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Selective intracoronary hypothermia in patients with ST-elevation myocardial infarction. Rationale and design of the EURO-ICE trial

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Introduction

In ST-elevation myocardial infarction (STEMI), early restoration of blood flow, preferably by primary percutaneous coronary intervention (PPCI), is paramount to limit infarct size (IS) and improve long-term outcomes[1]. However, reperfusion by itself may also cause damage to the myocardium and increase IS. This has been termed myocardial reperfusion injury[2].

In animal models of acute myocardial infarction, it has been demonstrated that hypothermia decreases IS[3]. In contrast, human studies applying systemic cooling methods have not yet been able to confirm this protective effect. Recently, we developed a new method to provide selective intracoronary hypothermia during PPCI[4]. The EUROpean Intracoronary Cooling Evaluation in patients with ST-elevation myocardial infarction (EURO-ICE) trial will assess the efficacy of this method.

Methods

STUDY OBJECTIVES

The primary objective of the EURO-ICE trial is to evaluate the effect of selective intracoronary hypothermia (SIH) on IS.

STUDY DESIGN

EURO-ICE is a prospective, multicentre, randomised controlled, proof-of-principle study. Two hundred patients with anterior wall STEMI and an occlusion of the proximal or mid left anterior descending (LAD) artery with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1 will be randomised in a 1:1 fashion to SIH during PPCI versus standard PPCI. The study flow chart and a complete overview of all inclusion and exclusion criteria are shown in **Supplementary Figure 1** and **Supplementary Table 1**, respectively.

SELECTIVE INTRACORONARY HYPOTHERMIA

When randomised to the experimental arm, SIH will be performed as described by Otterspoor et al[4]. First, the occlusion is crossed with a regular guidewire. Thereafter, an over-the-wire balloon (OTWB) is advanced into the LAD artery and inflated at the site of the occlusion. Next, a pressure/temperature wire (PressureWire™ X; Abbott, St. Paul, MN, USA) is advanced into the distal LAD for continuous recording of pressure and temperature. It may be necessary to deflate the OTWB for a short period of time to get the pressure/temperature wire past the balloon. After the guidewire is

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removed from the central lumen of the OTWB, this lumen is connected to two infusion pumps filled with saline at room temperature and 4°C, respectively **(Figure 1, Supplementary Appendix 1)**.

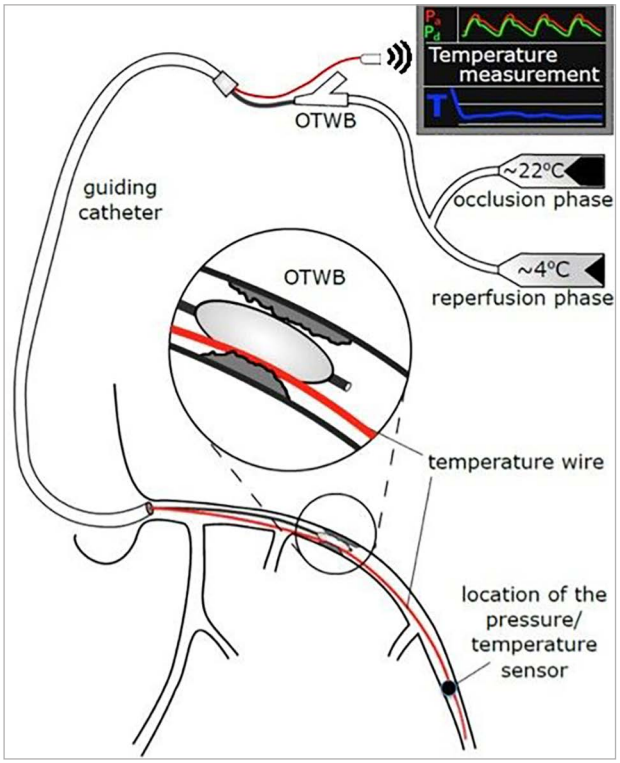

Figure 1. *Schematic drawing of the instrumentation for selective intracoronary hypothermia (adapted from Otterspoor et al[4], with permission). OTWB: over-the-wire balloon catheter*

First, saline at room temperature is infused for 7-10 minutes at a flow rate of 15-30 mL/min (occlusion phase) to maintain a distal coronary temperature of 6-8°C below body temperature. Next, the OTWB is deflated and the infusion continues for 7-10 more minutes, using the second infusion pump filled with saline at 4°C (reperfusion phase). The flow rate can be varied to maintain a distal coronary temperature of between 4 and 6°C below body temperature.

Finally, the OTWB is retracted and the procedure continues as per routine with placement of a drug-eluting stent(s).

ENDPOINTS

The primary endpoint of the study is infarct size as a percentage of left ventricular mass after three months assessed by cardiovascular magnetic resonance imaging, using late gadolinium enhancement analyses. Evaluation of the primary endpoint will be performed in the Glasgow Imaging Core Laboratory by experienced reviewers, blinded to the treatment allocation of the patients.

