CLINICAL STUDY PROTOCOL

Impact of rewarming rate after cardiac arrest and therapeutic hypothermia. Randomised pilot study.

Study code: ISOCRATE

NCT Number : NCT02555254

VERSION N°5 of 7 July 2020

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Registration number	RCB 2015-A00222-47
PPC	Approved on 10/07/2019 by the Comité de Protection des Personnes de Poitiers

List of abbreviations

RTA	Cardiopulmonary arrest
ACSOS	Secondary Systemic Brain Attack
ANSM	National Agency for the Safety of Medicines
CRA	Clinical Research Associate
BSAS	Bedside shivering assessment scale
CMRO2	Cerebral metabolic rate for oxygen
CPP	Committee for the Protection of Individuals
CPC	Glasgow Outcome Scale Cerebral Performance Category
CRC	Clinical Research Centre
DRI	Research and Innovation Directorate
AED	Semi-automatic defibrillator
SAE	Serious adverse event
ROS	Oxygen radical species
VF	Ventricular fibrillation
GM-CSF	Granulocyte macrophage colony-stimulating factor
IGS	Simplified severity index
It	Interleukin
ILCOR	International liaison committee on resuscitation
BMI	Body Mass Index
ITT	Intention to treat
IVD	Direct intravenous
MCE	External cardiac massage
OR	Odds ratio
MAP	Mean arterial pressure
PAPO	Occlusion pulmonary artery pressure
RASS	Richmond agitation sedation scale
CPR	Cardiopulmonary resuscitation
RL	Slow warming
RR	Rapid heating
ROSC	Return of spontaneous circulation
VT	Ventricular tachycardia

Signature page

SIGNATURE OF THE INVESTIGATOR

I have read all the pages of the protocol for the clinical trial for which the CHD Vendée is responsible. I confirm that it contains all the information required to conduct the trial. I undertake to carry out the trial in compliance with the protocol and the terms and conditions defined therein. I undertake to carry out the trial in compliance with :

- the principles of the Helsinki Declaration,
- international (ICH-E6) and French (rules of good clinical practice for biomedical research involving products for human use - decisions of 24 November 2006) rules and recommendations of good clinical practice
- national legislation and regulations relating to clinical trials,
- compliance with the EU Clinical Trials Directive, a copy of each of which was given to me by the institution responsible for the research.

I also undertake to ensure that the investigators and other qualified members of my team have access to copies of this protocol and documents relating to the conduct of the trial to enable them to work in compliance with the provisions set out in these documents.

NAME :

Signature : Date : _____

SIGNATURE OF THE INSTITUTION RESPONSIBLE FOR THE RESEARCH

Establishment responsible for the research: CHD Vendée

NAME: Francis Saint Hubert, Director of CHD Vendee

Signature: ..... Date :

NAME: Jean-Baptiste Lascarrou,
coordinating investigator

Signature: ..... Date :

I. General information

A. *Title*

ISOCRATE study.

Impact of rewarming rate after cardiac arrest and therapeutic hypothermia. Randomised pilot study.

Impact of Speed Of rewarming after CaRdiac Arrest and ThErapeutic hypothermia. A randomized pilot study.

B. *Coordination and monitoring of the study*

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C. *Investigators*

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II. Scientific justification and general description of the research

A. *Summary of the results of available non-clinical trials and clinical trials relevant to the biomedical research concerned*

1. Cardiac arrest, a public health problem

Cardiac arrest is still a major cause of death and disability for surviving victims. (1). In France, every year, there are 50,000 cardiac arrests responsible for 40,000 deaths. Less than 20% of patients suffering cardiac arrest leave hospital without serious neurological sequelae (2-4). Despite significant progress in its management over the last 50 years (5)RCA remains a major cause of death in France today, particularly in patients aged between 45 and 64 (6) and a source of disability for surviving patients. In fact, surviving patients have a reduced quality of life at 1 year post-RCA (7). This reduction in quality of life is marked by symptoms of fatigue, anxiety and depression, as well as elements that may be part of a post-traumatic stress state (8). As a result, less than 50% of patients are able to return to work after the RTA, and 25% are able to work part-time (9). In addition, there is a reduction in cognitive function, with memory problems (10). This deterioration in quality of life is then established over a longer period of time (11).

2. RTA, a condition with a poor prognosis

This poor prognosis is the result of a combination of specific lesions caused by cerebral anoxia during RTA and specific lesions caused by the immediate and delayed resuscitation of this RTA.

On the one hand, the restoration of cerebral circulation following cardiopulmonary resuscitation occurs after a period of cerebral anoxia that varies according to the circumstances. From the third minute, this cerebral anoxia leads to cellular lesions. These lesions are manifold and result in particular from dysfunction of the Na/K ATPase pump, which promotes the intracellular entry of chlorine, sodium and water, leading to neuronal oedema. Once the O2 supply has ceased, anaerobic glycolysis takes place. The accumulation of lactic acid secondary to this glycolysis then exacerbates the cellular damage.

On the other hand, the resumption of effective cardiac activity results in an intracellular influx of glutamate and calcium, and a significant production of free radicals, leading to a worsening of these cellular lesions, marking the appearance of a post-cardiac arrest syndrome and possibly leading to additional lesions combining myocardial ischaemia, circulatory dysfunction and ischaemia-reperfusion syndrome. Thus, the classic dogma according to which cerebral anoxia during RCA was responsible for all neuronal lesions has been called into question. It has been observed that during the post-cardiac arrest phase there is a decrease in cerebral blood flow associated with a decrease in cerebral oxygen extraction (12). All these phenomena explain why the post-cardiac arrest phase is so important in terms of treatment, so as not to aggravate the lesions resulting from the anoxia phase.

3. Hypothermia, the treatment of choice after RTA

Following early studies suggesting the benefits of hypothermia for cerebral protection (13)animal studies have shown encouraging results for neurological recovery after a period of controlled hypothermia (14). These animal studies have been confirmed by two randomised prospective studies now 10 years old, which have shown a significant improvement in the neurological prognosis of patients who have suffered a RTA and had a heart rhythm in VF or VT on medical management (15, 16).

The first European multicentre randomised study included 275 patients who were randomised into two groups: normothermia and hypothermia. The results showed an improvement in neurological prognosis in favour of the hypothermia group, since 55% of this group had a good neurological prognosis at 6 months, compared with only 39% in the control group treated with normothermia (OR: 1.4; p=0.009).

The second Australian single-centre randomised study published in the same issue of the *New England Journal of Medicine* included 77 patients, again randomised into two groups: normothermia and hypothermia. The results were identical, with an improvement in neurological prognosis in favour of the hypothermia group (49% versus 26%; p=0.046).

4. The mechanisms that explain the benefits of this procedure

There are many mechanisms behind this improvement in neurological prognosis.

The main and oldest hypothesis corresponded to the re-establishment of a better coupling between energy supply and demand (12) thanks to the reduction in CMRO2. However, other mechanisms appear to be just as important in explaining the neurological benefits of this procedure, in particular the reduction in the production of inflammatory cytokines. Indeed, *Fries* observed that performing a 32-34 CCT reduced the production of

interleukin 6 in all patients suffering from RTA (17)This in vivo data confirms previous in vitro data by Kimura (18). Other mechanisms also appear to be involved to a lesser extent:

- reduced production of radical species (19, 20)
- reduction in cell death phenomena (21, 22)as well as mitochondrial abnormalities (23)
- protection of the blood-brain barrier (24-26)
- reduction in intracranial pressure (27)
- reduction in "thermo-pooling" phenomena: after a neurological lesion, certain areas of the brain may have a temperature higher than the core temperature; this phenomenon may then aggravate neuronal lesions in these areas (28)This explains the beneficial effect of hypothermia in these same areas.

Finally, certain experimental studies argue in favour of a systemic effect of hypothermia leading to an improvement in haemodynamic parameters, possibly acting on the post-cardiac arrest syndrome (29). It is therefore possible that the mechanisms involved in the neurological benefits are also at play at the cardiac and vascular levels.

Because of the wide disparity in the pathological and physiological conditions described under the term therapeutic hypothermia: moderate, moderate, severe; and the conclusions of research involving accidental hypothermia extended to work involving therapeutic hypothermia, a recent international consensus has led to the abandonment of the term "therapeutic hypothermia" in favour of the term "targeted temperature control" associated with the desired temperature range. (30) either targeted temperature control between 32 and 34°C (CCT 32-34).

