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Neurotrauma: The Place for Cooling

- Cooling: to achieve hypothermia
  - History, evidence, open questions
- Cooling: to achieve normothermia
  - Evidence, open questions
- Cooling: Practical Aspects

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Hypothermia: History

- **Hypothermia for neuroprotection mentioned in Greek medical texts (acc. to** *Maas AIR & al., Chapter 20, Head Injury, Hodder Arnold, London, UK 2005***)**
- **1945 – 1975: widely used (on wards!)**
  - **“generalized refrigeration” (T. Fay)**
  - **“artificial hibernation” (w. phenothiazines)**
- **1975 – 1990: use discontinued due to management problems**

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Facts about Hypothermia

Hypothermia: beneficial metabolic effects

- **Reduces CBF by 5% / °C reduction of BT**
- **Reduces $CMRO_2$ and $avDO_2$**
- **Increases tissue ATP concentration**

Improves mismatch between blood flow and metabolism

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Facts about Hypothermia

Hypothermia: other beneficial effects

- **Reduces inflammatory response**
- **Reduces neurotransmitter turnover**

Hypothermia: unwanted effects

- **Cardiovascular instability (arrhythmia)**
- **Coagulopathy**
- **Electrolyte disorders**
- **Increased risk of infections**

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Hypothermia Trials 1993-2001

Author	Target BT	Pat (n)	% fav Hyp	% fav Con	OR
Clifton & al. 1993	32 - 33	45	52.2	36.4	0.52 (n.s.)
Shiozaki & al. 1993	33.5 – 34.5	33	50	6	0.10 (n.s.)
Hirayama & al. 1994	32 - 33	22	66.7	30	0.21 (n.s.)
Marion & al. 1997	32 - 33	81	61.5	38.1	0.38 (s.)
Meissner & al. 1998	32 - 33	25	75	76.9	1.11 (n.s.)
Shiozaki & al. 1999	33.5 – 34.5	16	75	87.5	2.33 (n.s.)
Aibiki & al. 2000	32 - 33	26	80	36.4	0.14 (s.)
Jiang & al. 2000	mild	87	46.5	27.3	0.43 (n.s.)
Clifton & al. 2001	32.5 - 34	368	43.2	42.7	0.98 (n.s.)
Shiozaki & al. 2001	33.5 – 34.5	91	46.7	58.7	1.62 (n.s.)

Adapted from: Maas AIR & al., Chapter 20, Head Injury, Hodder Arnold, London, UK 2005

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Recent Hypothermia Trials

- *Polderman & al. 2002*: **single center RCT**

  136 patients with a GCS of 8 or less on admission in whom intracranial pressure (ICP) remained above 20 mmHg in spite of therapy according to a step-up protocol. Those who responded to the last step of our protocol (barbiturate coma) constituted the control group (n=72). Those who did not respond to barbiturate coma (n=64) were treated with moderate hypothermia (32-34 degrees C). Average APACHE II scores were higher (28.9+/-14.4 vs 25.2+/-12.1, $p<0.01$) and average GCS at admission slightly lower (5.37+/-1.8 vs 5.9+/-2.1, $p<0.05$) in the hypothermia group, indicating greater severity of illness and more severe neurological injury.

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Recent Hypothermia Trials

- *Polderman & al. 2002*: **single center RCT,**
- Predicted mortality was 86% for the hypothermia group versus 80% in controls ($p<0.01$). Actual mortality rates were significantly lower: 62% versus 72%; the difference in mortality between hypothermic patients and controls was significant ($p<0.05$). The number of patients with good neurological outcome was also higher in the hypothermia group: 15.7% versus 9.7% for hypothermic patients versus controls, respectively ($p<0.02$).

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Recent Hypothermia Trials

- *Gal & al. 2002*: **single center RCT, 30 pts with severe TBI, mild hypothermia (34 °C),** hypothermia (fav. 87%) better (p = .0843) than control (fav. 47%); **ICP lower**
- *Shiozaki & al. 2003*: **single center case series, 22 pts w severe TBI and ICP > 40 mmHg during 34 °C were cooled to 31 °C (moderate hypothermia) –** 100% mortality (19 brain deaths, 3 MOF deaths)

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Recent Hypothermia Trials

- *Jiang & al. 2006*: **multi-center RCT, 215 pts with severe TBI, mild hypothermia for 5 vs 2 days.** 5-day hypothermia (fav. 43.5%) better ($p < .05$) than 2-day hypothermia (fav. 29%); **significant ICP rebound more frequently ($p < .05$) observed at re-warming after 2, but not after 5 days**

