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REVIEW ARTICLE

Therapeutic hypothermia applicable to cardiac surgery

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Abstract

Objective To review the beneficial and adverse effects of therapeutic hypothermia (TH) applicable to cardiac surgery with cardiopulmonary bypass (CPB) in the contexts of various temperature levels and techniques for achieving TH.

Databases used Multiple electronic literature searches were performed using PubMed and Google for articles published from June 2012 to December 2014. Relevant terms (e.g. 'hypothermia', 'cardiopulmonary bypass', 'cardiac surgery', 'neuroprotection') were used to search for original articles, letters and reviews without species limitation. Reviews were included despite potential publication bias. References from the studies identified were also searched to find other potentially relevant citations. Abstracts, case reports, conference presentations, editorials and expert opinions were excluded.

Conclusions Therapeutic hypothermia is an essential measure of neuroprotection during cardiac surgery that may be achieved most effectively by intravascular cooling using hypothermic CPB. For most cardiac surgical procedures, mild to modest (32–36 °C) TH will be sufficient to assure neuroprotection and will avoid most of the adverse effects of hypothermia that occur at lower body core temperatures.

Keywords adverse effects, cardiopulmonary bypass, cardiovascular surgery, hypothermia, neuroprotection.

Introduction

Therapeutic hypothermia (TH), the intentional reduction of the body core temperature (Geurts et al. 2014), has long been applied as a neuroprotective measure during cardiac surgeries in humans and animals (Bigelow et al. 1950; Nathan et al. 2001; Aydemir et al. 2012). Other indications for TH include coronary artery bypass surgery (Boodhwani et al. 2007), surgical repair of thoracoabdominal (Bush et al. 1995; Griepp & Di Luozzo 2013) and intracranial (Todd et al. 2005; Nguyen et al. 2010) aneurysms, pulmonary thromboendarterectomy (Conolly et al. 2010) and surgery for cerebral arteriovenous malformations (Conolly et al. 2010), as well as arterial switch operations (ASO) in neonates (Aydemir et al. 2012). Deep hypothermic circulatory arrest (DHCA) has also been recommended for surgical procedures which carry a high risk for profound intraoperative haemorrhage, such as renal tumours with caval invasion (Conolly et al. 2010).

Moreover, TH has become an integral part of treatment regimens for traumatic brain injury (TBI) (Mrozek et al. 2012; Adelson et al. 2013) and spinal cord injury (SCI) (Kwon et al. 2008; Batchelor et al. 2013; Ahmad et al. 2014), and in comatose human patients after successful cardiopulmonary resuscitation after out-of-hospital cardiac arrest (Kabon et al. 2003; Kelly & Nolan 2010; Diao et al. 2013) and for acute stroke (Berger et al. 2004; Lyden et al. 2006; Hennerici et al. 2013).

Furthermore, systemic reviews have indicated that TH may reduce the risk for mortality and

neurodevelopmental disability in paediatric patients suffering from neonatal hypoxic-ischaemic encephalopathy (HIE) attributable to acute perinatal asphyxia or TBI (Shankaran et al. 2005; Shah 2010; Adelson et al. 2013).

With respect to biomedical research, intentional hypothermia has been recommended as a method of achieving anaesthesia for surgery in neonatal rat and mouse pups (Phifer & Terry 1986; Danneman & Mandrell 1997), as well as in neonatal and early postnatal marsupial young (National Health and Medical Research Council 1990, 2014). Hypothermia has been shown to decrease anaesthetic needs in isoflurane-anaesthetized goats in a rectilinear fashion (Antognini 1993).

The main rationale for using TH, however, has concerned the preservation of the brain, heart and kidneys from ischaemic injury (Wagner et al. 2001; Anttila et al. 2004). The brain is the organ most susceptible to ischaemia during circulatory arrest (Conolly et al. 2010), thus making neuroprotection most vital for a successful outcome (Bernard & Buist 2003). Hypothermia exerts its neuroprotective effects by acting via numerous pathways during ischaemia and the post-ischaemic reperfusion period (Zhao et al. 2007; Lampe & Becker 2011).

More recently, however, the beneficial effects of TH have been discussed in the context of the numerous adverse effects reported for hypothermia, such as coagulopathy (Patt et al. 1988), cardiac dysrhythmias (Aslam et al. 2006) and wound infection (Sessler 2001).

In view of such ongoing discussions, the intention of this review is to elucidate and contrast the advantages and disadvantages associated with different temperatures and techniques of TH with an emphasis on cardiac surgeries that require hypothermic cardiopulmonary bypass (CPB). Therefore, the pathophysiology of ischaemic injury will be addressed first and will be followed by an overview on the mechanisms of action of TH and the various techniques for achieving it.

Ischaemic injury

The initial, acute stage of cerebral ischaemic injury leads to pathophysiological changes (e.g. loss of transmembrane ionic gradients) that occur within the first 90 minutes of the onset of ischaemia (Siesjö 1992; Small et al. 1999). These changes are induced by reduced oxygen and substrate delivery that is inadequate to meet metabolic demands (Wu & Grotta 2013). During hypoxia, intracellular adenosine-triphosphate (ATP) concentration decreases and the cellular metabolism switches into anaerobic glycolysis. Consequently, increases in hydrogen, inorganic phosphate and lactate ions occur in association with intracellular acidosis (Small et al. 1999; Sessler 2001).

The depletion of ATP stores and subsequent Na^+–K^+–ATPase pump failure may be seen as one major cause of the loss of ionic gradients (Hansen 1985; Svyatets et al. 2010). Very early during this stage, an efflux of potassium (K^+) ions occurs and is followed by an increase in Na^+ and Ca^{2+} influxes (Small et al. 1999). In addition to ATP-sensitive K^+ channels, Ca^{2+}-gated K^+ channels may be activated later during this stage when the intracellular calcium concentration ($[Ca^{2+}]_i$) is increased. The profound changes in the K^+ gradient may cause swelling and lysis of astrocytes (Siesjö 1992; Small et al. 1999).

Moreover, subsequent membrane depolarization initiates a marked increase in Ca^{2+} influx via voltage-gated calcium channels, which, in turn, further enhances membrane depolarization (Small et al. 1999).

The consequences of the marked increase in intracellular Ca^{2+} concentration during the initial stage of ischaemic injury are as follows.

Firstly, membrane depolarization causes an increased release of the excitatory neurotransmitter glutamate in the extracellular fluid (Siesjö et al. 1989; Choi 1990; Kempski 1994; Small et al. 1999). In addition, the reduced presynaptic glutamate reuptake attributable to the lack of energy-rich compounds (ATP, phosphocreatine) may further contribute to the high extracellular glutamate concentration (Benveniste et al. 1984).

Secondly, Ca^{2+} influx via both voltage-sensitive calcium channels and the ligand-gated NMDA (*N*-methyl-D-aspartate) receptor channel results in intracellular Ca^{2+} overload and destruction of cellular Ca^{2+} homeostasis (Small et al. 1999).

Thirdly, activation of phospholipases and proteases results in the generation of free fatty acids (e.g. arachidonic acid) and subsequent hydrolysis of mitochondrial and plasma membranes. Therefore, an intracellular Ca^{2+} overload has frequently been considered the major event in ischaemic brain cell death (Siesjö & Bengtsson 1989).

Glutamate, a ligand at both ionotropic receptors [NMDA, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), KA (kainate)] and metabotropic receptors (Siesjö et al. 1989; Small et al.