For example, the 2010 ERC recommendations (31) and ILCOR 2010 (32) recommend that a period of CCT32-34 should be performed in cardiac arrest patients who have recovered effective cardiac activity and who present with persistent impairment of consciousness (Glasgow score ≤ 8). Thanks to these recommendations, CCT32-34 is now one of the reference procedures for the management of this type of patient, and is used on a daily basis in most intensive care units around the world. (33-38).

5. What are the precise terms and conditions for the CCT 32-34?

Nevertheless, it is remarkable to note that despite the widespread use of this procedure, there are very few studies describing the optimal ways of carrying it out. For example, the speed with which the procedure is initiated and the time taken to reach a temperature of less than 34°C are crucial according to some studies (39) and less so according to others when the target temperature is reached within 4 to 5 hours (40).

In the specific context of CCT 32-34 after RTA, there are currently no randomised prospective studies that have determined the optimal rate of rewarming when this is performed. Furthermore, it is important to emphasise that international recommendations, including the most recent ones (31, 32) do not address the precise question of the rate of rewarming (except in the case of RCA in accidental hypothermia, during an avalanche for example) but encourage research to determine the methods of rewarming.

a) Arguments in favour of slow warming :

- One of the hypotheses to explain the clinical benefit of CCT32-34 is an attenuation of ischaemia-reperfusion lesions, and reperfusion lesions are linked to the influx of oxygen radical species during the rewarming phase. In cardiac surgery performed under extracorporeal circulation, randomised studies have demonstrated the benefit of a slow rewarming rate with successive stages of rewarming on the increased production of these radical species, which prevents the appearance of postoperative cognitive dysfunction (41, 42). It is possible that this increased production of radical species is responsible for activation of the membrane transition pore, leading to cell apoptosis. A slow rate of rewarming prevents activation of this membrane transition pore during hypothermia in cranial trauma patients (43).
- Slow, gradual and controlled rewarming allows better control of vasoplegia secondary to rewarming. (44) and thus reduces the risk of cardiovascular collapse during this phase, which can have an impact on neurological prognosis.
- In the different context of haemorrhagic shock and in animal experiments, it has been shown that a rapid rewarming rate leads to increased mortality, with surviving animals also showing neurological dysfunctions (45).
- Rapid warming can lead to increased CO2 production associated with disorders of cerebral vasoreactivity (46) resulting in a sudden increase in intracranial pressure (26, 47).
- Once rewarming has been achieved, it is preferable to avoid the onset of "rebound" hyperthermia, even if no clinical study has yet formally demonstrated the impact of this measure. (48). It is not known whether this is a direct deleterious effect of hyperthermia or a risk associated with CCT 32-34 through hyperthermic rebound after rewarming with activation of inflammatory cytokines, or whether it is a consequence of the infectious complications that are frequent in this context. (49). Nevertheless, slow rewarming allows better control of this phase (50).
- Rapid reheating can expose the cerebral circulation to temperatures above 37°C due to thermopooling phenomena, resulting in harmful localised hyperthermia (51).
- A Dutch team (52) observed that a rapid rewarming rate (>0.5°C/h) was associated with an unfavourable neurological prognosis at 6 months compared with a slow rewarming rate (<0.5°C/h), although this difference was no longer significant after adjustment for confounding factors.

b) Arguments in favour of rapid warming :

- An American study (53) observed that cerebral vasoreactivity was preserved when CCT 32-34 was performed after RTA. In addition, this study showed that during the hypothermia period, there was an increase in cerebral vascular resistance, which could lead to a reduction in cerebral perfusion. In view of these factors, rapid rewarming should enable cerebral perfusion to be rapidly normalised while preserving cerebral vasoreactivity.
- In the context of passive rewarming after CCT 32-34 for RTA, a Swiss team observed that a prolonged duration (600 minutes Vs 479 minutes) of rewarming was associated with an increase in mortality (54). However, it is possible that this difference in prognosis linked to the duration of rewarming, as in the

Dutch study, is linked solely to hypothalamic damage, independently of the other mechanisms described.

- Rapid rewarming should enable the sedation required for CCT 32-34 to be stopped just as quickly, thus enabling an early assessment of the prognosis of these patients. (55).
- In the 2 pivotal studies of CCT32-34 in RTA, the rate of rewarming was not similar:
    - Target of 6 hours with active rewarming, i.e. 0.5°C/h in the Australian study, with an OR of 1.4 for neurological prognosis. (16)
    - Target of 8 hours with passive rewarming, i.e. 0.37°C/h in the European study, with an OR of 5.25 for neurological prognosis (15)

  Although the populations in these studies are not comparable (no-flow duration, low-flow duration, age, etc.), it is possible that the difference in terms of neurological benefit (OR 1.4 Vs OR 5.25) is partially explained by these different reheating speeds.

6. What data are available following publication of the Targeted Temperature Management Trial?

The recent publication in the New England Journal of Medicine of a study comparing 2 thermal objectives when performing CCT after cardiac arrest does not call into question the rationale of the ISOCRATE study. This study compared a thermal objective set at 33°C with a thermal objective set at 36°C in the hospital management of cardiac arrest in shockable rhythm. This superiority study concluded with a negative result, making it impossible to conclude either that the 2 objectives were superior or equivalent. The publication of this study was accompanied by a warning from the authors about abandoning temperature control in post-cardiac arrest, and by a statement from the European Resuscitation Council to the effect that, in the light of this single study, the thermal objective should always be set at 33°C (https://www.erc.edu/index.php/docLibrary/en/viewDoc/2083/3/). Finally, some authors have noted that the rate of warming at the end of the procedure in this study was high, in excess of 0.5°C/h, which could attenuate the neurological benefit of a thermal target set at 33°C (56). The publication of this study does not therefore call into question the rationale, the methods used and the importance of the ISOCRATE study.

7. Conclusion

Determining the optimal rate of rewarming when performing a 32.5-33.5 CCT in RTA is important in order to improve the prognosis of these patients while improving our understanding of the pathophysiological mechanisms involved in this procedure. However, to date, no prospective clinical study has been published and no clinical study on this specific subject is currently underway, according to the international website *ClinicalTrial.gov*.

The aim of the present research is therefore to verify, within the framework of a prospective, randomised and controlled study, the hypothesis that a slow rate of rewarming (0.25°C/h) during a period of targeted temperature control between 32.5 and 33.5°C after the onset of cardiac arrest managed in shockable rhythm allows a reduction in the production of interleukin 6 which is correlated with the neurological prognosis. (57) in this type of patient compared with a rapid rewarming rate (0.5°C/h).

B. *Summary of benefits, if any, and foreseeable and known risks to persons undergoing research*

Foreseeable individual benefit: standardisation of the procedure for performing the 32.5-33.5 CCT, no additional risk in the 2 randomisation groups.

Foreseeable collective benefit: draw up recommendations on practical reheating methods when carrying out a CCT 32.5-33.5 procedure.

The primary endpoint of this study was to demonstrate a reduction in inflammatory phenomena in the slow reheating group compared with the rapid reheating group. This study therefore only looked at the last phase of the 32.5-33.5 CCT period after the induction and maintenance phases.

There are numerous studies on targeted temperature control between 32.5 and 33.5°C in the context of RTA or in other settings, which describe the expected complications of carrying out this procedure. (50)complications: hypovolaemia; electrocardiographic changes: prolongation of the PR and/or QT interval; hydro-electrolytic disorders: hypokalaemia, hypomagnesaemia; coagulation disorders; increased risk of infection; hyperglycaemia; skin complications: cyanosis, digital ischaemia; biological disorders: hepatic cytolysis, elevated lipase, thrombocytopenia, haemoconcentration; changes in the pharmacology of the various drugs administered, etc.

Nevertheless, in the context of an RTA in shockable rhythm, the performance of a CCT 32.5-33.5 is part of the international recommendations with a high level of evidence (grade A), and is therefore an integral part of the management of these patients. The patient, relatives or trusted support person will be informed of the possible occurrence of these expected adverse events, and a procedure for dealing with each of them is described in the paragraph entitled "Management of expected adverse events".

C. *Declaration that the research will be conducted in accordance with the protocol and good clinical practice*

The investigator also undertakes that this research will be conducted :
- in accordance with the laws and regulations in force in France and Europe,
- in accordance with current French and international good clinical practice.

