Early, rapid cooling is the key to successful outcomes following out-of-hospital cardiac arrest (OHCA), but how cold patients need to be – and for how long – remains uncertain. Growing evidence also supports targeted temperature management (TTM) for stroke, traumatic brain injury patients and possibly myocardial infarction patients, and results of important trials are eagerly awaited.

These were the main “take-home” messages for the 270 delegates from 28 countries who filled the Congress hall for the 2nd International TTM Teaching Course, in London, 21-22 November 2013.*

*This newsletter contains reports on all the topics covered at TTM 2013, but has focused on key presentations within those subject areas.
TTM Study Adds to Debate Over Temperature Target
Professor Friberg

Approximately half of patients are likely to survive OHCA, regardless of whether they are cooled to 33°C or 36°C, according to results of the recently published TTM trial presented at the meeting by Professor Hans Friberg, from Lund University, Sweden.

Data from 939 OHCA patients (median Glasgow Coma Scale [GCS] of 3) analysed at the end of the three-year trial showed that 50% of those in the 33°C group had died compared with 48% of those in the 36°C group (HR at 33°C, 1.06; 95% CI 0.89–1.28; p=0.51). Mortality at day 180 was 54% and 50% respectively (HR 1.02; 95% CI 0.88–1.16; p=0.70).

Professor Friberg explained that cause of death was similar in the two groups (mainly cerebrovascular), and there was no significant difference in neurological function outcomes. Adverse events, including serious events and fever, were also comparable, and hypokalaemia was the only event with a significant result 19% in the 33°C group vs 13% in the 36°C group (p=0.018).

Sub group analyses also showed no significant difference between the cooling regimens, though there was a slight trend favouring 36°C in women compared with men, and in patients < 65 years versus ≥ 65.

Professor Friberg reported that participating centres were required to have feedback-controlled cooling devices, and 76% used surface cooling and 24% used intravascular methods. Further analyses will examine neurological recovery and quality of life data, and a sub study is investigating biomarker outcomes.

Which cooling method? Professor Sunde

Clinicians should use the cooling technique best suited to their local setting and temperature management plan, concluded Professor Kjetil Sunde, from Oslo University Hospital, Norway, at the end of an extensive review of hypothermia methodology.

Professor Sunde presented data from the Hypothermia Network (2004-2008) which showed that the most popular methods for induction were cold fluid infusion (80%), circulating water blankets (47%) and ice packs (43%), with circulating water blankets preferred for maintenance treatment (63%). He reported studies showing that IV cold saline infusion combined with ice packs was effective in inducing and maintaining therapeutic hypothermia, and that cooling with water-circulating blankets, gel pads and intravascular cooling was more efficient than conventional cooling and air-circulating blankets.

Professor Sunde also discussed results from two studies which showed no significant difference in neurological function of survivors following intravascular versus surface cooling. In the first of these, 167 consecutive comatose OHCA patients were allocated to core or surface cooling (intravascular versus surface cooling). In the first of these, 167 consecutive comatose OHCA patients were allocated to core or surface cooling (intravascular versus surface cooling). In the second study (ICERA), there was no significant difference in survival at ICU discharge or CPC status at day 28 between external and intravascular cooling.

Turning to timing of hypothermia, Professor Sunde explained that there have been conflicting results from studies of early versus delayed hypothermia, and recently reported data from a study of pre-hospital cooling showed that, although this reduced the time to reach a temperature of 34°C, it did not impact on survival or neurological status.

However, as Professor Sunde pointed out, animal data have suggested that the therapeutic window for successful hypothermia is within 4 hours after return of spontaneous circulation (ROSC), with reduced survival and worse neurological outcomes if treatment is delayed until 6 hours. This animal study also showed higher mortality counts when hypothermia was maintained for 48 hours compared with 24 hours.

TTM 2013 London Event Photos
Temperature Management – For How Long?
Dr Peiuli

Temperature management should not finish after a 24-hour period of hypothermia, but should continue for at least 72 hours after a patient is hospitalised following OHCA because of the risks of post-rewarming, rebound hypothermia (RH) and fever, concluded Dr Tommaso Peiuli, from Santa Maria degli Angeli, Pordenone, Italy.

