IRB Protocol

Effects of Local Hypothermia on Neurological Outcome in Acute Ischemic Stroke

Scott Henneman

A. Study Purpose and Rationale

In the United States, there are an estimated 700,000 cases of new and recurrent strokes every year, of which 88% are ischemic and usually caused by occlusion or hemodynamically relevant narrowing of brain-supplying vessels[1, 2]. With an overall mortality rate of approximately 20% and long-term disability rate of up to 30% among survivors, stroke is a major burden for public health. Currently, there are approximately 5.5 million survivors of stroke living in the United States.

To date, the standard of care in acute ischemic stroke is thrombolysis via infusing the thrombolytic agent rtPA (recombinant tissue plasminogen activator) intravenously (systemically) within 3 hours of symptom onset[6]. However, due to this narrow time window, only 1-2% of all ischemic strokes are treated with thrombolytics[1,3-5]. Efforts to extend the therapeutic time window include endovascular procedures (acute angioplasty, local endovascular/intra-arterial use of thrombolytics and mechanical devices), use of other thrombolytic or antiaggregating drugs, and refining selection criteria for treatment using modern imaging methods (diffusion and perfusion weighted MR imaging)[10-17]. These treatment approaches are still considered experimental, but preliminary results suggest that the number of eligible patients is twice as high as for systemic thrombolysis[5]. Although these results are encouraging, it remains doubtful whether these approaches alone will lead to a significant increase in treatment eligibility and, in particular, whether these treatment options are safe and effective, due to the risk of common complications such as intracranial hemorrhage and cerebral reperfusion injury.

Therapeutic hypothermia (systemic/whole body cooling) has been shown to have a remarkable effect on global and focal ischemia. Unlike other therapeutic approaches, hypothermia acts using a diverse array of molecular pathways[27-32]: it reduces the extracellular excitatory amino acid concentrations, modulates ion homeostasis, suppresses the disruption of the blood-brain barrier, decreases cerebral metabolism (and thus oxygen demand and cerebral blood flow), and attenuates neutrophil infiltration. In animal models of global or focal cerebral ischemia it has been demonstrated that even slight reductions of the body temperature (29-35ºC) are neuroprotective[21, 22, 23]. Furthermore, selective local saline infusion was found to be neuroprotective in several species of animals[40-43]. Pre- and intra-ischemic hypothermia achieved dramatic neuroprotection by reducing infarction volume by 50-90%[44-47], suggesting that hypothermia plays a powerful role in preventing neurological injury when applied prior to or simultaneously with ischemic insult.

In humans, two randomized clinical trials established conclusively the neuroprotective effects and safety of hypothermia after cardiac arrest[24, 25]. Endovascular antero- and retrograde high volume perfusion has been routinely used in cardiopulmonary bypass and other cardiac surgery to induce moderate to deep hypothermia (<28 ^{o}C)[48-54] (Table 1). Furthermore, the feasibility of selective endovascular cooling has been reported in cardiac arrest and neurosurgical patients[55-58].

Mild or moderate hypothermia may prove to be an important and feasible method of inducing neuroprotection from ischemic events and minimizing complications resulting from reperfusion injury. However, induction of whole-body hypothermia is a time-consuming procedure[33-39] and may be associated with severe adverse effects. In many clinical studies, hypothermia is induced by surface/skin cooling with the use of cooling blankets, alcohol, and ice bags. Recent approaches investigating intravenous access to induce systemic hypothermia showed that this was feasible in severely affected

acute ischemic stroke patients (Table 1). However, it takes 3 to 7 hours to reach target temperature (32-34°C) and evidence on safety and effectiveness is still lacking.