D. *Legislative and regulatory provisions*

This research falls within the scope of routine care research as defined by paragraph 2 of article L 1121-1 and article R 1121-3 of the French Public Health Code.

E. *Description of the population to be studied*

This study will focus on adult patients admitted to intensive care following a RTA who had a shockable rhythm on the arrival of the emergency services, who had recovered an effective cardiac rhythm following medical management and who had a persistent coma assessed using the Glasgow score of less than or equal to 8 and for whom a 32.5-33.5°C CCT procedure was indicated and carried out using a thermal regulation device.

III. Research objectives

A. *Main objective of the study*

To compare the production of interleukin 6 (inflammation cytokine) according to two rewarming rates (slow rewarming rate: 0.25°C/h or high rewarming rate 0.5°C/h) during a period of targeted temperature control between 32.5° and 33.5°C after a cardiac arrest with a cardiac rhythm requiring an external electric shock (ventricular fibrillation, ventricular tachycardia) when the emergency services arrive (presence of an AED on site, AED from the fire brigade, manual defibrillator from the mobile emergency and resuscitation service team) and before injecting adrenaline.

B. *Secondary objectives*

The secondary objectives were to compare the 2 groups:

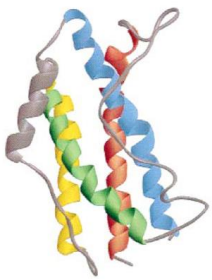
- Serum levels of Il2,Il4,Il8,Il10,GM-CSF,Interferon-beta, TNF-alpha, neurofilament
- Total antioxidant capacity using a serum test: Patrol®.
- Serum levels of CRP and Procalcitonin
- Mortality in intensive care
- Hospital mortality
- Mortality at D90
- Neurological functional status at D90
- Assessment of the patient's quality of life at D90
- Assessment of patient autonomy at D90
- Neurocognitive assessment of the patient at D90
- Estimation of the number of patients with post-traumatic stress symptoms at D90
- Length of stay in intensive care
- Duration of mechanical ventilation
- Need for vasopressor treatment in the first 72 hours

IV. Research design

A. *Precise statement of primary and, where appropriate, secondary evaluation criteria*

1. Primary endpoint

- Changes in serum levels of Il6 (inflammation marker) over the 48 hours following achievement of the thermal target (33°C) according to 2 reheating modalities during a targeted thermal control between 32.5° and 33.5°C: group with a slow reheating rate (RL; 0.25°C/h) compared with a group with a high reheating rate (RR; 0.5°C/h).
    - The choice of IL6 is based on the fact that it is one of the main interleukins produced during the inflammatory process. Several studies have demonstrated a strong correlation between Il6 levels and the neurological outcome of patients suffering cardiac arrest (57, 58). In addition, a description of the variations in Il6 during the performance of a 32.5-33.5 CCT after cardiac arrest has been carried out, making it possible to formulate the hypotheses necessary for calculating the number of patients in a cardiac arrest. (59).
    - H0 will be defined as the time at which the thermal target is reached, i.e. a body temperature of 33°C. This definition will make it possible to compare variations in inflammatory cytokines linked to rewarming rates and not to variations linked to the different times at which RTAs occur.
    - Given the high number of infectious complications expected (i.e. inhalation pneumonitis (49, 60)), given that it is not possible to perform a stratification on this pathology which nevertheless modifies the rates of Il6 (57)A record of these complications will be included in the data collection medium in order to ensure the homogeneity of the 2 groups of patients for these pathologies. Nevertheless, the diagnostic hypotheses take account of this high rate of infectious complications, since in the study used to formulate these hypotheses, patients who presented an infectious complication were included. (59). As for late complications, they may be linked to the rate of rewarming drawn at random by analogy with the infectious risk of hypothermia (61).
    - The immunology and immunomonitoring laboratory at Nantes University Hospital will be responsible for the technical aspects of the Il6 assay, after centrifugation and freezing at -80°C at the investigating centre. This centralised analysis will ensure a consistent technique for all samples.



Interleukin modelling after *Heinrich et al Biochem Journal 1998*

2. Secondary criteria

- Serum levels of Il2, Il4, Il8, Il10, GM-CSF, Interferon-beta, TNF-alpha, neurofilament.
- Patrol® test measurement. The principle of the Patrol® test is to irradiate the serum under study with a laser beam after adding a photosensitiser that generates large quantities of oxygen radical species (ROS). We then measure the fluorescence induced by the ROS (using a probe that is ultrasensitive to oxidation) that have not been neutralised by the anti-oxidant power of the serum: this is therefore an indirect measure of total anti-oxidant capacity that has been perfectly validated in clinical practice (62-65).
- Serum CRP levels (66) and Procalcitonin (67).
- Mortality in intensive care
- Hospital mortality
- Mortality at D90: We will consult the CEPIDC (Centre Epidémiologique sur les causes médicales de Décès) to formally search for a death at D90.
    - Neurological functional status at D90. This time was set at 3 months (D90) in accordance with recent recommendations (68). A good neurological outcome is considered to be a Glasgow-Pittsburgh Cerebral Performance Categories (CPC) score of 1 or 2, and a poor neurological outcome is considered to be a CPC score of 3, 4 or 5.
- Estimation of patient quality of life using the 36-Items Short Form for Health Survey at D90 (69). The "36-Items Short Form for Health Survey" questionnaire (appendix D) is a tool for assessing quality of life, covering both physical and mental dimensions, using 36 questions graded from 0 to 100. (8).
- Estimation of patient autonomy using the "Index Activity of Daily Living" questionnaire (70, 71) (appendix E), the modified Barthel Index (72) (appendix F) and a standardised double question on the after-effects of cardiac arrest (73) (appendix G) at D90.
- Neurocognitive assessment at 90 days using the validated telephone version of the Mini Mental State Examination (74) (appendix H).
- Estimation of the number of patients with post-traumatic stress symptoms assessed by the "Impact Event Scale Revised" questionnaire (75, 76) at D90. The Impact Event Scale-Revised (Appendix I) consists of 22 questions that assess stress reactions after a traumatic event, targeting psychological responses to intrusion and avoidance phenomena.
- Length of stay in intensive care.
- Duration of mechanical ventilation.
- Need for vasopressor treatment: comparison of doses of vasopressors in relation to weights (noradrenaline or adrenaline) required during the first 72 hours.

B. *Description of the research methodology, accompanied by a schematic presentation specifying in particular the visits and examinations planned*

1. Experimental design

This is a single-centre, open-label, randomised controlled clinical trial comparing two groups of patients successfully resuscitated for shockable rhythm RTA and presenting with persistent coma (Glasgow score less than or equal to 8) at inclusion: in the 2 groups, targeted temperature control between 32.5 and 33.5°C will be induced and maintained for 24 hours, then in the control group the rate of rewarming will be set at 0.5°C/h and in the intervention group it will be set at 0.25°C/h. In the 2 groups, a targeted control of the temperature between 36.5 and 37.5°C will be carried out for a total duration of 72 hours.

2. Conduct of the study

Inclusion period: 4 years and 6 months
Duration of a patient's participation in the study: 3 months maximum
Duration of statistical analysis: 3 months
Total duration of the study: 5 years

Each patient will benefit from a maximum follow-up of 3 months between the date of inclusion and the neurological assessment carried out at 3 months.

a) Inclusion

Patients must be included in the study within 5 hours of the onset of their RTA and the start of induction of targeted thermal control. Patients will be informed and asked if they have any objections to taking part in the study, either by a trusted support person or, failing that, by a close relative. A period of reflection will be allowed between the interview with the trusted support person or, failing this, one of the relatives, and the collection of any objections. If the information has been given to the trusted support person or, failing that, to one of the next of kin, the patient will be asked to express his or her non-opposition as soon as his or her level of consciousness allows. If the patient refuses to continue the study, he/she will be withdrawn from the trial. If the trusted support person or a close relative is not available, an emergency procedure will be available to include the patient. In all cases, the patient will be informed as soon as possible by the investigator, and the investigator will collect the patient's non-objection at a later stage.

A follow-up table will be kept for patients offered the study, noting the reasons for non-inclusion and any objections to participation.