He presented evidence from two recent studies showing adverse outcomes of RH or post-hypothermia fever (PHF). In an observational study of 141 OHCA patients who had received hypothermia treatment, those who experienced RH showed significantly higher hospital mortality compared to those who did not (64.3% vs 40.4%, p=0.011), and increased neurological morbidity (p=0.011). In a prospective study of 270 OHCA patients who survived TTM of 32-34°C, those with post-hypothermia fever (PHF) (median peak temperature >38.5°C) within 36h after rewarming had a significantly higher 30 day mortality rate than those without PHF (36% vs 22% corresponding to an adjusted hazard rate (HR) of 1.8 (95% CI 1.1-2.7), p=0.002). Good neurological outcome (CPC=1-2) at hospital discharge was found in 61% of the PHF group compared to 75% in those without PHF (p=0.02).

Dr Peiuli pointed out that the recent TTM study aimed to maintain body temperature at 37°C for at least 72 hours after cardiac arrest, by active temperature management in patients that remain unconscious. Data from the study showed that this was achieved in both treatment groups and that temperature management was successfully extended even to day 4 thus underlining the importance of continued temperature management.

Impact of Heat Transfer Rate
Dr Haugk | Dr Stratil

Support for early, rapid cooling came from Dr Moritz Haugk and Dr Peter Stratil from the Medical University of Vienna, Austria, following a review of recent studies.

In the latest published study in 172 cardiac arrest patients, every five minutes of delay in starting cooling was associated with a 6% worsening in neurological outcomes at discharge follow up. In addition, the likelihood of a poor outcome increased by 17% for every 30 minutes delay in reaching the target temperature. Given the growing emphasis on early, rapid cooling, Dr Haugk reported results from two recent studies in Vienna which investigated the heat transfer rate with Arctic Sun® surface cooling methods.

In an initial observational case study of 27 cardiac arrest patients treated from 2004-2005, the Arctic Sun® 2000 was shown to cool patients at a rate in line with other cooling devices, with a median reduction of 1.2°C per hour.

In a second observational study, precise cooling was demonstrated with the Arctic Sun® 5000 in 15 OHCA with a relatively high median BMI of 29. The six month survival rate for the group was 53%, and 47% of patients had a favourable neurological recovery. The median cooling rate was 1.3°C per hour and, during the maintenance phase, the deviation from the 33°C target was very small, i.e.: 0.2-0.3°C.

Dr Stratil concluded that fast early cooling with Arctic Sun® 5000 was achieved, despite the high BMI of the patients, and that surface cooling was very stable.

Can STEMi patients benefit from cooling? Professor Storm

Promising data from the CHILL-MI study of rapid cooling prior to primary percutaneous coronary intervention (PCI) in ST elevation myocardial infarction (STEMI) patients were discussed by Professor Christian Storm.

The results, which were presented at the 25th Annual Transcatheter Cardiovascular Therapeutics (TCT) conference in San Francisco showed that aggressive intravascular cooling below 35°C within 6 hours of symptom onset was associated with a non significant 13% reduction in infarct size (p=0.15) at 4 + 2 days. Amongst patients with anterior STEMi, the reduction was 27%, but this was also non significant as numbers were small.

Professor Storm explained that although the study missed its primary endpoint, there was a significantly lower incidence of clinical heart failure in patients who had received cooling (3% vs 14% (p=0.05)).

He concluded that a further RCT is now needed in patients with infarcts in anterior vessels which will focus on cooling within the first 4 hours after symptoms, so that patients are already at their target temperature by the time they reach hospital.

Key Points
• Cooling for Ischaemic Stroke Trial (COOLIST) investigates surface cooling within 4.5 hours after stroke onset
• Trial to compare conventional vs Arctic Sun® cooling to 34°C, 34.5°C, or 35°C
• Anti-shivering regimen includes IV pethidine and oral buspirone

Utrecht experience in ischaemic stroke
Dr Geurts

Therapeutic hypothermia is a promising approach for improving outcomes in ischaemic stroke patients but the optimal temperature remains uncertain, concluded Dr Maryline Geurts, from the University Medical Centre of Utrecht, Holland, at the end of a presentation focusing on a new study aimed at addressing this important knowledge gap.

She reported that 18 of a target 48 awake ischaemic stroke patients have been randomised to the phase II. Cooling for Ischaemic Stroke Trial (COOLIST) which is investigating the feasibility and safety of surface cooling started within 4.5 hours after stroke onset and maintained for 24 hours. Patients are being randomised to conventional treatment or surface cooling to 34°C, 34.5°C, or 35°C. Cooling starts with IV saline (4°C) over 30 to 60 minutes, followed by surface cooling with Arctic Sun®. An anti-shivering regimen includes IV pethidine and oral buspirone.