Because of the time-dependent nature of ischemic neuronal cell-death, there is a pressing need for rapid induction of neuroprotective brain cooling. Previous studies have shown that, with local intra-arterial infusion of cold saline, brain cooling can be achieved selectively, quickly, and maintained over a period of time. It is conceivable that safe application of selective brain cooling with rapid achievement of hypothermic neuroprotection will constitute an effective method for the treatment of ischemic brain injury both in concurrence with current rt-PA treatment and other experimental recanalization procedures. However, to this date, no study of this type has been performed. The effectiveness of this method of cooling in reducing brain temperature will have been established previously with MR thermographic methods and the measurement of ipsilateral jugular bulb temperature on patients undergoing angiography.

Table 1a/1b. Synopsis of systemic hypothermia therapy in patients with middle cerebral artery occlusion: Adverse events and outcome. These results suggest that systemic hypothermia is feasible, but no evidence for safety or effectiveness was found.

1a.

Study	Design	Subjects	#	Cooling Method	Target T (°C)/ Time to Target T	Cooled for (h)
Schwab[33] (1998)	Case series	Ischemic stroke/ Mean GCS 9	25	Surface+cold infusion	33/ 3.5-6.2h	48-72
Kammersgaard[34] (2000)	Historical Control group	Ischemic stroke/ NIHSS 26-28	17	Surface	35.5/ 6h	6
Krieger[35] (2001)	Medical Control group	Ischemic stroke/ Mean NIHSS 20/ IV/IA rtPA	10	Surface	31-33/ 3.5h	47
Schwab[36] (2001)	Case series	Ischemic stroke/ Mean NIHSS 25	50	Surface	32-33/ 6.5h	24-72 mean 55h
Georgiadis[37] (2001)	Case series	Ischemic stroke/ IV rtPA in 2 pat	6	Endovascular	32-33/ 3h	48-72 mean 67h
Georgiadis[38] (2002)	Case series	Ischemic stroke/ NIHSS 20/ IV rtPA in 4 pat	19	Endovascular	32-33/ 4h	24-116 mean 71h
De Georgia[39] (2004) CoolAid II	Randomized Clinical Trial	Ischemic stroke/ NIHSS 18/ 72% (13) IV/IA rtPA	18	Endovascular	33/ 13 patients 77 min	24h

GCS (Glasgow Coma Scale), NIHSS (NIH Stroke Scale), IV (intravenous), IA (intra-arterial), rtPA (recombinant tissue plasminogen activator).

1b.

Study	Time for Outcome	Death	Cardiovascular Complications	Infection	Systemic Complications	Other Complications	Result/ Conclusion
Schwab[33] (1998)	30 days	44% (11)	Arrhythmia 60% (15)	Pneumonia 40% (10) Sepsis 28% (7)	Platelet↓, K^+↓, Amylase-Lipase↑	None	Lowers ICP
Kammersgaard[34] (2000)	6 months	6% (1)	Systol. BP↓ HR↓	Infection 18% (3)	Hct↑,Hgb↑, K^+↑ Fibrinogen↑	None	Comparison with normotherm: N.S.
Krieger[35] (2001)	3 months	30% (3)	Arrhythmia 60% (6) MI 30% (3) Heart failure 20% (2) Hypotension 30% (3)	Pneumonia 30% (3)	None	Groin hematoma 10% (1)	comparison with normotherm: N.S.
Schwab[36] (2001)	3 months	38% (19)	Arrhythmia 62% (31) Hypotension 100% Cardiac failure 2% (1)	Pneumonia 48% (24)	K^+ 10%↓, Platelet 70% (35) ↓ Coagulopathy 6% Pancreatitis 6%	None	Lowers ICP during cooling, but rebound during rewarming
Georgiadis[37] (2001)	Peri-proced.	17% (1)	Arrhythmia 100% Hypotension 100%	Pneumonia 100%	Platelet↓ 33% (2) K^+↓ 33% (2)	Singultus 100%	Proof of feasibility
Georgiadis[38] (2002)	ICU stay Mean 13d	47% (9)	Arrhythmia 42% (8) Bradycardia 58% (11)	Pneumonia 78% (15)	Platelet↓ 37% (7) K^+↓ 26% (5) Coagulopathy 5% (1)	ICP↑ 53% (10) Singultus 100%	Increased ICP in 53%
De Georgia[39] (2004) CoolAid II	30 days	28% (5)	Arrhythmia (2) and shock (1) 17% (3)	Pneumonia 11% (2) UTI 6% (1)	None	DVT 17% (3) Sympt. hem. 11% (2)	Proof of feasibility; difference N.S.

