RCT, randomized controlled clinical trial; TBI, traumatic brain injury.

and O_2 consumption decreased in parallel with the reduction of body temperature as long as the normal thermoregulatory responses to hypothermia, particularly shivering and autonomic activation, were prevented by adequate anesthetic management. Differences between these modes of hypothermia are not limited to metabolism; for example, the increased production of pro-inflammatory cytokines reported with unintentional hypothermia contrasts with the consistent anti-inflammatory properties of therapeutic hypothermia (Aibiki et al., 1999; Vaquero and Blei, 2005). These observations indicate that therapeutic hypothermia entails more than simply lowering the body temperature of a patient, and that the mechanisms and adverse effects related to the development of unintentional or illness-related hypothermia may not be directly extrapolated to its therapeutic use. Since Bigelow's landmark observations, the neuroprotective properties of hypothermia have been extensively demonstrated in experimental models of brain ischemia-reperfusion, traumatic brain injury, myocardial infarction and other conditions, leading to the investigation of its clinical use (reviewed in (Bernard and Buist, 2003)). Several large randomized-controlled clinical trials (RCT) of therapeutic hypothermia have been performed in patients with traumatic brain injury (Clifton et al., 2001b; Marion et al., 1997), cardiac arrest, and other conditions, but only the RCTs of hypothermia for the treatment of out-of-hospital cardiac arrest (Hypothermia After Cardiac Arrest Study Group, 2002; Bernard et al., 2002) and of neonates with perinatal asphyxia (Azzopardi et al., 2009; Shankaran et al., 2005) have been sufficiently conclusive to recommend therapeutic hypothermia as standard of care (Nolan et al., 2003; Pfister and Soll, 2010) (Fig. 1). Despite the inability to show improved clinical outcomes in other conditions, therapeutic hypothermia is often used in patients with traumatic brain injury or intracranial bleeding due to its efficacy for reducing intracranial hypertension (Pemberton and Dinsmore, 2003).

Research on therapeutic hypothermia and its translation into clinical practice have evolved at a slower pace in ALF (Fig. 1). Prompted by the use of hypothermia (~30 °C) during the surgical treatment of patients with cirrhosis and variceal bleeding (Clauss et al., 1959), Schenker and Warren demonstrated in 1962 the efficacy of hypothermia (~28 °C) to provide resistance against the lethal toxicity of acute ammonia loads in mice (Schenker and Warren, 1962). In 1982, Peignoux et al. noted that rats undergoing total hepatectomy or hepatic devascularization survived longer if their body temperature was maintained at 35.5 °C as compared to 37.5 °C (Peignoux et al., 1982). In a landmark study from Dr. Andrés T. Blei's Laboratory, Traber et al. further demonstrated in 1989 the remarkable influence that body temperature had on the course and the neurological complications of experimental ALF (Traber et al., 1989). In this study, they showed that the spontaneous development of hypothermia (mean 26.9 °C, range 22.5–30 °C) in rats with ALF induced by hepatic devascularization was associated with longer time to develop coma and with a significant attenuation of brain edema, compared to rats maintained at normothermia. Ten years later, Jalan et al. reported the first series of patients with ALF treated with therapeutic hypothermia (Jalan et al., 1999a). Since then, the ability of hypothermia for preventing the cerebral complications of ALF and its potential mechanisms have been investigated in multiple experimental studies (Table 1), mainly from Dr. Butterworth's Laboratory, as well as in small series of patients with ALF (Table 2). Fourteen years after the first RCT of therapeutic hypothermia in traumatic brain injury was reported, the preliminary results of the first RCT of hypothermia in patients with ALF, involving a prophylactic use and three major European centers (King's College Hospital, London, UK; Queen Elizabeth Hospital, Birmingham, UK; and University Hospital of Copenhagen, Copenhagen, Denmark), have been presented at the 2011 European Association for the Study of the Liver (EASL) meeting recently held in Berlin (Larsen et al., 2011) (Fig. 1).

3. Does therapeutic hypothermia effectively control brain edema and intracranial hypertension in ALF?

There are currently no fully-published RCTs evaluating its efficacy in patients with ALF, but most available evidence suggest that