**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

**Clinical question.**
Your worksheet tracking number is NRP-031A

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<tr>
<th>Is this question addressing an intervention/therapy, prognosis or diagnosis?</th>
<th>Intervention</th>
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State if this is a proposed new topic or revision of existing worksheet: Revision of an existing topic

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

**Search strategy (including electronic databases searched).**

Since this was a modified revision and the prior search was through December 2004, this search was conducted from January 05 through September 09

Key words used included: hyperthermia, pyrexia, fever, cerebral ischemia, hypoxia-ischemia, asphyxia , maternal fever, newborn

Ovid “MeSH Terms” hyperthermia (5602 hits), brain injury (8130 hits) hyperthermia and brain injury (72 hits), maternal pyrexia (4 hits) hyperthermia + fever +newborn (9 hits (one retrieved), hypoxia ischemia + fever+ infant (81 hits), maternal fever + labor (45 hits (two retrieved ), maternal fever + treatment (15 hits (two retrieved)

Embase  Newborn + Hyperthermia + brain injury – (37 hits – one used), maternal fever+ newborn (16 hits )maternal fever + newborn + brain injury (one hit) , maternal fever + labor (41 hits (two retrieved ), maternal fever + treatment (15 hits (two retrieved)

Cochrane library- terms –hyperthermia, Maternal Fever, 0 hits

Review articles 2

End note library – fever, encephalopathy, hyperthermia -23 hits

Last searched September 09

- **State inclusion and exclusion criteria**
  
  Neonatal studies., Review articles on hyperthermia were searched for additional references.

  In the previous review animal studies were reviewed to determine the impact of elevated temperature on the extent of brain injury. Two of these are again included in this review. For the updated review only new human studies are included. Non English abstracts where found were reviewed.

  Excluded Case reports were excluded. No animal studies since 2005

- **Number of articles/sources meeting criteria for further review:**
  
  Identified five articles that directly or indirectly address the specific question
Summary of evidence

**Evidence Supporting Clinical Question**
In neonates born to febrile mothers does intervention to normalize temperature compared to standard care improve outcome

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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*
### Evidence Neutral to Clinical question

In neonates born to febrile mothers does intervention to normalize temperature compared to standard care improve outcome

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**Level of evidence**

A = Return of spontaneous circulation  
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E = Other endpoint  

*Italicics = Animal studies*

### Evidence Opposing Clinical Question

In neonates born to febrile mothers does intervention to normalize temperature compared to standard care improve outcome

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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  

*Italicics = Animal studies*
REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

There appears to be a reasonably consistent epidemiological association between maternal fever and adverse neonatal or infancy outcomes, both in preterm and term infants (Adamson, 1995, Badawi 1998, Lieberman, 2000, Lieberman, 2000, O'Shea, 1998, Petrova, 2001, Perlman, 1999, Impey 2002, Shalak 2005). It is important to note that for many of the studies the working definition for fever was clinical chorioamnionitis. All the studies are retrospective precluding any conjecture as to mechanism of injury. Thus it is unclear whether this association is mediated via infection, the fetal inflammatory reaction or other events.

Fever during labor at term has been associated with

1) Neonatal Depression - Infants whose mothers’ maximum temperature was >101 degrees F as compared to infants of afebrile women were more likely to require bag and mask resuscitation (11.5% vs 3.0%) (Lieberman, 2000) (LOE 4). The perinatal event most commonly associated with a 5-minute Apgar ≤ 5 was maternal fever in 19 infants (32%). By stepwise linear regression analysis, a 5-minute Apgar ≤ 5 was related only to the initial infant temperature (p = 0.009, r = 0.33) (Perlman, 1999 LOE 5).

2) Neonatal Seizures In a logistic regression analysis controlling for confounding factors, intrapartum fever was associated with a 3-4-fold increase in the risk of unexplained neonatal seizures (OR = 3.4, 95% CI = 1.03-9) (Lieberman, 2000 (LOE 4)). Intrapartum fever was also a risk factor for neonatal seizures in a retrospective cohort analysis amongst 11,246,042 singleton live births (Petrova, 2001) (LOE 4).

3) Increased Mortality - A retrospective cohort analysis among 11,246,042 singleton live births in the United States for the period 1995-1997 revealed intrapartum fever (at least 38°C) in 1.6% of cases. Intrapartum fever was associated with early neonatal mortality for both term 1.32(1.14,1.51) and preterm infants 1.32 (1.11,1.56) adjusted OR, 95% CI (Petrova, 2001 #102) (LOE 4).

4) Association with Cerebral Palsy (CP) - temperature > 38 °C in labor was associated with increased risk of unexplained CP (OR, 9.3; 95% CI, 2.7-31.0) (Grether, 1997 (LOE 4)), antepartum maternal temperature > 37.8°C was associated with CP (OR = 2.6 [1.1, 6.0]) in preterm infants (O'Shea, 1998 (LOE 4))

5) Neonatal Encephalopathy There is a three reports linking fever to neonatal encephalopathy (Impey, 2001 LOE 4 Blume 2008 LOE 4).

The mechanism/s contributing to the brain injury with fever remain unclear limiting a specific therapeutic intervention. Experimental elimination of fever with an anti-inflammatory agent (Coimbra LOE 5 1996) or with anesthesia (Koroiwa LOE 5 1991) prevents the progressive of brain injury. However a major limitation to these studies is a short duration of follow up. In one study, a substantial protective effect was observed after a few days but this was greatly attenuated after two months recovery.

There are two clinical studies (Goetz 2004 LOE 1, Goetzl, 2006 LOE 1) that have attempted to examine the effect of an intervention to lower maternal temperature on outcome. In the first study, mothers who were randomized to high or low dose corticosteroids, the fetal exposure to hyperthermia was significantly reduced as was the extent of inflammation (IL-6) with the high dose. However, maternal high-dose corticosteroids increased the rate of neonatal asymptomatic bacteremia. In a second small randomized study the administration of acetaminophen as compared to placebo do not prevent maternal fever. Neither study was powered to address any of the morbidities mentioned previously. Importantly newborns with fever at birth normalize temperature without any intervention with an hour following delivery. On balance the clinical data suggest that maternal fever during labor is associated with an increased risk of neonatal mortality and morbidity. There are no studies to indicate that lowering maternal temperature can reduce either neonatal mortality or morbidity. However in one study Goetzl 195; 1031:2006 the use of corticosteroids to lower temperature was associated with increased occurrence of asymptomatic bacteremia in the neonates.

Conclusion

DISCLAIMER: Potential possible wording for a Consen sus on Science Statement. Final wording will differ due to other input and discussion.

CONSENSUS ON SCIENCE:
Infants born to febrile mothers have been reported to have a higher incidence of perinatal respiratory depression, neonatal seizures, cerebral palsy and increased risk of mortality (LOE 4, Petrova 2001;98:20, Lieberman 2000;106:983, Grether 1997;278:207). In one study neonatal fever at birth resolved spontaneously within 60 minutes (LOE 4, Shalak, 2005 25, 447). In a randomized study high dose corticosteroids lowered maternal temperature but was associated with an increased number of cases of asymptomatic bacteremia in neonates (LOE 1, Goetzl 2006;195;1031).