BP (blood pressure), HR (heart rate), MI (myocardial infarction), DVT (deep venous thrombosis), N.S. (not significant).

B. Study Design and Statistical Analysis

Power Calculations:
Using an assumption of 50% favorable outcome (favorable outcome defined as NIHSS score of 0 or 1) as per the 1995 NINDS rt-PA trial,[59] we will need 182 subjects in each group to demonstrate a 30% difference in NIHSS score outcome at 80% power with an alpha of 0.05. 200 subjects will be enrolled in each group to account for an approximate 10% rate of attrition.

Design:
This is a prospective, double-blinded, randomized controlled trial. It will enroll patients presenting with acute ischemic stroke to study the effects of local brain hypothermia on neurological outcome as defined by the National Institute of Health Stroke Scale (NIHSS). The two hypotheses are:

(H1) The patient group randomized to treatment will have a greater proportion with favorable neurological outcome 24 hours after stroke onset.

(H2) The patient group randomized to treatment will have a greater proportion of subjects with favorable neurological outcome 3 months after stroke onset.

These hypotheses will be tested on patients presenting with acute stroke within 12 hours of stroke onset. Patients will be stratified by clinical center and further into four groups according to time after stroke onset, hereafter known as “time-to-treatment” groups : 1) 0-90 minutes, 2) 91-180 minutes, 3) 3-6 hours, and 4) 6-12 hours. Patients will be obtained from those presenting to CUMC or an affiliate center for treatment.

Definitions:
The NIHSS is a 42-point scale that assigns value to various neurological deficits. A score of 0 means no deficit. This scale, along with the Barthel index, has been found to be reliable and have reproducible results[60-62]. The Barthel index, however, will not be used for this study. The complete NIHSS scale can be found at:
http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf

Outcome:
As stated above, the outcome in this study is composed of two parts: neurological score 24 hours after the acute ischemic stroke, and neurological score 3 months after the stroke. A patient with an acute ischemic stroke will be defined as one presenting with a NIHSS-measurable neurological deficit beginning within the previous 12 hours and without a hemorrhagic insult as defined by CT scan.
Those included patients who have NIHSS scores of 0 or 1 at the specified time intervals will be defined as having a "favorable outcome."

Statistical Analysis:
The qualitative data will be analyzed using a 2x2 table chi-squared test, as shown below:

	Favorable outcome	Non-favorable outcome
Treatment Group		
Placebo Group		

The hypotheses H1 and H2 will be treated as separate tests, and thus will each be assigned individual tables. Subgroup analyses will then be performed similarly on the four "time-to-treatment" groups, as explained in *Design*, above.

If, during the course of the study, either the treatment or control placebo group demonstrate a difference in outcome with a z value of greater than 2.0, the study will be stopped and all patients will be assigned to the group with the greater favorable outcome.

C. Study Procedure
Patients who are candidates for inclusion in the study as specified below in Part G (Study Subjects) will undergo the following study procedure:

- Randomization to the treatment group or placebo group. Stratification according to time of stroke onset will be taken into account in this randomization.
- All patients will undergo arterial catheterization at the level of the femoral artery contralateral to the affected side (if such a distinction can be made); the catheter will then be guided superiorly under fluoroscopy to the level at which the internal carotid artery inserts into the circle of Willis.
- The treatment group will receive 30 mL/min of 4ºC saline via this catheter for 60 minutes. The placebo group will receive room temperature saline in the same manner and with the same rate and for the same duration. During this time, angiography will be performed to evaluate the location of insult and recanalization may be performed if deemed appropriate by the physician.
- All patients who are able to receive treatment within 180 minutes of stroke onset will be treated with IV rt-PA as is currently standard of care.
- All patients will be evaluated for neurological function by a blinded neurologist as per the NIH Stroke Scale 24 hours post stroke onset.
- All patients will be again evaluated at 3 months in a similar manner.