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Key Points
• Early, rapid cooling is essential after OHCA
• Arctic Sun® 5000 offers precise cooling during induction and maintenance
• High BMI does not impede effectiveness of Arctic Sun® 5000
How to Manage Shivering
Professor Storm | Professor Kollmar

“Progress past the shivering threshold of 34°C to 36°C as rapidly and aggressively as possible in cardiac arrest patients” was the advice of Professor Christian Storm, from the Charité – Universitätsmedizin, Berlin, Germany.

He recommended using a combination of a cooling device and infusion of 1-2 litres of cold saline, together with deep sedation, counter-warming of hands and feet (from the start) and magnesium 1-2mg IV to reduce the risk of shivering. Paralysis with a muscle relaxant should only be considered if all else has failed to prevent shivering, he added.

Professor Storm pointed out that shivering is least likely to occur if gas sedation is used, and this has the added advantage that patients wake more quickly than other forms of sedation. A number of speakers pointed out that awake patients find shivering very distressing; in addition shivering can have damaging effects in brain injury patients, due to reduced oxygenation of brain tissue.

However, Professor Rainer Kollmar, from Darmstadt Hospital, Darmstadt, Germany, warned that great care is needed when sedating stroke or brain injury patients during hypothermia, as this has been associated with respiratory depression and increased risk of pneumonia.

Professor Kollmar reported that, in the ongoing Eurohypo study in stroke patients, an anti-shivering regimen consisting of an IV bolus of ondansetron followed by an IV bolus of pethidine 50mg and oral buspirone 10mg, followed by further boluses of patient administered pethidine 25mg, is proving satisfactory.

Is Cooling After Cardiac Arrest Cost Effective?
Professor Behringer

Administrators and payers who are concerned that cooling patients after cardiac arrest is too expensive can be reassured that treatment is very cost effective. Results of a new analysis presented by Professor Wilhelm Behringer, from the Medical University of Vienna, Austria, showed a cost per quality adjusted life year (QALY) of €3,827 for hypothermia. This is well below the £24,000-£36,000/QALY used as a cost effectiveness threshold in the UK for NICE approval of novel treatments and the €30,000/QALY threshold used in Austria on whose healthcare costs the analysis was based.

Eurotherm Update
Professor Andrews

Recruitment is well on track for Eurotherm3235 – the international, multicentre, randomised controlled trial which is investigating the effects of induced therapeutic hypothermia (32-35°C) as a treatment for raised intracranial pressure (ICP) after traumatic brain injury.

Approximately half of the planned 600 patients have been randomised at 43 centres, but lead investigator, Professor Peter Andrews, from the University of Edinburgh, UK, is keen to hear from further interested centres who have appropriate facilities, in order to boost patient numbers towards their target.

Explaining the need for Eurotherm3235, Professor Andrews drew attention to the current lack of evidence about the impact of interventions on ICP, despite the strong association between raised ICP and poor outcome following traumatic brain injury. He added that, since hypothermia is a well established effective intervention following OHCA, it is a logical choice for investigation for ICP reduction.

Professor Andrews questioned the findings of a recent study which may have raised doubts about the importance of ICP monitoring following severe traumatic brain injury. He explained that the failure to show any advantage of ICP-monitoring over imaging and clinical examination in improving performance outcomes may have been due to the fact that patients in the ICP group had lower levels of ICP lowering interventions than the imaging group.

Professor Andrews presented results of a meta analysis of animal studies in brain injury which showed a median 43% reduction in infarct size following hypothermia at 32-35°C. He also shared data from a systematic review of clinical studies which demonstrated that reducing ICP with hypothermia after brain injury led to improved outcomes, though the best results were achieved with the smallest studies. In addition, a Cochrane review concluded that hypothermia may be effective in reducing death and unfavourable outcomes in patients with traumatic brain injury, but that significant benefit has only been shown in low quality trials.

EuroHyp Update
Professor Kollmar

Recruitment is also underway for EuroHyp – a pan-European, open, randomised, phase III clinical trial which will assess the benefit of therapeutic cooling (34-35°C) in adult patients with acute ischaemic stroke. Professor Rainer Kollmar explained that the aim is to recruit 1500 patients from some 80 centres in Europe within 4 years, with outcomes including efficacy, safety and the economic impact of therapeutic hypothermia.