TREATMENT RECOMMENDATION:

Acknowledgements:
## Citation List

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**Neonatal Studies**


**OBJECTIVE--**Preliminary investigation of the contribution of adverse antepartum and intrapartum factors to neonatal encephalopathy in singleton neonates born full term. DESIGN--Matched case-control study based on incidence density sampling of controls. SETTING--Two major teaching hospitals (one paediatric and one obstetric) and three peripheral maternity hospitals in Perth, Western Australia (population 1.2 million). SUBJECTS--89 cases, all the full term singleton neonates born during an eight month period in 1992 who fulfilled one or more of six criteria during the first week of life (seizures, abnormal conscious state, persistent hypertonia or hypotonia, and feeding or respiratory difficulties of central origin). One full term control infant without neonatal encephalopathy was matched to each case by sex, hospital of delivery, time of day and day of the week of birth, and maternal health insurance status. MAIN OUTCOME MEASURES--Odds ratio estimates of relative risk of neonatal encephalopathy associated with antepartum and intrapartum factors. RESULTS--Estimated incidence of moderate or severe encephalopathy in first week of life was 3.75 per 1000 full term live births. Thirteen cases and no controls had evidence suggestive of important intrapartum hypoxia, and in only five of these cases was the neurological condition at birth attributed to events during the intrapartum period. Univariate conditional logistic regression analysis identified significant differences between cases and controls for maternal vaginal bleeding in pregnancy, maternal thyroxine treatment, congenital abnormalities, induction of labour, interval from membrane rupture to delivery, maternal pyrexia in labour, augmentation of labour, abnormal intrapartum cardiotocograms, and meconium in labour. Family history of convulsions also approached significance. CONCLUSIONS--Our preliminary results suggest that intrapartum hypoxia, according to currently used criteria, was not the cause of neonatal encephalopathy in most cases in this population. Our findings suggest that many aetiologies of neonatal encephalopathy originate in the antepartum period.

Comment Retrospcective case control study. Maternal fever was one of several factors associated with neonatal encephalopathy

**Level of Evidence 4**

Quality of evidence-Fair

Evidence - Supportive


**OBJECTIVE:** To identify intrapartum predictors of newborn encephalopathy in term infants. DESIGN: Population based, unmatched case-control study. SETTING: Metropolitan area of Western Australia, June 1993 to September 1995. Subjects: All 164 term infants with moderate or severe newborn encephalopathy; 400 randomly selected controls. MAIN OUTCOME MEASURES: Adjusted odds ratio estimates. RESULTS: The birth prevalence of moderate or severe newborn encephalopathy was 3.8/1000 term live births. The neonatal mortality was 9.1%. Maternal pyrexia (odds ratio 3.82), a persistent occipitoposterior position (4.29), and an acute
intrapartum event (4.44) were all risk factors for newborn encephalopathy. More case infants than control infants were induced (41.5% and 30.5%, respectively) and fewer case infants were delivered by caesarean section without labour (3.7% and 14.5%, respectively). Operative vaginal delivery (2.34) and emergency caesarean section (2.17) were both associated with an increased risk. There was an inverse relation between elective caesarean section (0.17) and newborn encephalopathy. After application of a set of consensus criteria for elective caesarean section only three (7%) eligible case mothers compared with 33 (65%) eligible control mothers were sectioned electively. Of all the case infants, 113 (69%) had only antepartum risk factors for newborn encephalopathy identified; 39 (24%) had antepartum and intrapartum factors; eight (5%) had only intrapartum factors; and four (2%) had no recognised antepartum or intrapartum factors. Conclusions: The causes of newborn encephalopathy are heterogeneous and many relate to the antepartum period. Elective caesarean section has an inverse association with newborn encephalopathy. Intrapartum hypoxia alone accounts for only a small proportion of newborn encephalopathy. These results question the view that most risk factors for newborn encephalopathy lie in the intrapartum period.

Comment: Case control retrospective study from same authors as above. Maternal fever was one of several risk factors associated with neonatal encephalopathy

Level of Evidence 4
Quality of evidence-Fair
Evidence - Supportive

Blume HK, Li CI, Loch CM Koepsell TD Intrapartum fever and chorioamnionitis as risks for encephalopathy in term newborns Developmental Medicine & Child Neurology 2008;50:19-24

In this study we examined the relationship between diagnoses of isolated intrapartum fever or chorioamnionitis and the risk of encephalopathy in term newborns. We conducted a population-based, case2014-control study in Washington State using 1994 to 2002 linked data from the Washington State Birth Registry and the Comprehensive Hospital Abstract Reporting System (CHARS). We identified 1060 singleton, term newborns (602 males, 458 females) with International Classification of Diseases (ICD-9) diagnoses consistent with encephalopathy, and 5330 unaffected control newborns (2756 males, 2574 females). Intrapartum fever was defined by a diagnosis of intrapartum temperature ≥38°C in the birth registry or CHARS databases. Chorioamnionitis was defined using ICD-9 diagnoses recorded in CHARS. We identified 2.2 cases of encephalopathy per 1000 births. Isolated intrapartum fever was associated with a 3.1-fold (95% confidence interval [CI] 2.3-4.2) increased risk of newborn encephalopathy. Chorioamnionitis was associated with a 5.4-fold (95% CI 3.6-7.8) increased risk of encephalopathy. We found that isolated intrapartum fever and chorioamnionitis were independently associated with an increased risk of encephalopathy in term infants. Our data also indicate that there is a spectrum of risk for encephalopathy in term infants exposed to intrapartum fever. Infants born to women with signs of chorioamnionitis other than isolated intrapartum fever may be at higher risk of encephalopathy than those exposed only to isolated intrapartum fever.

Comment: Population based study that showed an independent risk of encephalopathy with isolated intrapartum fever

Level of Evidence 4
Quality of evidence-Fair
Evidence - Supportive


CONTEXT: Exposure to maternal or placental infection is related to risk of preterm birth and, in premature infants, of brain lesions predictive of cerebral palsy (CP). Few studies have investigated whether maternal infection during the admission for delivery as a possible risk factor for CP in infants born weighing 2500 g or more. DESIGN: Population-based case-control study. SETTING: All hospitals in 4 northern California counties, 1983 through 1985. PARTICIPANTS: A total of 46 children with disabling spastic CP who had no recognized prenatal encephalopathy Conclusion: Intrauterine exposure to maternal infection was associated with a marked increase in risk of CP in infants of normal birth weight. Newborns exposed to maternal infection, both cases and controls, had 5-minute Apgar scores below 6 more often than those unexposed. Among children with CP, those born to infected women were more often hypotensive, needed intubation, had neonatal seizures, and received a clinical diagnosis of hypoxic-ischemic encephalopathy Conclusion: Intrauterine exposure to maternal infection was associated with a marked increase in risk of CP in infants of normal birth weight. Maternal infection was also linked with low Apgar scores, other evidence of hypotension [corrected] and need for resuscitation, and neonatal seizures-signs commonly attributed to birth asphyxia.

Comment: Retrospective case control study-maternal fever was associated with 9.3 fold increased risk for unexplained CP. Also maternal infection was associated with lower 5 minute Apgar score and neonatal seizures

Level of Evidence 4
Quality of evidence-Good
Evidence - Supportive

Goetzl, Laura, Rivers, Jose, Evans, Tracy, Citron, Deborah R. Richardson, Barbara E.Lieberman, Ellice, Suresh, Maya S.Prophylactic Acetaminophen Does Not Prevent Epidural Fever in Nulliparous Women: A Double-Blind Placebo-Controlled Trial J Perinatol 24; 471-475 2004

OBJECTIVE: Epidural analgesia is associated with a four- to five- fold increase in noninfectious maternal fever in nulliparous women. Fever prophylaxis may safely reduce both unnecessary neonatal sepsis evaluations and the potential effect of fever on the fetus.