D. Study Drugs
No drugs will be administered that are particular to this study.

E. Medical Devices
The only device that may be considered partially unique to this study as compared to all stroke management procedures is an intra-arterial catheter that is used in many interventional neuroradiology procedures.

F. Study Questionnaires
No questionnaires will be distributed for this study.

G. Study Subjects
The patients in this study include all those age 18 or older who present to CUMC or an affiliate clinical center with the following inclusion criteria:

- Ischemic stroke with clearly defined time of onset.
- Time of onset under 12 hours.
- Neurological deficit measurable on the NIHSS.
- CT scan demonstrating no intracranial hemorrhage.

Exclusion criteria are the following:

- Hemorrhagic stroke or head trauma requiring hospitalization in the previous 3 months.
- Major surgery within the previous 14 days.
- Systolic BP > 185 mm Hg or diastolic BP > 110 mm Hg
- Rapidly improving or minor symptoms (NIHSS of 1).
- Symptoms suggestive of subarachnoid hemorrhage.
- GI or urinary tract hemorrhage in the previous 21 days.
- Platelet count below 100,000.
- Aggressive treatment needed to reduce blood pressure to specified limits.
- An application for waiver of consent will be submitted. However, if this cannot be obtained, inability to provide informed consent will be a de facto exclusion criterion.

Patients in both the placebo and control group have identical inclusion and exclusion criteria.

H. Recruitment
As described above, patients will be recruited from those patients presenting to CUMC or an affiliate center with an acute ischemic stroke with a definable time of onset.

I. Confidentiality
We will maintain strict confidentiality measures for all patient identifiers. Patients will be given a numerical identifier specific to the study, separate and unrelated to their medical record number, age, gender, or other personal identifiers.

Physical files will be stored in a locked closet belonging to the principal investigator. Only the senior investigators will have access to this closet.

Similarly, electronic identifiers and data will be kept on a server computer on an encrypted virtual drive partition, to which only the senior investigators have the password.

If a waiver of consent cannot be obtained, all patients will be consented and all consent forms will be stored in the above-mentioned locked closet.

J. Conflict of Interest
None – no private drug or device manufacturer is sponsoring the study.

K. Location
This prospective trial is designed to be based at multiple clinical centers, including CUMC.

L. Potential Risks
Potential risks of local hypothermia are assumed to be similar to, though of lesser magnitude than, the adverse affects of systemic hypothermia found in Table 1b. No adverse neurological outcomes (other than singultus/hiccups) have been reported with hypothermia.

Risks of intra-arterial catheterization and superior guidance under fluoroscopy includes arterial rupture, though this is rare. Vascular catheterization in general carries the risk of line infection, though the short amount of time it is left in the patient greatly reduces this risk.

M. Potential Benefits
By participating in this study, the patients will be shedding light on the effectiveness of local hypothermia in acute brain ischemia. Those patients randomized to the treatment arm of the study may, if the hypothesis proves correct, retain neurological function that they would normally lose under the current standard of care.

N. Alternative Therapies
Not applicable.

O. Compensation to Subjects
Patients will be compensated for all their treatment related to their ischemic stroke.

P. Costs to Subjects
None.

Q. Minors as Research Subjects
No minors will be participating in this study.

R. Radiation and Radioactive Substances
Patients will be exposed to X-ray radiation during their fluoroscopic and angiographic procedures, as necessary.