Diagram 1: Synopsis of the study for the rapid warming group

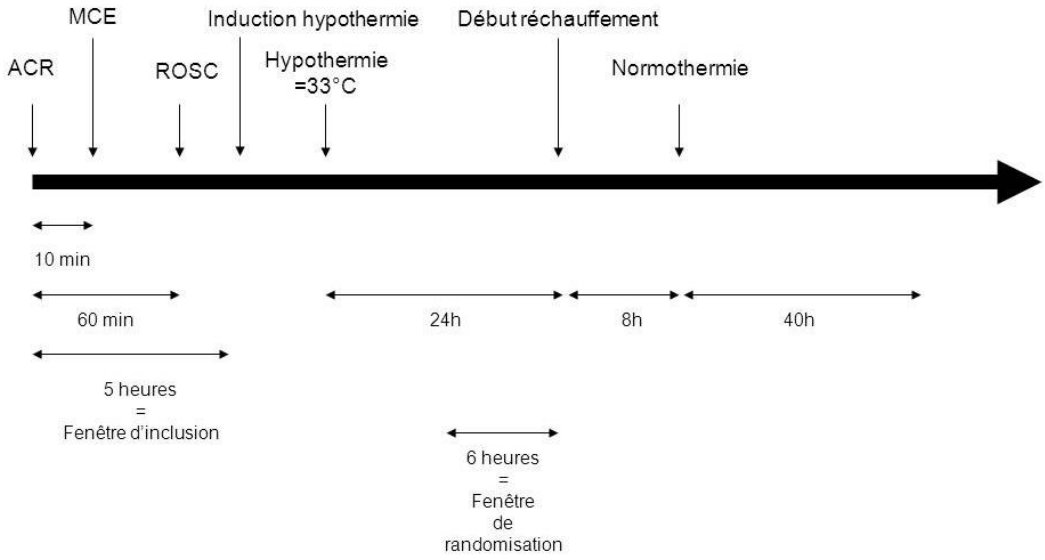
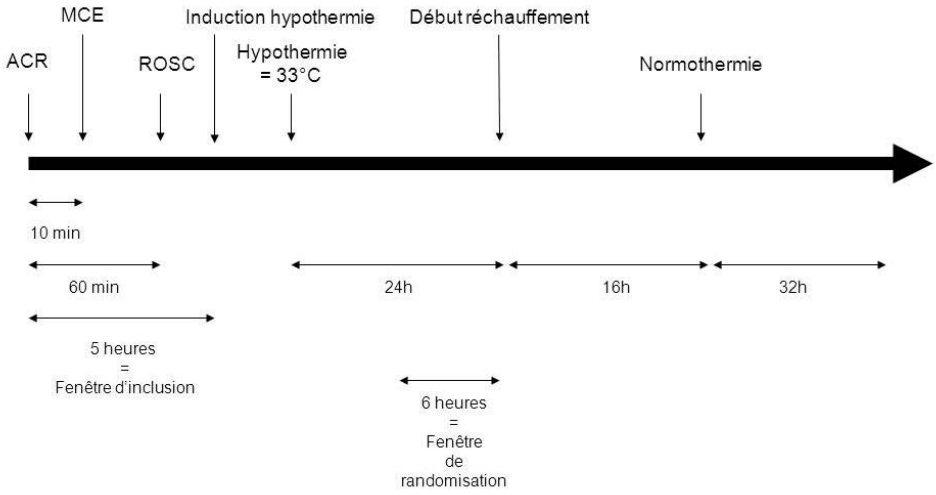


Diagram 2: Synopsis of the study for the slow warming group



Once the inclusion and non-inclusion criteria have been checked, and the patient's non-opposition or that of their relatives has been obtained, or an emergency procedure has been carried out, the investigator will be able to include the patient. On inclusion, the patient's demographic data, characteristics and vital signs will be collected: date of birth, sex, date of admission to intensive care, McCabe and Knaus scores, previous chronic pathologies, weight, height, body mass index, cardiac or extracardiac cause of the RTA, whether coronary angiography was performed, duration of no-flow, duration of low-flow, location of the RTA (home, public highway or outside the home, in hospital), number of external electric shocks. This data will be collected in accordance with the ILCOR recommendations on the conduct of clinical studies in the context of cardiac arrest (77) corresponding to the Utstein criteria.

Randomisation will be carried out within a 6-hour time window, the end of which will be determined by the 24ème hour after the target temperature of 33° is reached (i.e. H24). This time window will therefore be between H18 and H24. This method will make it possible not to randomise patients

who have had an unfavourable outcome between inclusion and the start of the rewarming period (death following a refractory state of shock). This randomisation will be carried out via computerised data collection (eCRF): the patient will then be assigned to a randomisation arm: RL group or RR group.

b) Performing sedation/analgesia

This sedation/analgesia will be carried out in the 2 groups (RR and RL) during the period of hypothermia and rewarming until a temperature of 36°C is reached:

- Continuous administration of a hypnotic (midazolam, propofol) at a titrated dose to obtain a RASS score of -5 in both groups.
- Continuous administration of a morphine (fentanyl, sufentanil, remifentanil) at a titrated dose to obtain a RASS score of -5 and the absence of painful symptoms using the usual scales (behavioural pain scale) in the 2 groups.

This sedation/analgesia will be discontinued once a temperature of 36° Celsius has been reached.

In the event of haemodynamic, respiratory or neurological instability (agitation, risk of self-extubation in particular), this sedation/analgesia may be continued beyond this period. This continuation will be recorded in the eCRF.

c) Shiver management strategy

In accordance with the published protocol for the intensive care unit at La Roche Sur Yon (78)the treatment strategy for shivering will initially be based on boluses of hypnotics and morphine, followed by curare as a last resort (50, 79). The severity of shivering should be assessed using the Bedside Shivering Assessment Scale (see appendix C), which has been validated and is correlated with the increase in metabolic demand associated with shivering phenomena (80). The aim is to obtain a BSAS score ≤ 1.

- Level 1 treatment for chills :
  - A bolus corresponding to a dose equal to the flow rate of the electric syringe administering the continuous infusion of the hypnotic and morphine administered (e.g. for an electric syringe flow rate of 5mg/h, a bolus of 5mg of the product concerned will be injected).
- Level 2 treatment for chills :
  - After failure of level 1
  - Bolus of non-depolarising curares: cisatracurium besilate (Nimbex®) bolus 0.1mg/kg, atracurium besilate (Tracrium®) bolus 0.5mg/kg
- Level 3 treatment for chills :
  - After failure of level 2
  - Bolus and maintenance of non-depolarising curares with monitoring of the BSAS score for a target ≤ 1: cisatracurium besilate (Nimbex®) boli 0.1mg/kg then 10mg/h with increase and decrease in steps of 1mg/h with a target BSAS score ≤ 1. If a curare infusion is started, it can be stopped once the warming phase has begun and a temperature of 35°C has been reached.

d) Management strategy for targeted temperature control between 32.5 and 33.5°C

Targeted temperature control between 32.5 and 33.5°C will be achieved using an external thermal regulation device of the ArticSun type (BARD, Louisville, Colorado, USA). The protocol will enable a number of parameters to be standardised: sedation, possible curarisation, management of expected adverse effects.

Indeed, although there are numerous methods available to date, none of which has demonstrated its superiority in achieving targeted temperature control between 32.5 and 33.5°C in the management of RTA (active external cooling (15, 16, 81-83)active internal cooling (84, 85)internal cooling with infusion of ice-cold isotonic saline solution (81, 86)), the active external device allows continuous control of temperature and the desired rate of rewarming, which is the subject of this study. In addition, the intensive care unit at La Roche Sur Yon already uses this type of device to perform the 32.5-33.5° CCT, and has the technical expertise to use it routinely.