STUDY DESIGN: We performed a randomized double-blind placebo-controlled study. Immediately after epidural placement, full-term nulliparas with a temperature ≥<99.5°F received acetaminophen 650 mg or placebo, per rectum, every 4 hours. Tympanic membrane temperatures were measured hourly. Our power was to detect an effect of acetaminophen treatment on maternal temperature over time was 90%.

RESULTS: In all, 21 subjects were randomized to each arm. Treatment with acetaminophen did not impact maternal temperature curves. Fever >100.4°F was identical in the acetaminophen and placebo groups (23.8%, p=1.0). Neonatal surveillance blood cultures did not reveal occult infection.

CONCLUSIONS: Acetaminophen prophylaxis prevented neither maternal hyperthermia nor fever secondary to epidural analgesia, suggesting that the mechanism underlying fever does not include centrally mediated perturbations of maternal thermoregulation.

Comment: Small randomized study that showed that acetaminophen did not prevent maternal fever-small study

Level of Evidence 1
Quality of evidence-Fair
Evidence - Neutral
OBJECTIVE: To determine whether the reported association of maternal fever with neonatal encephalopathy is independent of other associated intrapartum risk factors. DESIGN: Prospective cohort study. POPULATION: 4,915 low risk women in labor at 36-41 weeks of gestation. METHODS: Using logistic regression with odds ratios and 95% confidence intervals, the incidence of neonatal encephalopathy and other neonatal outcomes of women who had an intrapartum fever >37.5 degrees C was compared with those who did not.

Results: The cohort comprised 33% of all deliveries during the study period. Neonatal encephalopathy was diagnosed in 3.25/1,000 births. The incidence of intrapartum fever was 6.8%. Maternal fever was strongly associated with neonatal encephalopathy (crude OR 10.8, 95% CI 4.0-29.3). Univariate analysis showed maternal fever was associated with epidural analgesia, nulliparities, induction, longer labor, oxytocin administration, greater fetal birthweight and gestational age and instrumental vaginal delivery, but not with prolonged (>24 hours) prelabour rupture of the membranes. The association of fever with neonatal encephalopathy persisted having adjusted for these covariates (adjusted OR 4.72, 95% CI 1.28-17.4).

Conclusions: The association between maternal intrapartum fever and neonatal encephalopathy is independent of other known intrapartum risk factors. This provides further evidence for the role of inflammatory processes in the aetiology of neonatal neurological morbidity.

Comment: Cohort study showing an independent association between neonatal encephalopathy and maternal fever

Level of Evidence 4
Quality of evidence - Fair
Evidence – Supportive/Negative


OBJECTIVE: Early-onset neonatal seizures are a strong predictor of later morbidity and mortality in term infants. Although an association of noninfectious intrapartum fever with neonatal seizures in term infants has been reported, it was based on only a small number of neonates with seizures. We therefore conducted a case control study to investigate this association further. METHODS: All term infants with neonatal seizures born at Brigham and Women's Hospital between 1989 and 1996 were identified. For this study, cases consisted of all term neonates with a confirmed diagnosis of seizure born after a trial of labor for whom no proximal cause of seizure could be identified. Infants with sepsis or meningitis were excluded. Four controls matched by parity and date of birth were identified for each case. The rate of intrapartum maternal temperature >100.4 degrees F was compared for case infants and controls. Potential confounding was controlled in logistic regression analysis Results: Cases comprised 38 term infants with unexplained seizures after a trial of labor and 152 controls were identified. Infants with seizures were more likely to be born to mothers who were febrile during labor (31.6% vs 9.2%). In almost all cases, the fever developed during labor (94.7% cases, 97.4% controls). At admission, mothers of infants with seizures were not significantly more likely to have factors associated with concern about infection such as a white blood cell count >15 000/mm(3) (28.9% vs 19.1%) and premature rupture of the membranes (15.8% vs 17.8%). In a logistic regression analysis controlling for confounding factors, intrapartum fever was associated with a 3.4-fold increase in the risk of unexplained neonatal seizures (odds ratio = 3.4, 95% confidence interval = 1.03-10.9).

Conclusions: The data indicate that intrapartum fever, even when unlikely to be caused by infection, is associated with a fourfold increase in the risk of unexplained, early-onset seizures in term infants

Comment: Case control retrospective study. Fever was associated with 4 fold-increased risk of unexplained seizures

Level of Evidence 4
Quality of evidence - Good
Evidence - Supportive


OBJECTIVE: Much of fever during term labor may not be infectious but rather a consequence of the use of epidural analgesia. Thus the association of elevated maternal intrapartum temperature with neonatal outcome when the infant does not develop an infection was evaluated. METHODS: 1218 nulliparous women with singleton, term pregnancies in a vertex presentation and spontaneous labor were studied. Women were excluded if their temperature was >99.5 degrees F at admission for delivery, if they were diabetic or had an active genital herpes infection or if their infant developed a neonatal infection, or had a major malformation. Maximum intrapartum temperature was categorized as: <100.4 degrees F (afebrile), 100.5 degrees F to 101 degrees F, and >101 degrees F.

RESULTS: During labor, 123 women (10.1%) developed a fever >100.4 degrees F; 62 (5.1%) women had a maximum temperature of 100.5 degrees F to 101 degrees F and 61 (5.0%) women had a maximum temperature >101 degrees F. Of febrile women, 97.6% had received epidural analgesia for pain relief. Infants of women developing a fever >100.4 degrees F were more likely to have a 1-minute Apgar score <7 (22.8% for >100.4 degrees F vs 8.0% for afebrile) and to be hypotonic after delivery (4.8% for >100.4 degrees F vs 5.5% for afebrile). Compared with infants of afebrile women, infants whose mothers' maximum temperature was >101 degrees F were more likely to require bag and mask resuscitation (11.5% vs 3.0%) and to be given oxygen therapy in the nursery (8.2% vs 1.3%). A higher rate of neonatal
seizure with fever (3.3% vs.2%), but the number of infants with seizure was small (n = 4). All associations remained essentially the same after controlling for confounding in logistic regression analyses. CONCLUSIONS: Intrapartum maternal fever, particularly if >101 degrees F, was associated with a number of apparently transient adverse effects in the newborn. Larger studies are needed to investigate the association of intrapartum fever with neonatal seizures and to determine whether any lasting injury to the fetus may occur.

Critique: Retrospective cohort study evaluating the impact of varying maternal fever on early neonatal outcomes. Fever was associated with a one minute Apgar < 7 and a greater likelihood that an infant will require BMV in the DR. An increase in seizures was noted although numbers were small. No long term outcome data.