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Recent Hypothermia Trials

- *Hutchinson & al. 2008*: **multi-center RCT, 225 children, hypothermia (32 – 34 °C for 24 hours) vs. normothermia. Results better with normothermia: death 12% vs. 21% (p = .06) unfav. 22% vs. 31% (p = .14), more hypotension, more use of vasoactive medication with hypothermia**

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Recent Hypothermia Trials

- *Harris & al. 2009*: **single center RCT, 25 pts randomized to control or treatment (brain hypothermia via “cooling cap”, to avoid side effects of whole-body hypothermia). Target temp. of 33 °C (brain) reached in only 2/12 patients. Mortality 50% (cap) vs. 31% (control); not significant (p = .43).**
- **One ongoing multi-center RCT (by** *Clifton & al.***) will randomize 240 pts**

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Hypothermia: Open Questions

- **Hypothermia is neuroprotective; it works well for patients on cardiopulmonary bypass, and it has been shown to be beneficial for patients after CPR**

- **Why, then, are we unable to demonstrate benefits for patients with severe TBI?**

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Hypothermia: Open Questions

- Target temperature too low? – most RCTs aimed for 32 - 34 °C. Increased risk of complications at hypothermia <34 °C
- Duration of hypothermia too short? – most RCTs used 24 – 48 hours. Increased risk of rebound ICP increase after short duration of hypothermia
- Re-warming too fast? – most RCTs allowed for 24 hours of re-warming

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Hypothermia: Open Questions

- Hypothermia started too late? – Hypothermia works well if started prior to (CPB) or shortly after (CPR) the insult; much longer delay (4 – 8 hours) in TBI patients
- Hypothermia used for wrong indications? – intractable ICP
- Management problems? – especially in MRCTs if hypothermia is used in centers that have no experience with this

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Hypothermia: Conclusions

Further studies are urgently required to determine optimal

- **time to start cooling**
- **degree of hypothermia**
- **technique (whole-body vs. selective)**
- **duration of hypothermia**
- **duration of re-warming**

Therapeutic hypothermia has no proven benefit after severe TBI

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Facts about Hyperthermia

Fever

- **occurs in up to 70% of TBI pts**
- **is attributable to infection in 50% of pts**
- **“central” fever in 20-30% of pts (?)**
- **exacerbates inflammatory cascades**
- **increases neurotransmitter release and intracellular glutamate concentrations**
- **may lead to intracellular acidosis**

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Facts about Hyperthermia

- Brain temperature may be 0.5 – 2 °C higher than body core temperature
- This gap increases with higher BT
- Fever after severe TBI may be related to hypothalamic dysfunction
- Fever after severe TBI is associated with increased ICP, neurological impairment, and poor long-term outcome

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Fever Control: Evidence

- *Puccio AM & al. 2009*: **single center cohort study, 21 pts with induced normothermia (IV cooling) compared to 21 historic controls. ICP lower (12.7 vs. 16.4 mmHg), percentage of time with ICP >25 mmHg lower (p = .003), time with BT >38 °C 1.6% vs. 10.6% (p = .003).**
- *Hata JS & al. 2008*: **Cooling after TBI reduces systemic VO_2 only for non-shivering pts after TBI.**

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Side Effects of Fever Control

- *Schulman CI & al. 2005*: **single center trial, NO TBI pts, 82 ICU pts; 44 randomized to “aggressive” group, (treatment started at 38.5 °C), 38 to “permissive” group (treatment started at 40 °C). More infections (131 vs. 85, p = .26), more deaths (16% vs. 3%, p = .06) in the aggressive group. Study stopped during interim analysis. CONCLUSION: treating fever in ICU patients aggressively may lead to higher mortality rate.**

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Fever Control: Open Questions

- What should be monitored? – body or brain temperature
- What level of brain / body temperature is acceptable? – may be different for SAH vs. SDH with / without oedema
- With regard to fever - how long is the “vulnerable phase” of the injured brain? – 2 days, first week, 2 weeks???

