SELECTIVE INTRACORONARY HYPOTHERMIA IN PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION TO REDUCE INFARCT SIZE

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To evaluate the effectiveness of selective intracoronary hypothermia in patients with anterior wall ST-elevation myocardial infarction to limit reperfusion injury and to limit infarct size.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON48678

Source
ToetsingOnline

Brief title
EURO-ICE

Condition

- Coronary artery disorders

Synonym
heart attack, myocardial infarction

Research involving
Human

Sponsors and support

Primary sponsor: Catharina-ziekenhuis
Source(s) of monetary or material Support: Cathreine BV

Intervention

Keyword: Acute myocardial infarction, Hypothermia, Infarct size, Reperfusion injury

Outcome measures

Primary outcome

PRIMARY ENDPOINT

Infarct size (as a percentage of total left ventricular mass) on MRI at 3

months after the index event.

Secondary outcome

Composite of all-cause mortality and hospitalization for heart failure at 3

months

Composite of all-cause mortality and hospitalization for heart failure at 1 year

All-cause mortality at 3 months

All-cause mortality at 1 year

Hospitalization for heart failure at 3 months

Hospitalization for heart failure at 1 year

Cardiac death at 3 months

Cardiac death at 1 year

Implantation of internal cardiodefibrillators for primary prevention at 1 year.

Implantation of internal cardiodefibrillators for secondary prevention at 1

year.

MRI efficacy parameters as specified below

Peak value of high-sensitivity troponin T (hs-TnT)

Peak value of creatine kinase (CK)

Peak value of creatine kinase-MB mass (CK-MB)

N-terminal pro-brain natriuretic peptide (NT-proBNP) at 3 months

N-terminal pro-brain natriuretic peptide (NT-proBNP) at 1 year

Left ventricular ejection fraction measured by echocardiography (biplane

Simpson*s method) at 3 months

Left ventricular ejection fraction measured by echocardiography (biplane

Simpson*s method) at 1 year

Wall motion score index (WMSI) by echocardiography at 3 months

Wall motion score index (WMSI) by echocardiography at 1 year

Secondary MRI efficacy endpoints at baseline (5-7 days after the index event)

First pass microvascular obstruction extent (FP MVO); NB first pass will be

acquired in 3 SAX levels to provide an index of %LV FP MVO

Early MVO extent (% of LV) on 1 min post-gadolinium contrast enhanced MRI,

adjusted for area at-risk

Late MVO (presence / absence) on LGE

Initial infarct size (LGE)

Initial MSI (area-at-risk minus initial infarct size/area-at-risk)

Left ventricular end-diastolic volume index (LVEDVI)

Left ventricular end-systolic volume index (LVESVI)

Left ventricular global longitudinal strain

Left ventricular circumferential strain (mid-LV)

Left ventricular ejection fraction (LVEF)

Systolic wall thickening in the culprit artery territory

Wall motion score index (WMSI)

Myocardial haemorrhage (presence/absence)

Myocardial haemorrhage extent (% of LV)

Secondary MRI efficacy endpoints at follow-up (3 months after the index event)

Final myocardial salvage index (area-at-risk minus final infarct size/area-at-risk)

Change in infarct size 3 months after procedure (LGE at baseline minus LGE at 3 months)

Final left ventricular end-diastolic volume index (LVEDVI)

Final left ventricular end-systolic volume index (LVESVI)

Final left ventricular ejection fraction (LVEF)

Final left ventricular global longitudinal strain

Final left ventricular circumferential strain (mid-LV)

Change from baseline left ventricular end-diastolic volume index (LVEDVI)

Change from baseline left ventricular end-systolic volume index (LVESVI)

Change from baseline left ventricular ejection fraction (LVEF)

Change in left ventricular global longitudinal strain

Change in left ventricular circumferential strain (mid-LV)

Pre-specified subgroup analyses

These analyses will be performed between the hypothermia and control arm, as well as within each arm, as appropriate.

Comparison of outcomes by baseline features including diabetes status, sex, age and geographic location.

Comparison of outcomes by lesion location (proximal versus mid LAD)

Comparison of outcomes by TIMI grade flow (0 versus 1)

Comparison of outcomes by achieved decrease in distal temperature (using median

of cohort for threshold)