Level of Evidence 4
Quality of evidence: Good
Evidence - Supportive


Very low-birthweight infants constitute more than one-quarter of all new cases of cerebral palsy. A case-control study of associations between antenatal maternal infection and cerebral palsy in very low-birthweight infants was performed. Cases and controls were selected from a cohort of 1238 consecutive infants who: (1) had birthweights between 500 and 1500 g and no major congenital anomaly; (2) were born January 1986 to 31 December 1993 to a mother residing in 1 of 17 counties in north-west North Carolina; and (3) were delivered at the only tertiary obstetric referral centre in those same 17 counties. A total of 984 of these infants (79%) survived to 1 year of age (adjusted for degree of prematurity) and were scheduled for a multidisciplinary examination; 815 (83%) came as scheduled. Excluding two cases attributable to post-neonatal events, 62 cases of cerebral palsy were identified. Controls were the two infants, without cerebral palsy, born closest in time to each case. Medical records were reviewed by a nurse who was not aware of which subjects were cases. Among possible markers of intra-anniotic infection, those associated most strongly with cerebral palsy were chorioamnionitis diagnosed by an obstetrician (odds ratio [OR] adjusted for gestational age [95% confidence limits] = 2.6 [1.0, 6.5]), antepartum maternal temperature > 37.8 degrees C (OR = 2.6 [1.1, 6.0]), uterine tenderness (OR = 2.6 [0.8, 9.3]), maternal receipt of antibiotics (OR = 2.2 [1.0, 4.7]) and neonatal sepsis in the first week of life (OR = 2.9 [0.9, 8.9]). All of these associations were stronger for diplegia than the other clinical subtypes of cerebral palsy. The association with chorioamnionitis and spastic diplegia persisted when adjusted for maternal magnesium sulphate receipt, maternal betamethasone receipt, method of delivery (vaginal vs. abdominal), acidosis on the neonate's initial arterial blood gas, systolic blood pressure < 30 mmHg and the diagnosis of major neonatal neurosonographic abnormality.

Comment: Case control retrospective study in very low birthweight infants. Maternal fever OR = 2.6 was amongst other markers associated with CP at one year (mainly diplegia). Data does not distinguish fever from other putative markers of clinical infection.

Level of Evidence 4
Quality of evidence: Good
Evidence - Supportive


Objective: To examine the association of intrapartum fever with infant morbidity and early neonatal (0-6 days) and infant (0-364 days) death. Methods: A retrospective cohort analysis among singleton live births in the United States for the period 1995-1997 using the National Center for Health Statistics linked birth-infant death cohort data was carried out. Results: Among the 11,246,042 singleton live births during the study period, intrapartum fever (at least 38C) was recorded in 1.6%. Intrapartum fever was associated with early neonatal (adjusted odds ratio [OR], 95% confidence interval [CI] for preterm and term infants respectively: 1.32; 1.11, 1.56 and 1.67; 1.14, 2.46) and infant (OR, 95% CI for preterm and term, respectively: 1.31; 1.14, 1.51 and 1.27; 1.01, 1.59) death among nulliparous mothers. Among preterm infants of parous mothers, intrapartum fever was associated with early neonatal (OR 1.29, 95% CI 1.01, 1.64) death. In the combined analyses (infants of nulliparous and parous mothers), intrapartum fever was a strong predictor of infection-related death. These associations were stronger among term (OR 3.16, 95% CI 1.56, 6.40 for early neonatal; OR 1.75, 95% CI 1.20, 2.57 for infant death) than preterm infants (OR 1.52, 95% CI 1.15, 2.00 for early neonatal; OR 1.29, 95% CI 1.05, 1.57 for infant death). Intrapartum fever was also a risk factor for meconium aspiration syndrome, hyaline membrane disease, neonatal seizures, and assisted ventilation. CONCLUSION: Intrapartum fever is an important predictor of neonatal morbidity and infection-related mortality.

Critique: Retrospective cohort national study of singletons born over two years. Intrapartum fever was associated with increased mortality and morbidity including seizures. Clearly not a cause and effect relationship.

Level of Evidence 4
Quality of evidence: Good
Evidence - Supportive


The objectives of this study were to determine in term infants: (1) the importance of maternal fever (maternal temperature > 38 degrees C) as a risk factor for neonatal depression and (2) the clinical course of infants admitted to the Neonatal Intensive Care Unit (NICU) born to mothers with fever. For 2 years, 59 (0.24%) of 25,000 term infants had a 5-minute Apgar score < or = 5 and 22 (0.08%) infants were administered chest compressions with or without epinephrine as part of cardiopulmonary resuscitation (CPR) in the delivery room. The perinatal event most commonly associated with a 5-minute Apgar score < or = 5 was maternal fever in 19 infants (32%), with meconium + fetal heart rate abnormality (FHR) abnormalities in 15 (25%), and FHR abnormalities only in 13 (22%); additional associations (n = 13). By stepwise linear regression analysis, a 5-minute Apgar < or = 5 was related only to the initial infant temperature (p = 0.009, r = 0.33). Maternal fever noted in six infants (27%) was also commonly associated with CPR, as was the presence of meconium + FHR abnormalities in seven (32%), and FHR abnormalities only in four (18%). One hundred thirteen (7.5%) of the approximately 1,500 term infants born to mothers with maternal fever were admitted to the NICU. In addition to fever, the labor was complicated by meconium (in 16 infants), meconium + FHR abnormalities (in 19 infants), and FHR abnormalities only (in 11 infants). Resuscitative interventions in the delivery room included oxygen only in 43 infants, bag and mask ventilation in 38, continuous positive airway pressure in 10, intubation in 16, and CPR in six infants. Forty-nine infants (43%) had an initial temperature > 38 degrees C including 13 (11%) with an initial temperature > 39 degrees C. Twelve (10%) infants remained intubated on admission and five required ventilator support > 24 hours. One blood culture was positive although all mothers were pretreated with
Comment Case series. Maternal fever was associated with a low 5 minute Apgar score and the need for CPR

Level of Evidence 5
Quality of evidence-Fair
Evidence - Supportive


Objectives (1) To determine the incidence and the time course of elevated temperature following delivery in term infants with clinical chorioamnionitis (CHORIO) and (2) to determine if the extent of temperature elevation at birth is associated with increased likelihood of NICU Admissions, birth depression, or with short-term neurological abnormalities.

Methods The infants were divided into two groups based on the median admission rectal temperature of 37.8°C for the cohort. Depression at birth was defined as either the need of positive pressure ventilation for >2 minutes, intubation, or Apgar score <6 at 5 minutes. Neurological examination and assessment of encephalopathy (Sarnat staging) was performed at birth and daily thereafter, by one investigator blinded to temperature findings.

Results Infants with higher rectal temperature at 30 minutes of life were more likely to be admitted to NICU: OR (2.8, 95% confidence interval (CI) [1.8 to 4.3]), and were more likely to have birth depression OR (3.95% CI [1.4 to 6.5]). For infants in NICU, a rectal temperature above 37.8°C was present in 87% in the delivery room, persisted in 47% at 30 minutes, and declined to a normal temperature at 60 minutes of life in the absence of medical interventions. There was no relationship between neurological scores and neonatal temperature.

Conclusions Term infants exposed to CHORIO who had a higher neonatal temperature at 30 minutes of life, were more likely to be admitted to the NICU and to have birth depression, than infants with lesser degree of temperature elevation after birth. Within the NICU group, the extent of temperature elevation was not associated with worse neurological outcomes.