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Fever Control: Conclusions

- Hyperthermia may cause secondary brain insults and may worsen outcome after severe TBI
- Aggressive fever control in ICU patients may increase rate of infections and mortality
- There is no evidence to guide our treatment of patients with severe TBI

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Conclusions

- The injured brain is most vulnerable after the impact
- Hyperthermia may occur early after severe TBI
- The risk of infection increases over time

The logical approach would be to

- treat fever more aggressively during the first few days
- Accept higher temperature after the first few days

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Cooling: Practical Aspects

- Pharmacologic agents: require intact thermoregulation
  - Diclofenac, ibuprofen, acetaminophen
- External cooling: achieves heat loss by
  - Radiation: exposure of the skin
  - Convection: fan, cool-air blankets
  - Evaporation: water spray, sponge baths
  - Conduction: ice packs, cooling blankets
- Shivering must be prevented!

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Cooling: Practical Aspects

- Intravascular cooling:
  - Infusion of 4 °C normal saline
  - Cooling devices (cold saline circulating through balloons around catheters)
- IV cooling devices and blanket cooling are most effective; goals are reached faster than with other techniques, BT is maintained more closely to target temp (closed loop technology)

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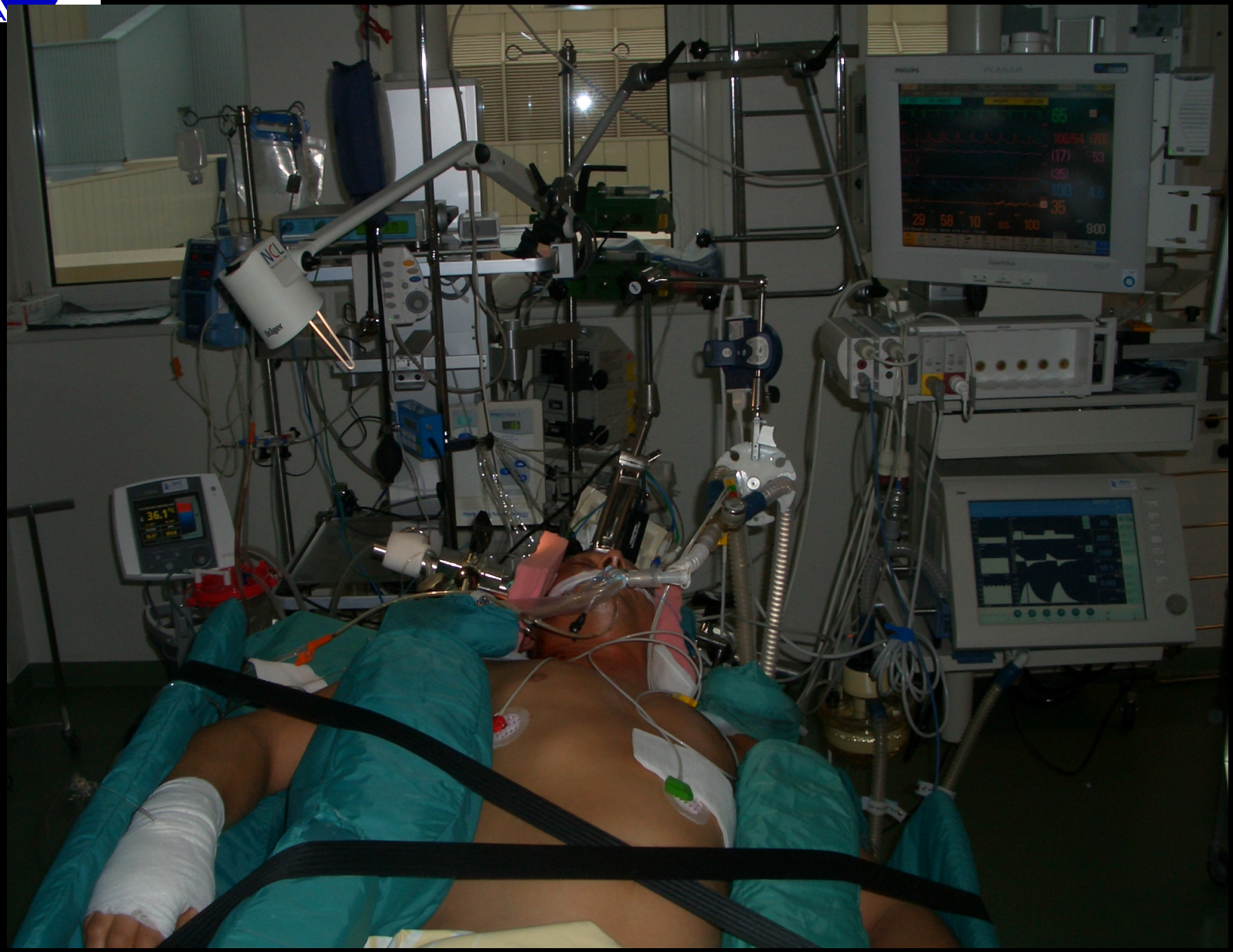