Key secondary endpoints are a composite of all-cause mortality and hospitalisation for heart failure at three months and at one year. A complete overview of all endpoints is shown in **Supplementary Appendix 2** and **Supplementary Appendix 3**.

SAMPLE SIZE AND STATISTICS

Since this study only includes patients with anterior wall STEMI due to a proximal or mid LAD artery occlusion, we assume that IS in the control arm will correspond to a mean of approximately 25% of left ventricular mass[5]. Assuming a normal distribution of IS with a mean of 25% in the control arm and a standard deviation of 15%, plus typical statistical assumptions (unpaired, two-tailed t-test, alpha of 0.05, power 0.80), a sample size of 91 subjects per arm is sufficient to detect an absolute reduction of 6.25%, i.e., a relative reduction of 25%. To account for patients lost to follow-up, 200 patients will be enrolled.

The secondary endpoints of three- and 12-month clinical outcomes will be compared by applying a chi-squared or Fisher's exact test to a 2×2 table of binary events/group. Similarly, for the secondary endpoints involving imaging or blood samples, an unpaired, two-tailed t-test or Mann-Whitney U test will be used to compare values between the groups.

ORGANISATION/ETHICAL CONCERNS (Supplementary Appendix 4)

The study protocol is approved at each participating centre by their local ethics committee and/or internal review board. All investigators will adhere to the principles of the Declaration of Helsinki.

An independent data safety and monitoring board (DSMB) will oversee safety and a blinded interim analysis of IS will be performed after 40 patients have been included and thereafter as judged appropriate.

Discussion

Despite early revascularisation through PPCI in patients with STEMI, large infarctions still occur frequently. Consequently, mortality after STEMI remains high and many patients develop complications such as heart failure[5].

A logical target for therapy beyond PPCI is the attenuation of myocardial reperfusion injury. In contrast to preclinical studies, human trials applying systemic cooling have failed to demonstrate a decrease in IS, most likely due to an inability to reach the therapeutic target temperature before reperfusion.

SIH overcomes most limitations of systemic cooling. Hypothermia is administered selectively into the infarcted area, with a rapid and sufficient decrease of the myocardial temperature before reperfusion occurs **(Supplementary Appendix 5)**.

After having tested this method in a small safety and feasibility pilot study in humans[4], we have designed the EURO-ICE study.

Limitations

Importantly, although the procedure will be prolonged by approximately 20 minutes in the experimental arm, ischaemic time will be prolonged by only 7 to 10 minutes. The hypothesised beneficial effects of hypothermia should at least counterbalance the prolongation of the ischaemic time.

Conclusions

The EURO-ICE trial is a European multicentre, randomised controlled, proof-of-principle study comparing SIH during PPCI with standard PPCI in 200 patients with anterior wall STEMI.

Impact on daily practice

The EURO-ICE trial investigates whether SIH during PPCI decreases IS. If such a beneficial effect can be demonstrated, this will translate into a lower risk of complications, such as heart failure and mortality, and will be a next step in PPCI for patients with STEMI.

Funding

The EURO-ICE trial is an investigator-initiated trial without any commercial purpose or pursuit of profit by the sponsor of the study, Cathreine B.V. The trial is financed by a research grant from Abbott. Their support remains limited to funding only, with no influence on study design, data collection or analysis, or final manuscript publication.

Conflict of interest statement

B. De Bruyne reports grants from Abbott, Boston Scientific, Biotronik, and St. Jude Medical, and receives consulting fees from St. Jude, Abbott, Opsens, and Boston Scientific, outside the submitted work; he has equity in Siemens, GE, Bayer, Philips, HeartFlow, Edwards Lifesciences and Celyad. T. Engstrom reports personal fees from Bayer, BMS and Abbott, outside the submitted work. C. Berry reports grants from Abbott, Siemens Healthcare and Coroventis, outside the submitted work. N. Pijls reports consultancy fees from Abbott and Opsens, institutional grants from Abbott and Hexacath, outside the submitted work, and has equity in Philips, ASML, HeartFlow and GE Health. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Cool Cell Catheter.

Supplementary Appendix 2. Endpoints and pre-specified subgroup analyses.

Supplementary Appendix 3. Definitions.

Supplementary Appendix 4. EURO-ICE trial organisation, leadership, committees and core laboratory.

Supplementary Appendix 5. Advantages of selective intracoronary hypothermia versus systemic cooling.

Supplementary Figure 1. Study flow chart of the EURO-ICE trial.

Supplementary Table 1. Inclusion and exclusion criteria.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00471

Supplementary data

Supplementary Appendix 1. Cool Cell Catheter

In the near future, the instrumentation for this procedure will be more practical by use of a dedicated monorail infusion catheter with a balloon at its tip, the so-called Cool Cell Catheter (Hexacath, Paris, France). The Cool Cell Catheter is in process of CE approval presently and will be used in this trial when available.

When using the Cool Cell Catheter, the procedure starts by advancing a pressure/temperature wire across the culprit lesion into the distal LAD artery, after equalising it in the proximal LCA. Immediately thereafter, the Cool Cell Catheter is advanced over this pressure/temperature wire and the balloon is inflated at the site of the occlusion. Because it is a monorail infusion catheter, the lumen of the Cool Cell Catheter can be used for infusion of saline in the distal LAD artery. The rest of the procedure is the same as described in the article.