Comment Cohort study that infants born to mothers with chorioamnionitis were an elevated rectal temperature at 30 minutes of life were more likely to be admitted to intensive care, were more likely to have birth depression. Temperature declined within 60 minutes spontaneously. Ws not associated with neurologic morbidity but was not powered to address this question

Level of Evidence 4
Quality of evidence-Good
Evidence - Supportive

Pediatric


Twenty children who were successfully resuscitated after cardiac arrest (CA) were retrospectively studied to examine the hypothesis that children with CA may have a worse neurological outcome in hot weather than in cold weather. Of 7 children with CA in the cold season (atmospheric temperature < 14 degrees C), 4 in the warm season (14-24 degrees C) and 9 in the hot season (> 24 degrees C), 5 (71%), 2 (50%), and 1 (11%), respectively, recovered consciousness (P < 0.05). Postresuscitative hyperthermia tended to be frequently observed in the group of children who suffered CA in the hot season, and it appeared to be associated with neurological damage. This preliminary study suggests that the neurological outcome of children with CA changes with the seasons, with a worse neurological outcome for CA in hot weather than in cold weather. A prospective study is required to determine whether, in a hot season or area, cooling of pediatric cardiac arrest victims during cardiopulmonary resuscitation on the scene improves the neurological outcome.

Criticite- Worse outcome was noted during the hot season than during the cold seasons –the association with neurologic outcome was weak

Level of Evidence 5
Quality of evidence-Fair
Evidence - Supportive

Adult Studies


BACKGROUND AND PURPOSE: No definitive data are yet available on the effects of body temperature on neurological damage after cerebral ischemia in humans. Experimental animal models have provided much evidence, but to our knowledge, only two studies on the relationship between fever and prognosis of stroke in humans have been published. The aim of our study was to investigate the prognostic role of fever in the first 7 days of hospitalization in a cohort of patients admitted to our hospital for acute stroke. METHODS: We analyzed the data of 183 patients included in a prospective observational prognostic study. Vital status at 30 days was considered the main outcome and was obtained for all patients. Age, level of consciousness, and glycemia at the time of hospitalization were considered covariates for an exact logistic regression analysis. The maximum temperature recorded during the first 7 days dichotomized as "no or low fever" versus "high fever" was added to the model. Death within 10 days, taken as a secondary outcome suggestive of death from neurological causes, was analyzed with exact permutation tests. RESULTS: Of the 183 patients analyzed in this study, 43% had fever during the first 7 days after hospitalization. The mean value of the maximum temperature recorded during the first 7 days in the 78 febrile patients was 38.3 degrees C, and the median was 37.9 degrees C. Onset of fever occurred in only 15% of febrile patients during the first day and in 49% on the second. The prognostic roles of age, level of consciousness, and glycemia were confirmed by exact logistic regression. Degree of consciousness impairment was the strongest prognostic variable, with an odds ratio (OR) of 11.4 (95% confidence interval [CI], 4.4 to 31.6). High fever (maximum temperature recorded during the first 7 days > or = 37.9 degrees C) was an independent factor for a worse prognosis, with an OR of 3.4 (95% CI, 1.2 to 9.5). The OR of dying within 10 days versus dying between 11 and 30 days was 4.9 (95% CI, 1.2 to 25.2) in patients with high fever with respect to all other patients.

CONCLUSIONS: Fever in the first 7 days was an independent predictor of poor outcome during the first month after a stroke. No data were available on the underlying causes of fever, but the higher risk of death in the first 10 days, most frequently attributed to neurological mechanisms, suggested that high temperature was an independent component of poor prognosis and not only an epiphenomenon of other complications in the course after a stroke. In agreement with animal studies, we found that patients with higher temperature had a worse stroke outcome
Level of Evidence 5
Quality of evidence-Fair
Evidence – Supportive


BACKGROUND and PURPOSE: The association between hyperthermia and early neurological deterioration, increased morbidity, and mortality in acute ischemic stroke is well known. However, the timing at which the cerebral lesion may be aggravated by high temperature has not been firmly established. The aim of this study was to determine the prognostic value of body temperature measured at different times after onset of stroke. METHODS: Axillary temperature was recorded every 2 hour hours for 72 hours in 260 patients with a hemispheric cerebral infarction of <24 hours' duration. A potential infectious focus was examined in all patients with hyperthermia (temperature >37.5 degreesC in any of the assessments). Stroke severity was quantified with the Canadian Stroke Scale on admission. The relationship between the highest temperature recorded in each 6-hour interval from stroke onset and stroke outcome (Canadian Stroke Scale and Barthel Index at 3 months) or infarct volume was evaluated by correlation analyses. The importance of the time at which hyperthermia was first detected was assessed by logistic regression analysis. RESULTS: During the first 72 hours, 158 patients (60.8%) had hyperthermia, and in 57.6% of them an infectious cause was identified. Mortality rate at 3 months was 1% in normothermic patients and 15.8% in hyperthermic patients (P<0.001). The correlation coefficients between the final infarct volume, Canadian Stroke Scale and Barthel Index scores at 3 months, and each temperature recording decreased progressively over time from symptom onset. Hyperthermia initiated within the first 24 hours from stroke onset, but not afterward, was independently related to larger infarct volume (odds ratio [OR]=3.23, 95% CI=1.63 to 6.43; P<0.001) and higher neurological deficit (OR=3.06, 95% CI=1.70 to 5.33; P<0.001) and dependency (OR=3.41, 95% CI=1.69 to 6.88; P<0.002) at 3 months. The infectious origin of hyperthermia was not associated with poorer outcome or greater infarct volume. CONCLUSIONS: The relationship between brain damage and high temperature is greater the earlier the increase in temperature occurs. However, only body temperature within the first 24 hours from stroke onset is associated with poor outcome and large cerebral infarcts.

Level of Evidence 5
Quality of evidence-Fair
Evidence – Supportive


Previous studies showed that elevated body temperature early after ischemic stroke is associated with severe neurological deficit and a poor outcome. The aim of this study was to analyse the prevalence and putative etiology of febrile body temperature (>38.0 degrees C) early after stroke and to investigate the association between body temperature, stroke severity and outcome. We investigated 119 consecutive patients who were admitted within 24 h after ischemic stroke. Patients were examined for infection before ischemia using a standardized questionnaire and received daily clinical examination after stroke. In case of fever, standardized radiological and microbiological examinations were performed. Fever within 48 h after stroke was observed in 30 (25.2%) patients. The probable cause of fever was infective or chemical aspiration pneumonia (n=12), other respiratory tract infection (n=7), urinary tract infection (n=4), viral infections (n=3) or insufficiently defined (n=5). (One patient had two potential causes of fever.) In thirteen of these patients, infection was most probably acquired before stroke. Fever newly developed more often during day 1 to 2 than day 3 to 7 after stroke (P=0.016). Fever was associated with a more severe deficit on admission independent from age, vascular diseases and risk factors (odds ratio 9.6; 95% confidence interval 3.1-29). Fever is a frequent complication early after stroke and in the majority of cases, it can be explained by infection or chemical aspiration pneumonia. In about half of the infected patients, infection was most probably acquired before stroke. Fever was associated with a more severe neurological deficit on admission.

Level of Evidence 5
Quality of evidence-Fair
Evidence – Supportive


BACKGROUND AND PURPOSE: The effect of pyrexia on cerebral ischemia has been extensively studied in animals. In humans, however, such studies are small and the results conflicting. We undertook a meta-analysis using all such published studies on the effect of hyperthermia on stroke outcome. METHODS: Three databases were searched for all published studies that examined the relationship of raised temperature after stroke onset and eventual outcome. Combined probability values and odds ratios were obtained. A heterogeneity test was performed to ensure that the data were suitable for such an analysis. Morbidity and mortality were used as outcome measures. RESULTS: Nine studies were identified totaling 3790 patients, providing the study with 99% power to detect a 9% increase in morbidity and 84% power to detect a 1% increase in mortality for the pyrexial group. The combined odds ratio for mortality was 1.19 (95% CI, 0.90 to 1.45). A heterogeneity test was highly nonsignificant (P=0.05) for mortality, suggesting that the data were sufficiently similar to be meta-analysed. Combined probability values were highly significant for both morbidity (P<0.0001) and mortality (P<0.00000001). CONCLUSIONS: The results from this meta-analysis suggest that pyrexia after stroke onset is associated with a marked increase in morbidity and mortality. Measures should be taken to combat fever in the clinical setting to prevent stroke progression. The possible benefit of therapeutic hypothermia in the management of acute stroke should be further investigated.