The implementation protocol for CCT 32.5-33.5 breaks down as follows:

- Rapid intravenous injection of 1500 ml of isotonic saline at 4°C. This technique enables the target temperature to be reached rapidly, with a high safety profile (81, 87).
- After fitting the specific pads, induction continued and hypothermia was maintained at a target temperature of 33°C (allowing the same target temperature to be chosen for the 2 randomisation groups) for 24 hours.
- H0 is defined as the time at which the patient's body temperature reaches 33°C. Taking the sample.
- H12: sample taken
- Time window H18-H24: randomisation via the eCRF.
- H24: sampling and modification of the target internal temperature according to the software for a target of 37°C with a heating rate set according to the randomisation group (0.5°C/h for RR or 0.25°C/h for RL).
- Stop any curarisation once a temperature of 35°C has been reached
- Stop sedation once a temperature of 36°C has been reached
- H32: taking the sample
- H40: sample taken
- H48: sample taken

Diagram 3: Synopsis of biological samples taken in the rapid heating group

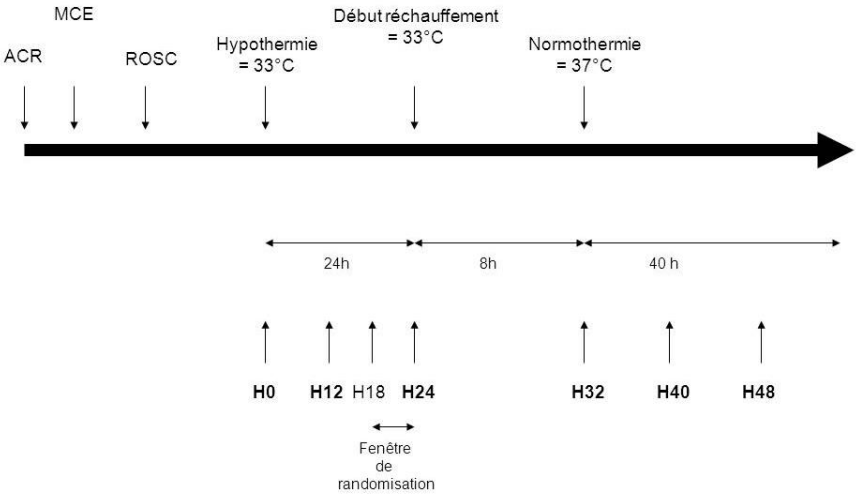
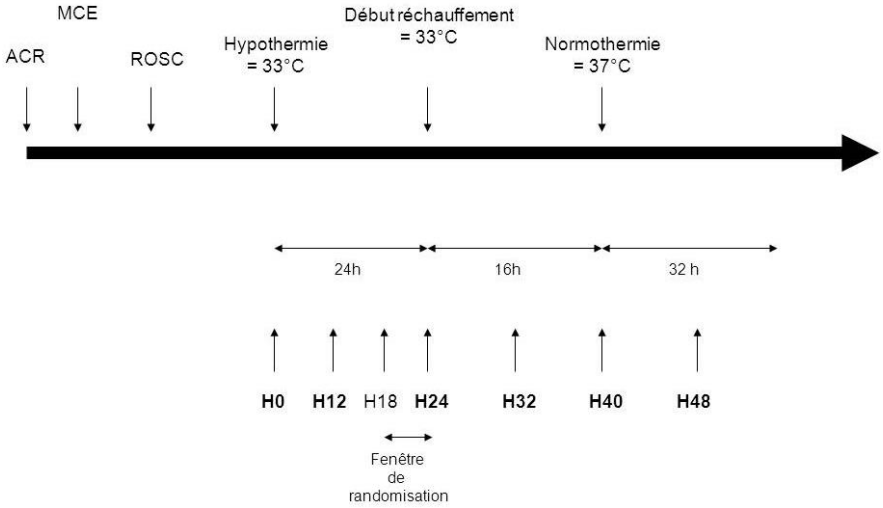


Diagram 4: Synopsis of biological sampling in the slow warming group



a) Management of secondary cerebral stress of systemic origin

A book of recommendations will be provided to the investigator in the absence of a service protocol containing information on the various existing factors of aggression and their respective treatments.

(1) Low blood pressure

A haemodynamic assessment will be carried out to optimise the patient's blood volume. In the event of hypovolaemia, vascular filling will be carried out using crystalloids or colloids in accordance with the department's usual practices. The patient's haemodynamic status will be reassessed as required. In accordance with recommendations, a mean arterial pressure target of 65 mmHg and, if used, a ScvO2 greater than or equal to 70% will be considered reasonable targets (31, 32). The introduction of treatment with vasoactive amines should be left to the clinician's discretion, in accordance with international recommendations (31, 32).

(2) Hypoxemia

Regular monitoring of arterial O2 pressure and continuous monitoring of pulsed oxygen saturation (SpO2). Objective of maintaining SpO2 at or above 92% in accordance with recommendations (88). In order to avoid potentially deleterious hyperoxia in the context of post-cardiac arrest syndrome, the upper SpO2 target will be set at 96%. (89).

(3) Hypercapnia/Hypocapnia

Regular monitoring of arterial CO2 pressure and/or regular monitoring of tele-expiratory CO2 pressure. Maintenance of a PaCO2 between 35 and 40 mmHg with a PaCO2 value corrected for the patient's body temperature.

(4) Anemia

Regular monitoring of blood counts. Aim to maintain haemoglobin levels ≥ 7g/dL for patients without ischaemic heart disease and ≥ 10g/dL for patients with ischaemic heart disease in accordance with recommendations (90).

(5) Hyperglycaemia

A blood glucose monitoring protocol (capillary or blood) will be available to the doctor in charge of the patient. In accordance with recommendations (31, 32)specific treatment will be recommended when blood glucose levels fall outside the range of 3.33 to 10 mmol/l (i.e. 60 to 180 mg/dL).

b) Patient follow-up

Analyses will be carried out locally or off-site depending on the examinations concerned:

Off-site analyses (CHU Nantes): Il2, Il4, Il6, Il8, Il10, GM-CSF, TNF-alpha, INF-beta, neurofilament. All these analyses can be performed using a 5 ml blood tube for all the analyses (i.e. a total of 60 ml of blood taken, taking into account the safety sample kept on the investigator's site). The principles of the LuminexTM assay and the Patrol test are explained in appendix J.

Local tests: blood count, arterial blood gases (pH, pO2, pCO2, HCO3), lactates, blood ionogram (Na, K, Cl, Urea, Creatinemia, Ca), troponin, CRP, procalcitonin.

Local examination: 12-lead electrocardiogram

Neurological analysis using the CPC score will be carried out by telephone by an expert blinded to the randomisation group (psychologist carrying out a semi-directive interview, blinded to the randomisation group).

Flow Chart :

	Inclusion	J0	J1	J2	Jn	J90
Eligibility: check the study's eligibility criteria	X					
Informing the next of kin with a cooling-off period	X					
No-objection search	X					
Demographic data	X					
Randomisation		X				
Patient characteristics	X					
Data : coronary angiography	X					
Data: ventilation	X	X	X	X	X	
Biology	X	X	X	X		
Electrocardiogram	X		X	X		
Clinical evaluation	X		X	X	X	X
Treatments administered		X	X	X	X	
Definitive extubation					X	X
Living / Deceased		X	X	X	X	X
Blind neurological assessment by a psychologist						X

D0 corresponds to the start of the hypothermia procedure.

Jn corresponds to discharge from intensive care

B. *Description of measures taken to reduce and avoid bias*

1. Prize draw

This randomisation will be carried out directly on the electronic observation notebook provided (see Data collection). Randomisation will be carried out according to a 1:1 ratio with blocks of variable size, as the study will be open-label. No stratification factors will be taken into account. Randomisation will be generated by the CIC INSERM 1415 biometrics unit, which is independent of the patient recruitment process. It will be carried out within a time window of 6 hours, the end of which will correspond to the end of the CCT 32.5-33.5 period (i.e. between H18 and H24). This delayed randomisation will allow only patients alive at the end of the 32.5-33.5 CCT period to be randomised, and not patients who died during the first phase (e.g. progressing to refractory shock).

2. Blinding method

The trial will be open-label, since the rewarming technique is performed by the medical team and the procedure is specific to the RR or RL group. However, this lack of blinding should not lead to bias since the primary endpoint is a biological assay and this is an objective criterion. (91). In addition, the assay will be performed blind to the randomisation group and centrally at the Nantes University Hospital. In addition, the **assessment of functional status neurological will be carried out at D90 by telephone in a blinded fashion by an independent psychologist who does not know the patient's randomisation group and is not participating in the study**.

C. *Expected duration of participation of individuals and description of the chronology and duration of all trial periods, including follow-up, if applicable*

The duration of patient follow-up in the study will depend on the patient's progress and will be a maximum of 90 days. Patients will be followed until they are discharged from hospital. Their living or deceased status will be determined on discharge from intensive care, from hospital and at D90. Their neurological status will be assessed at D90. It has been established that neurological functional assessment at D90 allows an assessment of neurological, functional and cognitive sequelae which are fixed without modification afterwards (92, 93). Assessments of quality of life, the existence of post-traumatic stress symptoms and the patient's autonomy will be carried out using specific questionnaires completed during a telephone interview with the patient by the independent psychologist responsible for the neurological assessment at D90. A neurocognitive assessment will also be carried out at D90 using the validated telephone version of the Mini Mental State Examination questionnaire.