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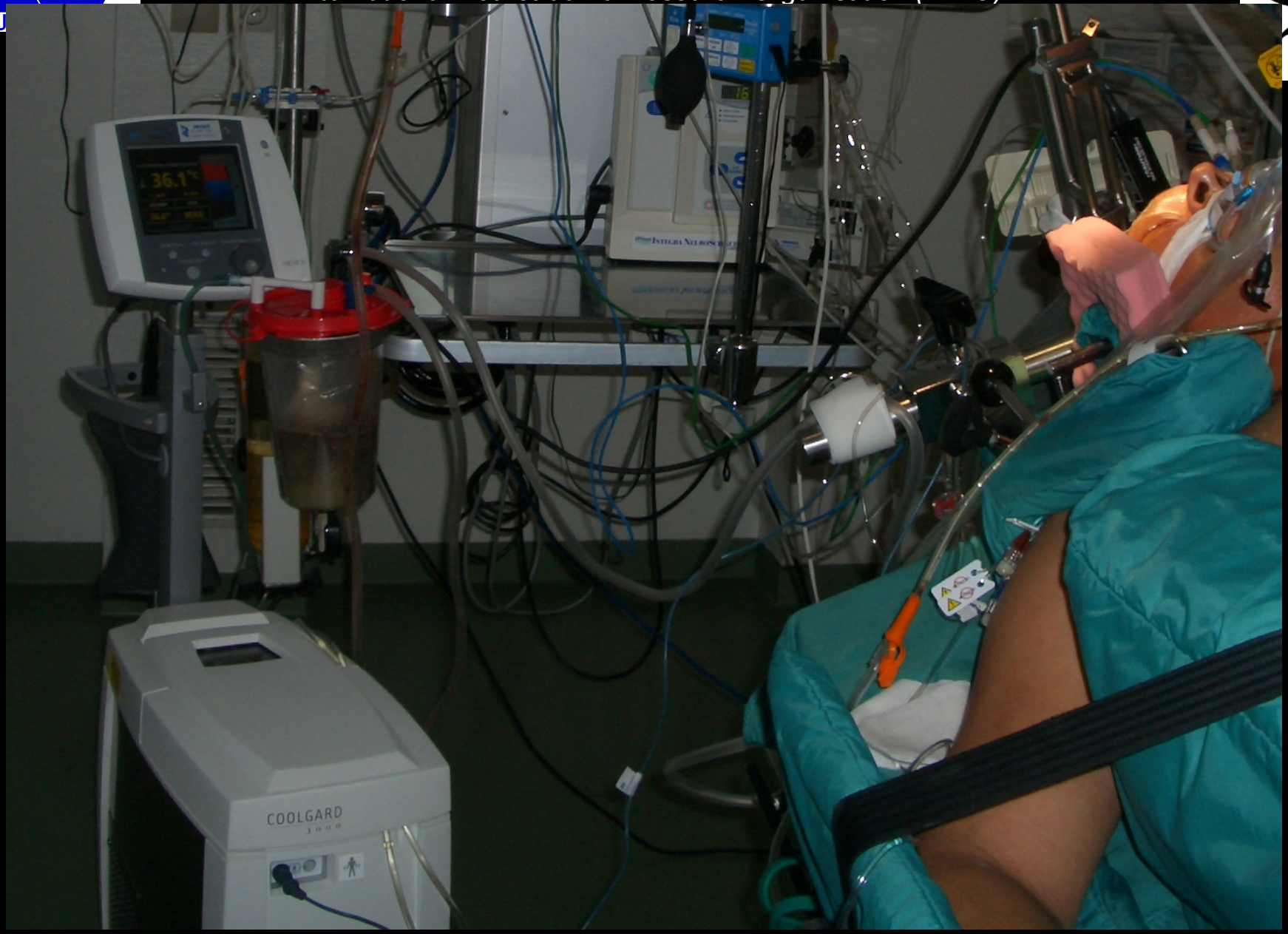

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Summary

- Hypothermia has no proven benefit
- Fever during the first days after severe TBI may impair outcome
- Normothermia should be maintained for the first few (3 – 7) days after TBI (= body temperature should not exceed 37.5 °C)
- After the first week fever should be treated less aggressively