Comment- Meta analysis showing high probability values for both mortality and morbidity with fever following a stroke. Again no cause and effect
Level of Evidence 5
Quality of evidence-Good
Evidence - Supportive

**Animal Studies**


We investigated whether moderate, transient whole-body hyperthermia (approximately 39.6 degrees C), if imposed 1 day following a brief episode of forebrain ischemia, would affect the neuropathologic outcome. Forty-two Wistar rats were subjected to either a 5- or 7-minute period of bilateral common carotid artery occlusion plus hypotension (50 mm Hg), or to the equivalent sham procedure. Twenty-four hours later, rats of one subgroup were placed into a hyperthermic chamber containing high-intensity lamps designed to elevate rectal temperature to 39 to 40 degrees C for 3 hours. Normothermic subgroups received the same procedures, but the heating lamps were turned off. Eight days after brain ischemia or the sham procedure, brains were perfusion-fixed, and numbers of ischemic-appearing CA1 pyramidal neurons were counted. In rats with 7-minute forebrain ischemia, delayed hyperthermia increased mean numbers of ischemic neurons by 2.6- to 2,7-fold in all subsectors of area CA1 (p < 0.05, ANOVA). Delayed hyperthermia in 5-minute ischemic rats also tended to increase mean numbers of ischemic neurons (by 11-fold in lateral, 6-fold in middle, and 5-fold in medial CA1 subsectors), but these differences were not statistically significant. We conclude that moderate, transient hyperthermia, even if occurring 1 day after a 7-minute global ischemic insult, exacerbates the extent of ischemic neuronal injury.

Comment Global ischemic model showing the delayed adverse effect (24 hours) of hyperthermia in a rat model

Level of Evidence 5
Quality of evidence-Good
Evidence - Supportive


OBJECTIVE: To examine whether hyperthermia aggravates cerebral injury in acute ischemia by an excitotoxic mechanism, we studied the relationship between body temperature on admission and CSF concentrations of neuroexcitatory amino acids in 128 patients with acute ischemic stroke of less than 24 h duration. METHODS: Stroke worsening was defined as the percent change between the Canadian Stroke Scale (CSS) at 48 h and the CSS on admission. Infarct volume was measured on days 4-7 on cranial computed tomography. Excitatory amino acids were analyzed using HPLC. RESULTS: Glutamate concentration [median (min.-max.)] was 11 (2-19) micromol/l in hyperthermic patients (body temperature >37.5 degreesC) and 5 (2-22) micromol/l in normothermic patients (p < 0.0001). Glycine concentration in hyperthermic and normothermic patients was 16 (3-21) micromol/l and 9 (3-50) micromol/l, respectively (p < 0.0001). Glutamate was significantly higher in patients with hyperthermia only during the first 12 h after the onset of symptoms. The CSF concentrations of glutamate (r = 0.52; p < 0.0001) and glycine (r = 0.62; p < 0.0001) correlated with body temperature. Body temperature was significantly related to stroke worsening and infarct size, but this effect was dependent on the glutamate effect. CONCLUSION: Glutamate and glycine release during the acute phase of cerebral ischemia could be responsible for the increased brain damage in hyperthermia.

Comment Data suggest that temperature elevation results in glutamate and/or glycine release from neurons that may represent one mechanism of injury.

Level of Evidence 5
Quality of evidence-Good
Evidence - Supportive


We investigated the effect of mild whole-body hyperthermia (40 degrees C) on a permanent middle cerebral artery occlusion (MCAo) model in Fisher rats by subjecting them to MCAo under the following conditions: (1) normothermia (n = 20); (2) hyperthermia (n = 14) before (1 hour), during, and after (1 hour) MCAo; and (3) post-MCAo hyperthermia (n = 14) for 1 hour. We measured brain and body temperatures during the experiment using micro-thermocouples and blood-brain-barrier (BBB) permeability using Evans blue staining of the brain. We measured the volume of the infarcted brain tissue 4 days after MCAo. We detected no differences in BBB permeability among three groups. The volume of infarcted tissue was significantly greater (p < 0.05) for the two groups of hyperthermic animals than the normothermic animals. Our data suggest that mild hyperthermia, both during and after induction of ischemia, has a detrimental effect on the ischemic infarct volume in this model.

Comment This study demonstrates the adverse effect of hyperthermia both during and following the hypoxic-ischemic insult

Level of Evidence 5
Quality of evidence-Good
Evidence - Supportive


BACKGROUND AND PURPOSE: It has been recognized that postischemic pharmacological interventions may delay the evolution of neuronal damage rather than provide long-lasting neuroprotection. Also, fever complicates recovery after stroke in humans. Here we report the effects of late postischemic treatment with hypothermia and an antipyretic/anti-inflammatory drug, dipryone, on cell damage at 1 week and 2 months of survival. METHODS: Rats were subjected to 10 minutes of forebrain ischemia. Hypothermia (33 degrees C) was induced at 2 hours of recovery and maintained for 7 hours. Dipryone (100 mg.kg-1/IP) was given every 3 hours from 14 to 72 hours of recovery. Temperature was measured every 6 hours for 60 days. Neuronal damage was assessed at 7 days and 2 months of recovery.

RESULTS: From 17 to 72 hours of recovery, a period of hyperthermia was observed, which dipyrone abolished but postischemic hypothermia treatment did not. Dipyrone treatment diminished neuronal damage by 43% at 7 days, and at 2 months of survival, a minor (16%) protection was seen. Postischemic hypothermia treatment alone delayed neuronal damage. In contrast, combined treatment of hypothermia followed by dipyrone markedly diminished neuronal damage by more than

50% at both 7 days and 2 months of recovery. CONCLUSIONS: Neuronal degeneration may be ongoing for months after a transient ischemic insult, and prolonged protective measures need to be instituted for long-lasting neuroprotective effects. Hyperthermia during recovery worsens ischemic damage, and processes associated with inflammation may contribute to the development of neuronal damage. An early and extended period of postischemic hyperthermia provides a powerful and long-lasting protection if followed by treatment with anti-inflammatory/antipyretic drug.

Comment The effect of post-ischemic hyperthermia was partly transient. Long lasting and clinically important protection required a combination of early and extended post-ischemic hyperthermia in combination with antipyretic treatment. Speaks directly to the issue of fever and brain injury.