1. Stopping a person's participation in research

Participation in the study will be discontinued in the event of secondary opposition from the patient or relatives.

2. Stopping part or all of the research

No interim analysis is planned as part of this research. However, in the case of this routine care study, if a consensus following a scientific publication were to call into question the main hypothesis or the management of patients treated by targeted temperature control between 32.5 and 33.5°C, this research could be stopped early at the decision of the sponsor.

II. Selecting and excluding people from research

A. *Inclusion criteria for research subjects*

- Patient managed for cardiac arrest in shockable rhythm on arrival of emergency services and successfully resuscitated.

- Persistent coma on admission to intensive care (Glasgow score less than or equal to 8) in the absence of sedation. If the patient is sedated on admission to intensive care, the Glasgow score used will be the last score assessed by the doctor who provided pre-hospital care for the patient.
- Technical implementation of the CCT 32.5-33.5 with a specific thermoregulation device.

B. *Criteria for non-inclusion of research subjects*

- No-flow time > 10 minutes (period between the onset of cardiac arrest and the start of external cardiac massage).
- Low-flow time > 60 minutes (period between the start of external cardiac massage and recovery of haemodynamically effective cardiac activity).
- Major haemodynamic instability (dose of Noradrenaline and/or Adrenaline > 1 µg/kg/min to maintain MAP > 65 mmHg).
- Time between onset of cardiac arrest and start of induction of targeted thermal control greater than 5 hours.
- Moribund.
- Presence of histologically confirmed Child C cirrhosis.
- Taking an IL6 receptor inhibitor (tocilizumab or Ro-Actemra®).
- Patient on corticosteroid treatment (dose > 5mg prednisolone equivalent).
- Minors (<18 years)
- Pregnant, parturient or breast-feeding women.
- Patient hospitalised without consent and/or deprived of liberty by court order
- Patient under guardianship or trusteeship
- Prior inclusion in a research protocol with a random draw, and for which the primary endpoint is the bioassay of interleukin 6
- No social security
- Refusal of the trusted support person or the patient

C. *Recruitment procedures*

Recruitment will take place within the intensive care unit of the CHD Vendée. It is planned to include 60 patients admitted to the intensive care unit following a RTA, presenting a shockable rhythm on the arrival of the emergency services and justifying targeted temperature control between 32.5° and 33.5°C, after reading the information letter and obtaining the non-opposition of the trusted support person. The patient's non-opposition will be collected after reading the information letter.

D. *Pre-hospital care*

As this is a routine care study, no changes will be made to pre-hospital management. In particular, there is no published study showing any benefit from early CCT between 32.5 and 33.5°C compared with a few hours later. (87, 94, 95).

III. Procedures and treatments administered to research subjects

A. *Targeted temperature control procedure between 32.5° and 33.5° Celsius*

The targeted temperature control procedure consists of lowering the patient's body temperature to between 32.5° and 33.5°C for 24 hours. It comprises 3 phases: an induction phase, a maintenance phase and a rewarming phase.

The induction phase enables the target temperature to be reached quickly by injecting intravenous fluids. During this phase, the patient develops mechanisms to combat the chill, requiring considerable sedation in order to reduce shivering, which is the body's normal reaction to cold. The induction phase is achieved by administering isotonic saline at 4°C, combined with the Artic Sun® device in hypothermia mode.

The maintenance phase then enables the body temperature to be maintained between 32.5° and 33.5°C for 24 hours. This maintenance phase also requires sedation to be maintained, both for the patient's comfort and to prevent the body from fighting the cold. This phase will be ensured by the installation of a specific device enabling the patient to be cooled by a convection mechanism.

The reheating phase allows a gradual return to a temperature of 37°C. The time taken to complete this reheating phase is the subject of this research. The specific device used for the maintenance phase will allow this gradual rewarming. As with the previous two phases, the patient's physiological reactions (shivering) must be countered mainly by sedation.

B. *Specific external device for targeted temperature control between 32.5° and 33.5°C*

This type of non-invasive device is used to produce a 32.5-33.5 CCT using adhesive pads and a thermal probe for continuous temperature measurement. This continuous temperature measurement is then integrated into the central console, using a feedback loop to continuously adapt the temperature of the fluid circulating in the pads to achieve the desired body temperature. The centre console is fitted with a reservoir of heat-insulating fluid. This central console circulates the cooled or heated fluid in a closed circuit. The temperature is continuously monitored by a thermal probe placed in the oesophagus or bladder. The correlation between these different temperatures is excellent (96).

C. *Authorised treatments*

As this is a routine care study, all the drugs normally used in the management of intensive care patients will be used according to the specific needs of each patient.

D. *Unauthorised treatments*

As this is a routine care study, no drugs used in its indication are prohibited.

IV. Safety assessment

A. *Independent Supervisory Committee*

No independent monitoring committee is planned as part of this study.

B. *Undesirable effects*

The occurrence of an Adverse Reaction linked to the patient's care during the course of this protocol will give rise to a declaration to the appropriate vigilance system (pharmacovigilance, biovigilance, haemovigilance, materialovigilance, etc.).

C. *Management of expected adverse events in the 2 randomisation groups*

a) Death, including death following a procedure to limit or stop treatment

Deaths following a procedure to limit or stop treatment will be recorded in the computerised eCRF database, together with the characteristics describing the reasons for the decision. For information, investigators will be provided with the opinion of the SRLF ethics committee concerning the decision to limit or stop treatment in adults in post-anoxic coma following cardiac arrest. (97).

b) Inhalation pneumonitis

A procedure of recommendations for use by the doctors in charge of the patient will be made available to them, including the anamnestic, clinical, biological and radiographic data that should suggest inhalation pneumonitis, together with a recommendation for antibiotic therapy in line with expert recommendations. (98).

c) Hypovolaemia

A haemodynamic assessment will be carried out to optimise the patient's blood volume. In the event of hypovolaemia, vascular filling will be carried out using crystalloids or colloids in accordance with the department's usual practices. The patient's haemodynamic status will be reassessed as required. In accordance with recommendations, and in the absence of specific studies, a mean arterial pressure target of 65 mmHg and, if used, a ScvO2 greater than or equal to 70% will be considered reasonable targets (31, 32). The introduction of treatment with vasoactive amines should be left to the clinician's discretion, in accordance with international recommendations (31, 32).

d) Electrocardiographic changes: prolongation of PR and/or QT interval

An electrocardiogram will be performed on patient admission and a reminder of the changes induced by commonly used drugs will be made available to the doctor in charge of the patient.

e) Fluid and electrolyte disorders: hypokalaemia, hypomagnesaemia

Biological monitoring will be carried out during the induction phase of targeted temperature control between 32.5 and 33.5°C, as well as during the maintenance and rewarming phase. Recommendations for the correction of kalaemia and magnesaemia ionic disorders will be made available to the doctor in charge of the patient.

f) Coagulation disorders

Biological monitoring will be carried out during the induction phase of targeted temperature control between 32.5 and 33.5°C, as well as during the maintenance and reheating phase.

g) Hyperglycaemia

A blood glucose monitoring protocol (capillary or blood) will be available to the doctor in charge of the patient. In accordance with recommendations (31, 32)specific treatment will be recommended when blood glucose levels fall outside the range of 3.33 to 10 mmol/l (i.e. 60 to 180 mg/dL).

h) Skin complications: cyanosis, digital ischaemia

Any skin complications will be monitored clinically. In the event of a threatening complication, the doctor in charge of the patient will be able to interrupt the targeted temperature control procedure between 32.5° and 33.5°C. This interruption will be recorded in the eCRF.

i) Biological disorders: hepatic cytolysis, elevated lipase, thrombocytopenia, haemoconcentration

Biological parameters will be monitored.

V. Statistics

A. *Description of planned statistical methods, including timetable for planned interim analyses*

The statistical analysis will be carried out according to a pre-established analysis plan. The analysis will be conducted according to the principle of intention-to-treat analysis. A statistical analysis report will be written incorporating all the elements that must be reported, as recommended by the CONSORT Statement, taking into account the specificities linked to the fact that this is a non-pharmacological trial.