S. Selected References

1. Heart Disease and Stroke Statistics-2006 Update. A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006; 113: e85-e151.
2. Sacco RL, Adams R, Albers, G, et al. Guidelines for prevention of stroke in patients with ischemic stroke of transient ischemic attack. Stroke 2006; 37: 577-17.
3. Katzan IL, Furlan AJ, Lloyd LE, et al. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland are experience. JAMA 2000; 283: 1151-8.
4. Heuschmann PU, Berger K, Misselwitz B, et al. Frequency of thrombolytic therapy in patients with acute ischemic stroke and the risk of in-hospital mortality: the German Stroke Registry Study Group. Stroke 2003; 34: 1106-13.

5. Choi JH, Bateman BT, Mangla S, et al. Endovascular recanalization therapy in acute ischemic stroke. Stroke 2006; 37:419-24.
6. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333: 1581-7.
7. Grotta JC, Burgin WS, El-Mitwalli A, et al. Intravenous tissue-type plasminogen activator therapy for ischemic stroke: Houston experience 1996 to 2000. Arch Neurol 2001; 56: 2009-13.
8. Grond M, Stenzel C, Schmulling S, et al. Early intravenous thrombolysis for acute ischemic stroke in a community-based approach. Stroke 1998; 29: 1544-9.
9. Qureshi AI, Kirmani JF, Sayed MA, et al. Time to hospital arrival, use of thrombolytics, and in-hospital outcomes in ischemic stroke. Neurology; 2005: 2115-20.
10. The DIAS Study Group. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. Stroke 2005; 36: 66–73.
11. Kidwell CS, Saver JL, Starkman S, et al. Late secondary ischemic injury in patients receiving intraarterial thrombolysis. Ann Neurol 2002; 52: 698 –703.
12. Ribo M, Molina CA, Rovira A, et al. Safety and efficacy of intravenous tissue plasminogen activator stroke treatment in the 3- to 6-hour window using multimodal transcranial Doppler/MRI selection protocol. Stroke 2005;36:602–6.
13. Kent DM, Ruthazer R, Selker HP. Are some patients likely to benefit from hours from symptom onset? Stroke 2003; 34: 464–7.
14. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke: PROACT II study-a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA 1999; 282: 2003–11.
15. Lewandowski CA, Frankel M, Tomsick TA, et al. Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial. Stroke 1999; 30: 2598–605.
16. IMS Study Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. Stroke 2004; 35: 904 –11.
17. Gobin YP, Starkman S, Duckwiler GR, et al. MERCI 1: a phase 1 study of mechanical embolus removal in cerebral ischemia. Stroke 2004; 35: 2848–54.
18. Peters O, Back T, Lindauer U, et al. Increased formation of reactive oxygen species after permanent and reversible middle cerebral artery occlusion in the rat. J Cereb Blood Flow Metab 1998; 18: 196-205.
19. Kumura E, Yoshimine T, Iwatsuki KI, et al. Generation of nitric oxide and superoxide during reperfusion after focal cerebral ischemia in rats. Am J Physiol 1996; 270: c748-c52.
20. Barinaga M. Stroke-damaged neurons may commit cellular suicide. Science 1998; 281: 1302-3.
21. Sterz F, Safar P, Tisherman S, et al. Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. Crit Care Med 1991; 19**:** 379-89.
22. Yanamoto H, Hong SC, Soleau S, et al. Mild postischemic hypothermia limits cerebral injury following transient focal ischemia in rat neocortex. Brain Res 1996; 718**:** 207-11.
23. Maier CM, Sun GH, Kunis D, et al. Delayed induction and long-term effects of mild hypothermia in a focal model of transient cerebral ischemia: neurological outcome and infarct size. J Neurosurg 2001; 94**:** 90-6.
24. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002; 346: 549-56.

25. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002; 346**:** 557-63.
26. Mora CT, Henson MB, Weintraub WS, et al. The effect of temperature management during cardiopulmonary bypass on neurologic and neuropsychologic outcomes in patients undergoing coronary revascularization. Journal of Thoracic & Cardiovascular Surgery 1996; 112**:** 514-22.
27. Busto R, Globus MY, Dietrich WD, et al. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 1989; 20**:** 904-10.
28. Nakashima K, Todd MM. Effects of hypothermia on the rate of excitatory amino acid release after ischemic depolarization. Stroke 1996; 27**:** 913-8.
29. Sick TJ, Xu G, Perez-Pinzon MA. Mild hypothermia improves recovery of cortical extracellular potassium ion activity and excitability after middle cerebral artery occlusion in the rat. Stroke 1999; 30**:** 2416-21.
30. Huang ZG, Xue D, Preston E, et al. Biphasic opening of the blood-brain barrier following transient focal ischemia: effects of hypothermia. Can J Neurol Sci 1999;26**:** 298-304.
31. Ishikawa M, Sekizuka E, Sato S, et al. Effects of moderate hypothermia on leukocyte-endothelium interaction in the rat pial microvasculature after transient middle cerebral artery occlusion. Stroke 1999; 30**:** 1679-86.
32. Toyoda T, Suzuki S, Kassell NF, Lee KS. Intraischemic hypothermia attenuates neutrophil infiltration in the rat neocortex after focal ischemia-reperfusion injury. Neurosurgery 1996; 39**:** 1200-5.
33. Schwab S, Schwarz S, Spranger M, et al. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. Stroke 1998; 29**:** 2461-6.
34. Kammersgaard LP, Rasmussen BH, Jorgensen HS, et al. Feasibility and safety of inducing modest hypothermia in awake patients with acute stroke through surface cooling: A case-control study: the Copenhagen Stroke Study. Stroke 2000; 31**:** 2251-6.
35. Krieger DW, De Georgia MA, Abou-Chebl A, et al. Cooling for acute ischemic brain damage (cool aid): an open pilot study of induced hypothermia in acute ischemic stroke. Stroke 2001; 32**:** 1847-54.
36. Schwab S, Georgiadis D, Berrouschot J, et al. Feasibility and safety of moderate hypothermia after massive hemispheric infarction. Stroke 2001; **32:** 2033-5.
37. Georgiadis D, Schwarz S, Kollmar R, Schwab S. Endovascular cooling for moderate hypothermia in patients with acute stroke: first results of a novel approach. Stroke 2001; 32**:** 2550-3.
38. Geogiadis D, Schwartz S, Aschoff A, Schwab S. Hemicraniectomy and moderate hypothermia in patients with severe ischemic stroke. Stroke 2002; 33**:** 1584-1588.
39. De Georgia MA, Krieger DW, Abou-Chebl A, et al. Cooling for Acute Ischemic Brain Damage (COOL AID): a feasibility trial of endovascular cooling. Neurology 2004; 63: 312-317.
40. Corbett RJ, Laptook AR. Failure of localized head cooling to reduce brain temperature in adult humans. Neuroreport 1998; 9**:** 2721-5.
41. Wolfson SI, WY; Kavianian, A; Icoz, MV. Preferential cerebral hypothermia for circulatory arrest. Surgery 1965; 57**:** 846-55.
42. Bacalzo LV, Jr., Wolfson SK, Jr. Resuscitation after unexpected circulatory arrest: tolerance to cerebral ischemia provided by cold carotid perfusion. Biomedical Sciences Instrumentation 1969; 5**:** 75-8.
43. Schwartz AE, Stone JG, Finck AD, et al. Isolated cerebral hypothermia by single carotid artery perfusion of extracorporeally cooled blood in baboons. Neurosurgery 1996; 39**:** 577-81; discussion 581-2.
44. Chen H, Chopp M, Zhang ZG, Garcia JH. The effect of hypothermia on transient middle cerebral artery occlusion in the rat. J Cereb Blood Flow Metab 1992; 12**:** 621-8.