Level of Evidence 5
Quality of evidence-Good
Evidence - Supportive

The morphological consequences of delayed posttraumatic brain hyperthermia (39 degrees C) after fluid percussion brain injury were assessed in rats. Sprague-Dawley rats anesthetized with 4% halothane and maintained on a 70:30 mixture of nitrous oxide:oxygen and 0.5% halothane underwent moderate (1.5-2.0 atm) traumatic brain injury with the injury screw positioned parasagittally over the right parieto-occipital cortex. At 24 hours after traumatic brain injury, the rats were reanesthetized and randomized into two groups in which either a 3-hour period of brain normothermia (36.5 degrees C, n = 18) or hyperthermia (39 degrees C, n = 18) was maintained. Sham-operated controls (n = 10) underwent all surgical and temperature-monitoring procedures. After the 3-hour monitoring period, the rats were allowed to survive for 3 days for light microscopic analysis or were injected with the protein tracer horseradish peroxidase and were perfusion-fixed 15 minutes later for light and electron microscopic analysis. At 4 days after traumatic brain injury, delayed posttraumatic hyperthermia (n = 12) significantly increased mortality (47%) and contusion volume (1.7 +/- 0.69 mm3, mean +/- standard error of the mean), compared to normothermia (n = 12) (18% mortality and 0.13 +/- 0.21 mm3 contusion volume) (P < 0.01, analysis of variance). At 15 minutes after the 3-hour hyperthermic period, the area of hemorrhage and horseradish peroxidase extravasation overlying the lateral external capsule was significantly increased (2.52 +/- 0.71 mm2, mean +/- standard error of the mean, versus 0.43 +/- 0.16 mm2) (P < 0.01).

Comment Hyperthermia worsened the extent of brain injury in a post-traumatic brain model.

Level of Evidence 5
Quality of evidence-Good
Evidence - Supportive

Brief and non-lethal cerebral ischemia produces most severe neuronal damage when such ischemia is induced repeatedly at 1-h intervals. We examined whether spontaneous postischemic hyperthermia is an aggravating factor for the cumulative damage following repeated ischemia in the gerbil. We maintained body and cranial temperature at normothermia throughout the initial reperfusion period, but could not observe an amelioration of histopathological brain damage following two 2-min bilateral carotid artery occlusions at a 1-h interval as compared to hyperthermic conditions. The results suggest that postischemic hyperthermia is not a major aggravating factor for the cumulative damage following repeated ischemic insults.

Comment Gerbil model demonstrating no adverse effect of hyperthermia following brief global hypoxia-ischemia

Level of Evidence 5
Quality of evidence-Good
Evidence - Neutral

BACKGROUND AND PURPOSE: Over the past several years, it has been demonstrated that mild intrasichemic or immediate postischemic hyperthermia worsens ischemic outcome in models of global and focal ischemia. Periods of hyperthermia are commonly seen in patients after stroke and cardiac arrest. The hypothesis tested in this study was that a brief hyperthermic period, even when occurring days after an ischemic insult, has detrimental effects on the pathological outcome of focal ischemia. METHODS: Rats were subjected to 60 minutes of transient middle cerebral artery occlusion by insertion of an intraluminal filament. Twenty-four hours after reperfusion, awake rats were subjected to temperature modulation for 3 hours in a heating chamber. The brain temperature was equilibrated to either 37 degrees C to 38 degrees C, or 40 degrees C. Changes in rectal temperature and blood glucose concentration were evaluated during and just after temperature modulation. Behavioral tests were also assessed. Three days after temperature modulation, brains were perfusion-fixed, and infarct volumes were determined. RESULTS: In animals with 40 degrees C hyperthermia, cortical and total infarct volumes were markedly greater (92.2 +/- 63.1 and 126.5 +/- 72.3 mm3) and in animals with 39 degrees C hyperthermia (16.5 +/- 28.7 and 40.9 +/- 34.3 mm3) (P < .05), whereas there was no significant difference between normothermic and 39 degrees C hyperthermic animals. In addition, animals with 40 degrees C hyperthermia displayed worsened neurological scores compared with normothermic and 39 degrees C hyperthermic rats. In the 39 degrees C hyperthermia group, rectal temperatures were significantly lower (by 0.2 degree C to 0.5 degree C) than brain temperatures throughout the modulation period. CONCLUSIONS: The present findings provide evidence that, after a transient focal ischemic insult, the postischemic brain becomes abnormally sensitive to the effects of delayed temperature elevation, even of moderate degree. The threshold for aggravation of ischemic injury by delayed hyperthermia appears to be approximately 40 degrees C. Body-
temperature measurements, in both awake and anesthetized animals, may not accurately reflect brain temperature under these conditions. The present study stresses that fever of even moderate degree in the days following brain ischemia may markedly exacerbate brain injury.

Comment Focal ischemic model demonstrating the delayed adverse effects of hyperthermia: a threshold of 40°C is suggested

Level of Evidence 5
Quality of evidence-Good
Evidence - Supportive


Halothane-anesthetized Mongolian gerbils were submitted to 5-min bilateral carotid artery occlusion. After ischemia, halothane anesthesia was continued for various periods of up to 85 min, and the degree of CA1 neuronal injury was estimated 7 days later by counting the number of surviving pyramidal cells. During ischemia and postischemic halothane anesthesia, rectal and cranial temperature was kept at control level (37.7 and 37.0 degrees C, respectively) using a feedback-controlled heating system. When anesthesia was discontinued after ischemia, transient hyperthermia occurred. In animals with 0- and 15-min postischemic halothane anesthesia, both cranial and rectal temperature rose by approximately 1.5 degrees C, and the number of surviving CA1 neurons amounted to less than 25% of control. After 45- or 85-min postischemic anesthesia, hyperthermia was significantly reduced and the number of surviving neurons increased to 65 and 89%, respectively. The protective effect of postischemic anesthesia was lost when anesthetized animals were submitted to the same hyperthermic profile as nonanesthetized ones, using a feedback-controlled heating system (16% surviving neurons in hyperthermia vs. 89% in normothermia, respectively). These observations demonstrate that postischemic anesthesia with 1% halothane protects against delayed neuronal death by preventing postischemic hyperthermia and not by its anesthetetic effects.

Comment Another example of when hyperthermia is prevented, this time with anesthesia, that delayed neuronal death is prevented

Level of Evidence 5
Quality of evidence-Good
Evidence - Supportive


The influence of hyperthermia and hypothermia on epileptic brain damage was studied in rats, in which status epilepticus was induced by flurothyl. Histopathological changes were examined by light microscopy after 1 or 7 days of recovery. Two series of animals were studied. In the first, short periods of seizures (20 and 25 min) were employed to examine whether moderate hyperthermia (39.5 degrees C) would aggravate epileptic brain damage, and a longer period (45 min) was used to investigate whether moderate hypothermia (32.5 degrees C) would ameliorate the damage. The second series investigated whether brief periods of status epilepticus (10 min) would cause brain damage if hyperthermia were high or excessive. For this series, animals with body temperatures of 37.0, 39.0, and 41.0 degrees C were studied. Data from normothermic animals (37.5 degrees C) confirmed previously described neuronal damage. Although hyperthermic animals failed to show increased damage in the CA1 sector, or in the hilar region of the dentate gyrus, they showed enhanced damage in the neocortex and globus pallidus (GP). In substantia nigra pars reticulata (SNPR) four out of five hyperthermic animals had bilateral infaracts after 20 min of status epilepticus, whereas no normothermic animal showed such damage. Hyperthermia seemed to ameliorate epileptic brain damage in the neocortex (n.s.) and GP (P < 0.05) following status epilepticus for 45 min. Three out of seven hypothermic animals had mild SNPR involvement compared to severe infarction of the nucleus in five out of six normothermic animals (P < 0.05). Thus, hyperthermia aggravated and hyperthermia ameliorated epileptic brain damage both in regions showing selective neuronal necrosis (neocortex) and in regions developing pan-necrosis (GP and SNPR). The second series displayed an unexpected result of excessive hyperthermia. Animals subjected to only 10 min of status epilepticus at a temperature of 41 degrees C showed not only neocortical lesions, but also moderate to extensive damage to the hippocampus (CA1, subiculum, and dentate gyrus). It is concluded that at high body and brain temperature, brief periods of status epilepticus can yield extensive brain damage, primarily affecting the hippocampus.