Description of inclusion samples

The groups resulting from randomisation will be studied using descriptive statistics. No statistical tests will be performed.

Analysis samples

The analysis will be carried out on an intention-to-treat basis, with each subject remaining in the group to which they were randomised, whatever happens.

Analysis of primary endpoint

The primary endpoint will be analysed using a linear mixed model. If necessary, the data will be transformed beforehand.

Analysis of secondary endpoints

Secondary endpoints associated with a binary variable will be analysed using Fisher's exact test.

Secondary endpoints associated with a quantitative variable will be analysed using the same strategy as for the primary endpoint, using Student (or Wilcoxon) tests if the data are not repeated.

Finally, the parameters of the repeated measurements will be analysed using mixed models.

B. *Expected number of people to be included in the research, and expected number of people in each research location with statistical justification*

The headcount calculation is based on the work of Borm (99) and Vickers (100).

In this trial, the primary endpoint (interleukin 6 levels) is measured repeatedly. To calculate the number of patients required, the following parameters are required:

- The standard deviation of the interleukin 6 assay was set at 40 pg/ml.
- The main hypothesis is that a high heating rate (>0.5°C/h) leads to an increase in inflammatory phenomena measured by IL6. In this case, according to previous studies (101)the mean level of IL6 expected in the slow rewarming group will be 100 pg/ml.
- A 15% increase (superiority analysis) in these phenomena is assumed (i.e. an Il6 level of 115 pg/ml in the RR group compared with 100 pg/ml in the RL group).
- The correlation between 2 measurements of interleukin 6 in the same subject was set at 0.85. This correlation was estimated by the manufacturer at 0.89, but we have chosen to adopt a slightly lower value, as a conservative approach.
- The errors of the first and second kind were set at 5% and 10% respectively.

If the trial were planned with a single interleukin 6 assay, it would be necessary to include 151 patients per group.

Taking into account a measurement of interleukin 6 at inclusion, and considering that the correlation between the assessments at inclusion and at H32 was 0.85, the number of patients was reduced to 42 per group.

Taking into account the fact that there were 2 intermediate assessments (H12, H24), and that the correlation between the assessments was 0.85, the number of patients was reduced to 25 per arm.

Taking into account an estimated 20% of patients who may have been included but not randomised (patients who died or progressed to refractory shock despite treatment), the plan is to include 30 patients per group, i.e. a total of 60 patients.

C. *Expected level of statistical significance*

All statistical tests will be carried out with a significance level of 5%.

D. *Method for taking into account missing, unused or invalid data*

A second serum sample from each analysis will be kept locally after the first sample is sent to the laboratory (Nantes University Hospital) carrying out the centralised analyses, so that a "safety" sample can be sent in case the first sample is accidentally lost or destroyed.

Randomisation immediately before the start of the warm-up procedure will avoid missing data for the primary endpoint (Interleukin 6 assay).

E. *Managing changes to the initial strategy analysis plan*

The statistical analysis plan will be finalised when the database is frozen.

F. *Choosing the people to be included in the analyses*

The analysis will be carried out on an intention-to-treat basis.

VI. Justification for requesting validation of research in routine care

In accordance with the decree of 9 March 2007 and taking into account all the elements presented in the project, the person responsible for the research qualifies it as **research in routine care**, since :

- ✓ All procedures and protocols for targeted temperature control between 32.5 and 33.5°C are carried out as usual.
- ✓ The aim is to evaluate combinations of procedures and medical strategies for prevention and diagnosis (protocol for targeted temperature control between 32.5 and 33.5°C, determination of rewarming rate) that are standard practice, i.e. that are the subject of a professional consensus in compliance with their indications.
- ✓ This research does not focus on techniques or strategies that are either innovative or obsolete.
- ✓ The research compares two medical strategies (determining a fast or slow rate of rewarming during a period of targeted temperature control between 32.5 and 33.5°C), neither of which can, in the current state of knowledge, be considered superior to the other in terms of safety and efficacy. In fact, the North American recommendations do not specify a target heating rate. They only advise avoiding

active rewarming in patients admitted with hypothermia, a situation outside the scope of CCT 32.5-33.5 (32) ("Active rewarming should be avoided in comatose patients who spontaneously develop a mild degree of hypothermia after resuscitation from cardiac arrest during the first 48 hours after ROSC"). The same applies to European recommendations (31) which also stress the need for studies to determine the optimal rewarming methods ("Furthermore the optimal method, onset, duration and rewarming rate, and therapeutic window remain unknown").

- ✓ As stated in the project, the risks and monitoring constraints associated with the protocol are considered negligible compared with the usual management of these patients.
- ✓ The specific procedures implemented in the research should reduce the risks (through a reinforced protocol for targeted temperature control between 32.5 and 33.5°C) and represent negligible constraints for the person undergoing the research (Article R 1121-3 of the Public Health Code (CSP), decree no. 2006-477 of 26 April 2006).
- ✓ A survey of practice carried out within the departments of the Association des Réanimateurs du Centre Ouest (unpublished data) observed that the target rate of rewarming at the end of the period of therapeutic hypothermia was set between 0.25 and 0.5°C/h in 56% of cases, between 0.5°C/h and 0.75°C/h in 34% of cases and was greater than 0.75°C/h in 8% of cases.

Thus, after exhaustive analysis of the evidence-based medicine data, it is not possible to determine whether there is a superiority in the choice of rewarming rate when deciding whether or not to carry out targeted temperature control between 32.5° and 33.5°C in the event of cardiac arrest managed in shockable rhythm. There is uncertainty at the individual level and clinical equipoise at the collective level (102) which makes the randomisation procedure acceptable at an individual level and desirable at a collective level. Of course, if this uncertainty is removed (external data), the trial will be stopped. Finally, all the inclusion and non-inclusion criteria will make it possible to conduct the study within the framework of a "poorly selected" population and therefore as close as possible to our daily practices, in order to answer the question for all patients.

Before any research is carried out, the person responsible for the research will therefore submit the study protocol to the CPP Ouest III for a favourable opinion and confirmation of the research's qualification, in accordance with article L 1121-1 of the Public Health Code (CSP), as amended by laws no. 2004-806 of 9 August 2004 and no. 2006-450 of 18 April 2006 relating to public health policy.

VII. Right of access to source data and documents

1. Data access

Each patient's medical data will only be transmitted to the organisation to which the person responsible for the research is attached, or to any person duly authorised by that organisation, under conditions guaranteeing confidentiality.

2. Source documents

Where applicable, the organisation to which the person responsible is attached may request direct access to the medical file in order to verify the research procedures and/or data, without breaching confidentiality and within the limits authorised by the laws and regulations.

3. Data confidentiality

Persons with direct access will take all the necessary precautions to ensure the confidentiality of information relating to the persons concerned, in particular as regards their identity and the results obtained. These persons, in the same way as the investigators themselves, are subject to professional secrecy (under the conditions defined by articles 226-13 and 226-14 of the French Penal Code).

During or at the end of the research, the data collected on the people who take part and transmitted by those involved will be rendered anonymous.

Under no circumstances may the names or addresses of the persons concerned appear in clear text.

Only the first letter of the subject's surname and the first letter of the first name will be recorded, together with a coded number specific to the study indicating the order of inclusion of the subjects.

VIII. Quality assurance

Quality control will be carried out by Clinical Research Associates appointed by the institution responsible for the research.

The nature and frequency of monitoring will be established in accordance with the established monitoring/risk grid. Throughout the study, the CRAs will carry out planned monitoring visits with the investigator:

- Data collected during the study
- No objections from trusted third parties and all included patients

To this end, the investigator undertakes to make the following information available to the CRAs during their monitoring visits

- Patient medical records
- Data collection notebooks

This monitoring by the ARCs will enable us to assess :

- Protecting people
- Reliability of data in relation to source documents
- Compliance of the trial with the protocol, Good Clinical Practice and current biomedical research legislation

At the end of this quality control, a monitoring report will be drawn up by the CRAs and given to the principal investigator, who will take instructions based on the conclusions of this report.

IX. Ethical assessments and methods for protecting individuals

A. *Individual Protection Committee*

Before implementing the research, the establishment responsible for the research will submit the project to the CPP Ouest for its opinion and will provide it with all the necessary information (research protocol,

patient and family information leaflet). The trial may only begin once the CHD Vendée has been informed of the unqualified favourable opinion issued by the CPP.