45. Goto Y, Kassell NF, Hiramatsu K, et al. Effects of intraischemic hypothermia on cerebral damage in a model of reversible focal ischemia. Neurology 1993; 32: 980-4; discussion 984-5.
46. Karibe H, Chen J, Zarow GJ, et al. Delayed induction of mild hypothermia to reduce infarct vome after temporary middle cerebral arter occlusion in rats. J Neurosurg 1994; 80: 112-9.
47. Ridenour TR, Warner DS, Todd MM, McAllister AC. Mild hypothermia reduces infarct size resulting from temporary but not permanent focal ischemia in rats. Stroke 1992; 23**:** 733-8.
48. Anonymous. Randomised trial of normothermic versus hypothermic coronary bypass surgery. The Warm Heart Investigators. Lancet 1994; **343:** 559-63.
49. Martin TD, Craver JM, Gott JP, et al. Prospective, randomized trial of retrograde warm blood cardioplegia: myocardial benefit and neurologic threat. Annals of Thoracic Surgery 1994; 57**:** 298-302; discussion 302-4.
50. Regragui I, Birdi I, Izzat MB, et al. The effects of cardiopulmonary bypass temperature on neuropsychologic outcome after coronary artery operations: a prospective randomized trial. Journal of Thoracic & Cardiovascular Surgery 1996; 112**:** 1036-45.
51. Engelman RM, Pleet AB, Rousou JA, et al. What is the best perfusion temperature for coronary revascularization? Journal of Thoracic & Cardiovascular Surgery 1996; 112**:** 1622-32; discussion 1632-3.
52. Plourde G, Leduc AS, Morin JE, et al. Temperature during cardiopulmonary bypass for coronary artery operations does not influence postoperative cognitive function: a prospective, randomized trial. Journal of Thoracic & Cardiovascular Surgery 1997; 114**:** 123-8.
53. Grimm M, Czerny M, Baumer H, et al. Normothermic cardiopulmonary bypass is beneficial for cognitive brain function after coronary artery bypass grafting--a prospective randomized trial. European Journal of Cardio-Thoracic Surgery 2000; 18**:** 270-5.
54. Grigore AM, Mathew J, Grocott HP, et al. Prospective randomized trial of normothermic versus hypothermic cardiopulmonary bypass on cognitive function after coronary artery bypass graft surgery. Anesthesiology 2001; 95**:** 1110-9.
55. Morikawa E, Ginsberg MD, Dietrich WD, et al. The significance of brain temperature in focal cerebral ichemia: histopathological consequences of middle cerebral artery occlusion in the rat. J Cereb Blood Flow Metab 1992; 12: 380-9.
56. Marion DW, Leonov Y, Ginsberg M, et al. Resuscitative hypothermia. Crit Care Med 1996; 24**:** S81-9.
57. Selker RG, Wolfson SK, Maroon JC, Steichen FM. Preferential cerebral hypothermia with elective cardiac arrest: resection of "giant" aneurysm. Surgical Neurology 1976: 3: 173-9.
58. Wolfson SK, Jr., Selker RG. Carotid perfusion hypothermia for brain surgery using cardiac arrest without bypass. Journal of Surgical Research 1973; 14**:** 449-58.
59. National Institute of Neurological Disorders and Stroke rt-PA Study Group. Tissue Plasminogen Activator for Acute Ischemic Stroke. N Engl J Med 1995; 333: 1581-7.
60. Lyden P, Brott T, Tilley B, et al. Improved reliability of the NIH Stroke Scale using video training. Stroke 1994;25:2220-6.
61. Albanese MA, Clarke WR, Adams HP Jr, Woolson RF. Ensuring reliability of outcome measures in multicenter clinical trials of treatments for acute ischemic stroke: the program developed for the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Stroke 1994;25:1746-51.
62. Lyden PD, Broderick J, Mascha E. Reliability of the Barthel Index used for the NINDS t-PA Stroke Trial. In: Yamaguchi T, Mori E, Minematsuk K, del Zoppo GJ, eds. Thrombolytic therapy in acute stroke III. Tokyo, Japan: Springer-Verlag (in press).