Comment Rat model demonstrating aggravated neocortical and hippocampal injury with hyperthermia during seizures, an effect that was ameliorated by hypothermia.

Level of Evidence 5
Quality of evidence-Good
Evidence – Supportive


This study examined the time course and effects of postischemic spontaneous hyperthermia after transient and permanent focal ischemia. Rats underwent a 90-min, 120-min, or permanent middle cerebral artery occlusion (MCAO). Body temperatures started rising 15-20 min after MCAO and reached 39-40.5 degrees C during the first hour. Sustained hyperthermia was observed during the rest of the first 24 h. In another experiment, rats were subjected to the same interventions, but a normothermic body temperature was maintained. Spontaneous hyperthermia significantly increased the infarct volumes measured 48 h after MCAO in all groups. Reperfusion 2 h after the onset of ischemia was not beneficial in the hyperthermic animals in contrast to the normothermic group. We also examined the effect of spontaneous hyperthermia on the temporal progression of infarcted and penumbral areas 4, 12, or 48 h after MCAO. During spontaneous hyperthermia, penumbral areas became infarcted areas more rapidly, which was most expressed at 4 h. These findings demonstrate that severe spontaneous hyperthermia can occur in rats after MCAO and that it not only increases the infarct volumes in both transient and permanent ischemia, but also accelerates the incorporation of penumbral areas into necrotic areas, which significantly decreases the window of opportunity for therapeutic interventions.

Comment Study demonstrating the worsening of brain injury including the incorporation of the penumbral areas into necrotic areas in a spontaneous hyperthermia model

Level of Evidence 5
Quality of evidence-Good
Evidence – Supportive
BACKGROUND: Aggressive surface warming is a common practice in the pediatric intensive care unit. However, recent rodent data emphasize the protective effect of mild (2 degrees - 3 degrees C) hypothermia after cerebral ischemia. This study evaluates different temperature regulation strategies after deep hypothermic circulatory arrest with a survival piglet model. METHODS: Fifteen piglets were randomly assigned to 3 groups. All groups underwent 100 minutes of deep hypothermic circulatory arrest at 15 degrees C. Brain temperature was maintained at 34 degrees C for 24 hours after cardiopulmonary bypass in group I, 37 degrees C in group II, and 40 degrees C in group III. Neurobehavioral recovery was evaluated daily for 3 days after extubation by neurologic deficit score (0, normal; 500, brain death) and overall performance category (1, normal; 5, brain death). Histologic examination was assessed for hypoxic-ischemic injury (0, normal; 5, necrosis) in a blinded fashion. RESULTS: All results are expressed as mean +/- standard deviation. Recovery of neurologic deficit score (12.0 +/- 17.8, 47.0 +/- 49.95, 191.0 +/- 179.83; P = .05 for group I vs III), overall performance category (1.0 +/- 0.6, 1.4 +/- 0.6, 2.8 +/- 1.3; P < .05 for group I vs III), and histologic scores (0.0 +/- 0.0, 1.0 +/- 1.2, 2.8 +/- 1.8; P < .05 for group I vs III cortex) were significantly worse in hyperthermic group III. These findings were associated with a significantly lower cytochrome aa3 recovery determined by near-infrared spectroscopy in group III animals (P = .0041 for group I vs III). No animal recovered to baseline electroencephalographic value by 48 hours after deep hypothermic circulatory arrest. Recovery was significantly delayed in the hyperthermic group III animals, with a lower amplitude 14 hours after the operation, which gradually increased with time (P < .05 for group III vs groups I and II). CONCLUSIONS: Mild postischemic hyperthermia significantly exacerbates functional and structural neurologic injury after deep hypothermic circulatory arrest and should therefore be avoided.

Comment: Piglet model demonstrating the adverse effects of hyperthermia following deep hypothermia.


To determine the effect of pre-hypoxic-ischemic (HI) hypo and hyperthermia on neuropathologic outcome in the immature brain, groups of 7-day rat pups underwent unilateral common carotid artery ligation and exposure to hypoxia in 8% oxygen at 37 degrees C for 3 h. Prior to HI, rat pups were divided into three groups and received either: (a) 3-1 h periods, at 8-h intervals, 24 h prior to HI, (b) 1-3 h period, 24 h prior to HI, or (c) 1-3 h period, immediately prior to HI, of exposure to environmental temperatures of 28 degrees C, 31 degrees C, 34 degrees C, 37 degrees C, or 39 degrees C. Following HI, all animals were returned to their dams for neuropathologic assessment at 30 days of age. Mortality was highest among those animals exposed to pre-HI hypothermia at 28 degrees C. Only those animals who were pre-conditioned with hyperthermia at either 37 degrees C or 39 degrees C, immediately prior to HI, displayed a significant reduction in brain damage compared to control (p<0.01). These results indicate that hyperthermia induced prior to HI protects the immature brain from damage. This study further emphasizes the importance of a cautionary approach in implementing systemic hypothermia during clinical trials, and the need to further understand the timing and effects of thermoregulation on the immature brain.

Comment: Newborn model indicating that hyperthermia prior to hypoxia-ischemia protects the immature brain.

Level of Evidence 5
Quality of evidence-Good
Evidence – Supporting

Tomimatsu, T. Fukuda, H. Kanagawa, T. et al Effects of hyperthermia on hypoxic-ischemic brain damage in the immature rat: its influence on caspase-3-like protease

OBJECTIVE: Recent clinical studies suggested that intrapartum maternal fever is a strong independent risk factor for neonatal encephalopathy. With use of a well-studied rat model of neonatal hypoxic-ischemic encephalopathy, this study investigated the hypothesis that intraschismic hyperthermia accelerates and worsens brain injury in immature animals and examined whether apoptotic cell death machinery is involved in the underlying mechanisms. STUDY DESIGN: Seven-day-old rats underwent a combination of left common carotid artery ligation and exposure to 8% oxygen for 15 minutes (n = 32 rats). During the 15-minute hypoxic insult, body temperature was elevated to 40 degrees C in 16 animals (hypothermic hypoxic insult group), and was maintained at 37 degrees C in 16 animals (normothermic hypoxic insult group). Then both groups were placed in the same chamber in a water bath at 37 degrees C for 24 hours and finally returned to the mothers. Caspase-3-like activity was assessed 36 hours after the hypoxic-ischemic insult. One week later, microtubule-associated protein-2 immunostaining was used to examine neuronal damage. RESULTS: Intraschismic hyperthermia was shown to activate the caspase-3 activity 36 hours after hypoxia-ischemia while caspase-3 was activated insignificantly in the normothermic hypoxic insult group at that time. The hyperthermic hypoxic insult group also showed a reduced microtubule-associated protein-2 positive area 7 days after hypoxia-ischemia compared with that in the normothermia group. CONCLUSION: Hyperthermia during hypoxia-ischemia makes the immature brain inordinately susceptible to hypoxic-ischemic insult and causes brain injury, even if hypoxic-ischemic insult is so mild that it causes no or little injury by itself. This effect may be mediated by the escalation of the apoptotic cell death pathway in the immature animal.

Level of Evidence 5
Quality of evidence-Good
Evidence – Opposing