Study description

Background summary

In acute myocardial infarction, early restoration of epicardial and myocardial blood flow is of paramount importance to limit infarction size and create optimum conditions for favourable long-term outcome.
Currently, restoration of epicardial blood flow is preferably and effectively obtained by primary percutaneous coronary intervention (PPCI). After opening the occluded artery, however, the reperfusion process itself causes damage to the myocardium, the so called *reperfusion injury*[6,7]. The phenomenon of reperfusion injury is incompletely understood and currently there is no established therapy for preventing it. Contributory factors are intramyocardial edema with compression of the microvasculature, oxidative stress, calcium overload, mitochondrial transition pore opening, micro embolization, neutrophil plugging and hyper contracture. This results in myocardial stunning, reperfusion arrhythmias and ongoing myocardial necrosis.
There is general agreement that a large part of the cell death caused by myocardial reperfusion injury occurs during the first few minutes of reperfusion, and that early treatment is required to prevent it.
Myocardial hypothermia may attenuate the pathological mechanisms mentioned above. However, limited data are available on the beneficial effects of hypothermia to protect the myocardium from reperfusion damage. In animals, several studies demonstrated a protective effect of hypothermia on the infarction area. This effect was only noted when hypothermia was established before reperfusion. Hypothermia is therefore thought to attenuate several damaging acute reperfusion processes such as oxidative stress, release of cytokines and development of interstitial or cellular edema. Furthermore, it has been shown that induced hypothermia resulted in increased ATP-preservation in the ischemic myocardium compared to normothermia.
The intracoronary use of hypothermia by infused cold saline in pigs was demonstrated to be safe by Otake et al[9]. In their study, saline of 4°C was used without complications (such as vasospasm, hemodynamic instability or bradycardia) and it even attenuated ventricular arrhythmia significantly.
Studies in humans, however, have not been able to confirm this effect, which is believed to be mainly due to the fact that the therapeutic temperature could

not reached before reperfusion in the majority of patients or not achieved at all. Furthermore, in these studies it was intended to induce total body hypothermia, which in turn may lead to systemic reactions such as shivering and enhanced adrenergic state often requiring sedatives, which may necessitate artificial ventilation.

In fact, up to now any attempt to achieve therapeutic myocardial hypothermia in humans with myocardial infarction, is fundamentally limited because of four reasons:
1. Inability to cool the myocardium timely, i.e. before reperfusion
2. Inability to cool the diseased myocardium selectively
3. Inability to achieve an adequate decrease of temperature quick enough (i.e. within minutes)
4. Inability to achieve an adequate decrease of temperature large enough (at least 4°C below body temperature)

Consequently, every attempt to achieve effective hypothermia in ST-segment myocardial infarction in humans has been severely hampered and was inadequate.

In the last two years, we have developed a methodology overcoming all of the limitations mentioned above. At first, we have tested that methodology in isolated beating pig hearts with coronary artery occlusion and next, we have tested the safety and feasibility of this methodology in humans.
Therefore, the time has come to perform a proof-of-principle study in humans, which is the subject of this protocol.

Study objective

To evaluate the effectiveness of selective intracoronary hypothermia in patients with anterior wall ST-elevation myocardial infarction to limit reperfusion injury and to limit infarct size.

Study design

Patients will be randomized in a 1:1 fashion to either routine PPCI (control group) or intra-coronary cooling (intervention group).

Intervention

Additional procedures for the study in the intervention group
1) A normal pressure wire temperature will be positioned in the distal coronary artery
2) Hypothermia is started during 10 min (induction phase).
3) Deflation of the balloon after 10 min of hypothermia while the cooling continues.

4) Then the normal PCI is performed according the normal procedure.

Study burden and risks

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS
The initial procedure will be the emergent coronary angiography identical to the first part of a regular PPCI and implantation of stents. There are no additional associated risks with that part of the procedure.
In patients eligible for the study and assigned to the hypothermia group, the equipment and drugs used are not different from the standard equipment.
The procedure is prolonged by approximately 20 minutes, but the Ischemic time is only prolonged by 10 minutes, thereby hypothesizing that this does not significantly affects infarct size, especially with the potentially protective effects of hypothermia in mind.
In the safety and feasibility study which has been performed in humans, no adverse effects of the cooling were observed in anterior wall infarctions. In none of the patients unexpected side effects such as hemodynamically instability or arrhythmias were noted during the intracoronary hypothermia.
Finally and importantly, in the Catharina Hospital, except from the safety and feasibility study for the hypothermia in STEMI patients, we have extensive experience with saline infusion at room temperature in stable patients (n=53) and patients with acute myocardial infarction (n=20).
The third phase of the procedure (i.e. placing the stent) and the further treatment of the patients is not different from normal routine.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients will be eligible for this study if they are admitted for acute anterior wall ST-elevation myocardial infarction with a total ST-segment deviation of at least 5 mm and presenting within 6 hours after onset of complaints.
Patients should have a TIMI 0 or 1 flow in the infarction related artery.
Patients should be hemodynamically stable and in an acceptable clinical condition.

Exclusion criteria

* Age <18 year or >80 year
* Cardiogenic shock or hemodynamically unstable patients
* Patients with previous myocardial infarction in the culprit artery of with previous bypass surgery
* Very tortuous or calcified coronary arteries
* Complex or long-lasting primary PCI expected
* Severe concomitant disease or conditions with a life expectancy of less than one year
* Inability to understand and give informed consent
* Known contra-indication for MRI
* Pregnancy
* Severe conduction disturbances necessitating implantation of temporary Pacemaker

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-01-2019
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	26-09-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-08-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT03447834
CCMO	NL64836.100.18