B. *Ethics Committee of the Société de Réanimation de Langue Française (French Resuscitation Society)*

The protocol was submitted to the ethics committee of the Société de Réanimation de Langue Française for an opinion on 5 September 2013 and received a favourable opinion from this committee on 20 September 2013 (see Appendix K).

C. *Substantial changes*

Any substantial modification to the study protocol must be notified to the Comité de Protection des Personnes in order to ensure that the proposed modifications do not alter at any time the guarantees provided to the persons undergoing the research.

An updated version of the amended protocol must be dated.

D. *Information and objection letter*

Patients who are unable to express themselves due to their clinical condition at the time of enrolment, the trusted support person or, failing this, their relatives, will be fully and fairly informed, in comprehensible terms, of the objectives and constraints of the study, any risks involved, the necessary monitoring and safety measures, their right to refuse to allow their relative to take part in the study and the possibility of withdrawing at any time.

The trusted support person or, failing that, the next of kin will be informed that, in the event of opposition to participation in the study, the rate of rewarming during a targeted temperature control procedure between 32.5 and 33.5°C will be decided by the doctor in charge of the patient in accordance with the existing service protocol.

All this information is contained in an information leaflet, a copy of which will be given to the trusted support person or, failing that, to the patient's family, and the investigator will keep the original.

After a period of reflection, and after ensuring that the form has been properly understood, the investigator will ask the trusted support person not to object.

As a last resort, and in the absence of a trusted support person or relative, an emergency procedure will be available to include the patient. In all cases, the patient will be informed as soon as possible by the investigator, and the patient's non-objection will be collected secondarily by the investigator, or a doctor representing him/her.

E. *Definition of the exclusion period*

There is no exclusion period for this research.

F. *Support for research*

The management of the patients included in this study was modelled on the management usually recommended for cardiorespiratory arrest.

G. *Collection of data concerning the limitation or cessation of resuscitation therapies*

The collection of computerised data will include information on any procedure for limiting or stopping treatment and on how this is carried out, in accordance with the recommendations of the SRLF in 2010. (103). Each procedure for limiting or stopping treatment and the way in which it is carried out, in accordance with the 2010 SRLF recommendations, will be the subject of a specific record in the CRF (in particular, a record of clinical elements enabling the patient's short-, medium- and long-term prognosis to be assessed; any biological, imaging or physiological tests enabling the patient's short-, medium- and long-term prognosis to be assessed); any recourse to a consultant from outside the department concerned; the patient's advance directives or consultation of the trusted support person, referent or next of kin concerning the decision to limit or stop life-sustaining treatment; the procedures for implementing this decision; the support offered to the trusted support person, referent and next of kin).

H. *Justification for requesting patient inclusion under an emergency protocol*

This research falls within the scope of article L. 1122-1-2 of the French Public Health Code. In fact, the inclusion criteria imply the inclusion of patients with a Glasgow score of less than or equal to 8. Patients will therefore not be in a position to give their consent to participate in the study. In accordance with article L. 1122-1-2 of the Public Health Code, the information and absence of opposition from the trusted support person or, failing that, a close relative, will therefore be sought by all available means from the associated investigator at the time of the patient's admission.

As underlined above, the sequence of targeted temperature control between 32.5 and 33.5°C implies a maximum delay in order to include the patient in the ISOCRATE protocol to carry out the blood tests required for this study. Therefore, if it is not possible to obtain the unopposed consent of the trusted support person or a relative, an emergency procedure involving the investigating doctor will be put in place.

The information and lack of opposition of the patient, the trusted support person or a close relative will be collected as soon as possible.

X. Data processing and storage of documents and data

A. *Observation booklet*

An electronic data collection medium will be used for this study. All that is required is an Internet connection and a browser. Investigators will be provided with a document to help them use this tool.

Data consistency tests will be integrated into the electronic format. An audit function is integrated into the electronic notebook, enabling any changes to study data to be tracked. This function also makes it possible to clearly identify the person who made the modification and the date. If required, a justification can be included as a comment.

B. *Data input and output*

Data will be entered electronically via a web browser.

C. *CNIL*

The CCTIRS (Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé) will be asked to give its opinion on the implementation of the data processing required for the study, followed by a request for authorisation from the CNIL (Commission Nationale Informatique et Libertés) for the processing of personal data for the purpose of clinical research.

D. *Archiving*

The following documents will be archived by the name of the study on the premises of the Réanimation Polyvalente department of the CHD Vendée until the end of the period of practical use.
These documents are :

- Protocols and annexes, any amendments,
- Information leaflets and objection forms
- Individual data (authenticated copies of raw data),
- Follow-up documents,
- Statistical analysis,
- Final report of the study.

At the end of the period of practical use, all the documents to be archived, as defined in the CHD Vendée's procedure for filing and archiving documents relating to biomedical research, will be transferred to the archiving site (CHD Vendée Clinical Research Centre) and will be placed under the responsibility of the establishment responsible for the research for 15 years after the end of the study, in accordance with institutional practices.

They may not be moved or destroyed without the agreement of the institution responsible for the research. At the end of the 15-year period, the institution responsible for the research will be consulted for destruction. All data, documents and reports may be audited or inspected.

XI. Financing and insurance

A. *Study budget*

Insofar as this trial is a routine care study, medical procedures will not be reimbursed. The expected duration of the study is 3 years for 1 centre. The unit cost grid by profession published and updated by the DGOS Bureau PF4 in 2014 was used. Thus, the costs associated with this research are as follows:

Estimate based on 50 randomised patients.

- Time for the psychologist to carry out blind telephone interviews with the randomisation group at D90 (2 hours for 50 patients at €38/hour) 3 800 €
- Data management :

- Data management time : 8 000 €
- Statistical analysis : 4 000 €

- Stationery for information and opt-out letters to patients or their relatives, bedside monitoring sheets : 500 €
- Transport of samples from local laboratories to the centralised laboratory : 200 €
- Biology analyses :
    - Cytokine assays at the rate of 6 assays per patient for 50 patients, i.e. 300 assays: 13 414 €
    - Oxidative stress testing at a rate of 6 tests per patient for 50 patients: 4 500 €
- Presentation of results (conference) : 500 €

The total cost is estimated at **34,914** euros.

B. *Insurance*

Insofar as the research is qualified as Research in routine care by the requested CPP, which means that there is no additional risk associated with the study, the insurance will be that of the establishment responsible for the care (article L. 1142-2).

XII. Feasibility of the study

- Analysis of the cohort of patients admitted for RTA in the intensive care unit at La Roche Sur Yon showed that more than 60 patients per year were admitted for RTA, including 30 patients who met the inclusion and exclusion criteria of the protocol (104). Extrapolating these figures, it is estimated that a minimum of 1.5 patients per month could be included, giving a maximum planned study duration of 2 years and 6 months, with a maximum duration of participation of 3 months per patient (i.e. a planned inclusion rate of 33% in relation to the number of patients screened).

- The main investigating centre recently conducted a large-scale clinical trial under the direction of Dr Jean Reignier. This study, with the acronym NUTRIREA-1 (NCT01137487), aimed to assess the value of systematically measuring gastric residue in mechanically ventilated intensive care patients during enteral nutrition. This study included 452 patients and was recently presented at the European Intensive Care Society Congress (ESICM Abstract 1157) and published in a high-impact generalist journal (JAMA). At the same time, the main investigating centre is currently conducting 2 other multicentre studies (NUTRIREA2 and HYPERION), one of which is looking at the benefits of therapeutic hypothermia after non-shockable cardiac arrest (**no competitive recruitment compared with the ISOCRATE study**). The ISOCRATE project protocol has many elements in common with the HYPERION study mentioned above, in particular the same methodologist. This prior experience seems to us to be a decisive advantage in the success of our project.

- The inclusion criteria for patients in our study are the recognised and accepted criteria for assessing the impact of strategies in the population of patients commonly admitted to intensive care in France and Europe for RTA. There are few non-inclusion criteria, which should allow a high rate of inclusion.

XIII. Publication rules

Scientific communications and reports relating to this study will be produced under the responsibility of the study's coordinating investigator, with the agreement of the investigators in charge. The co-authors of the report and publications will be the investigators and clinicians involved, in proportion to their contribution to the study, as well as the biostatistician and associated researchers. Publication rules will follow international recommendations (105). The study will be registered on an open-access website (Clinical Trial) before the inclusion of the 1er patient in the study.

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