Supplementary Appendix 2. Endpoints and pre-specified subgroup analyses

Primary endpoint

The primary endpoint is final infarct size as a percentage of total left ventricular mass after three months, assessed by MRI with late gadolinium enhancement (LGE) 10-15 minutes after contrast administration.

Secondary endpoints

• Composite of all-cause mortality and hospitalisation for heart failure at three months.

• Composite of all-cause mortality and hospitalisation for heart failure at one year.

• All-cause mortality at three months.

• All-cause mortality at one year.

• Implantation of cardioverter defibrillator for primary prevention at one year.

• Implantation of cardioverter defibrillator for secondary prevention at one year.

• Implantation of cardioverter defibrillator for both primary and secondary prevention at one year.

• Hospitalisation for heart failure at three months.

• Hospitalisation for heart failure at one year.

• Cardiac death at three months.

• Cardiac death at one year.

• Peak value of high-sensitivity troponin T (hs-TnT) while in-patient.

• Peak value of creatine kinase (CK) while in-patient.

• Peak value of creatine kinase-MB mass (CK-MB) while in-patient.

• N-terminal pro-brain natriuretic peptide (NT-proBNP) at three months.

• N-terminal pro-brain natriuretic peptide (NT-proBNP) at one year.

• Left ventricular ejection fraction measured by echocardiography (biplane Simpson's method) at three months.

• Left ventricular ejection fraction measured by echocardiography (biplane Simpson's method) at one year.

• Wall motion score index (WMSI) by echocardiography at three months.

• Wall motion score index (WMSI) by echocardiography at one year.

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

• Late microvascular obstruction (MVO) extent in percentage of LV mass.

• Late MVO (presence/absence).

• Initial infarct size (IS), assessed with LGE, 10-15 minutes after contrast administration.

• Initial myocardial salvage index (MSI, area-at-risk minus initial infarct size/area-at-risk, AAR).

• Initial left ventricular end-diastolic volume index (LVEDVI).

• Initial left ventricular end-systolic volume index (LVESVI).

• Initial left ventricular global longitudinal strain (GLS).

• Initial left ventricular circumferential strain (GCS).

• Initial left ventricular ejection fraction (LVEF).

• Systolic wall thickening in the culprit artery territory.

• Wall motion score index (WMSI).

• Myocardial haemorrhage (presence/absence).

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

• Final infarct size in grams.

• Final MSI (AAR-final IS/AAR).

• Change in IS, 3 months after the procedure.

• 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 (GLS).

• Final left ventricular circumferential strain (GCS).

• Change in left ventricular end-diastolic volume index (LVEDVI).

• Change in left ventricular end-systolic volume index (LVESVI).

• Change in left ventricular ejection fraction (LVEF).

• Change in left ventricular global longitudinal strain (GLS).

• Change in left ventricular circumferential strain (GCS).

Pre-specified subgroup analyses

To exclude important influence on specific endpoints, a subgroup analysis will be performed. These designated endpoints will be compared without adjustment for other covariates. These subgroups comprise categorical or continuous data. When these covariates are continuous data, a threshold (median or other) will be used to create a binary variable.

Categorical subgroups

• Diabetes status (yes versus no; 2 categories).

• Gender (male versus female; 2 categories).

• Geographic location (participating sites; categories are number of participating sites).

• History of previous PCI (yes versus no; 2 categories).

• History of previous myocardial infarction (yes versus no; 2 categories).

• Number of diseased vessels (1 versus 2 versus 3; 3 categories)

• Lesion location (proximal versus mid LAD artery; 2 categories)

• TIMI flow grade (0 versus 1; 2 categories)

Continuous subgroups

• Age (binary using median of cohort for threshold).

• Symptom-onset-to-balloon time (binary using median of cohort for threshold).

• Achieved decrease in distal temperature (binary using median of cohort for threshold).

• Previous ejection fraction (binary using ejection fraction of 50% for threshold).

Supplementary Appendix 3. Definitions

All-cause mortality is defined as all deaths, regardless of the cause of death.

Hospitalisation for heart failure is defined as an event which requires hospitalisation for at least 24 hours in any inpatient unit or ward in the hospital, because the patient has clinical signs of heart failure, including dyspnoea, orthopnoea and increasing fatigue or signs and/or symptoms of volume overload. Treatment should consist of at least intravenous drug administration, such as diuretics or vasoactive agents.

Cardiac death is defined as any sudden death, death related to acute myocardial infarction, arrhythmia or congestive heart failure, death secondary to a cerebrovascular accident, or death directly related to PCI, even if the ultimate cause of death is not clearly a cardiac event (e.g., infection).

Supplementary Appendix 4. EURO-ICE trial organisation, leadership, committees and core laboratory

Principal Investigator: Nico H.J. Pijls, Catharina Hospital, Eindhoven, the Netherlands

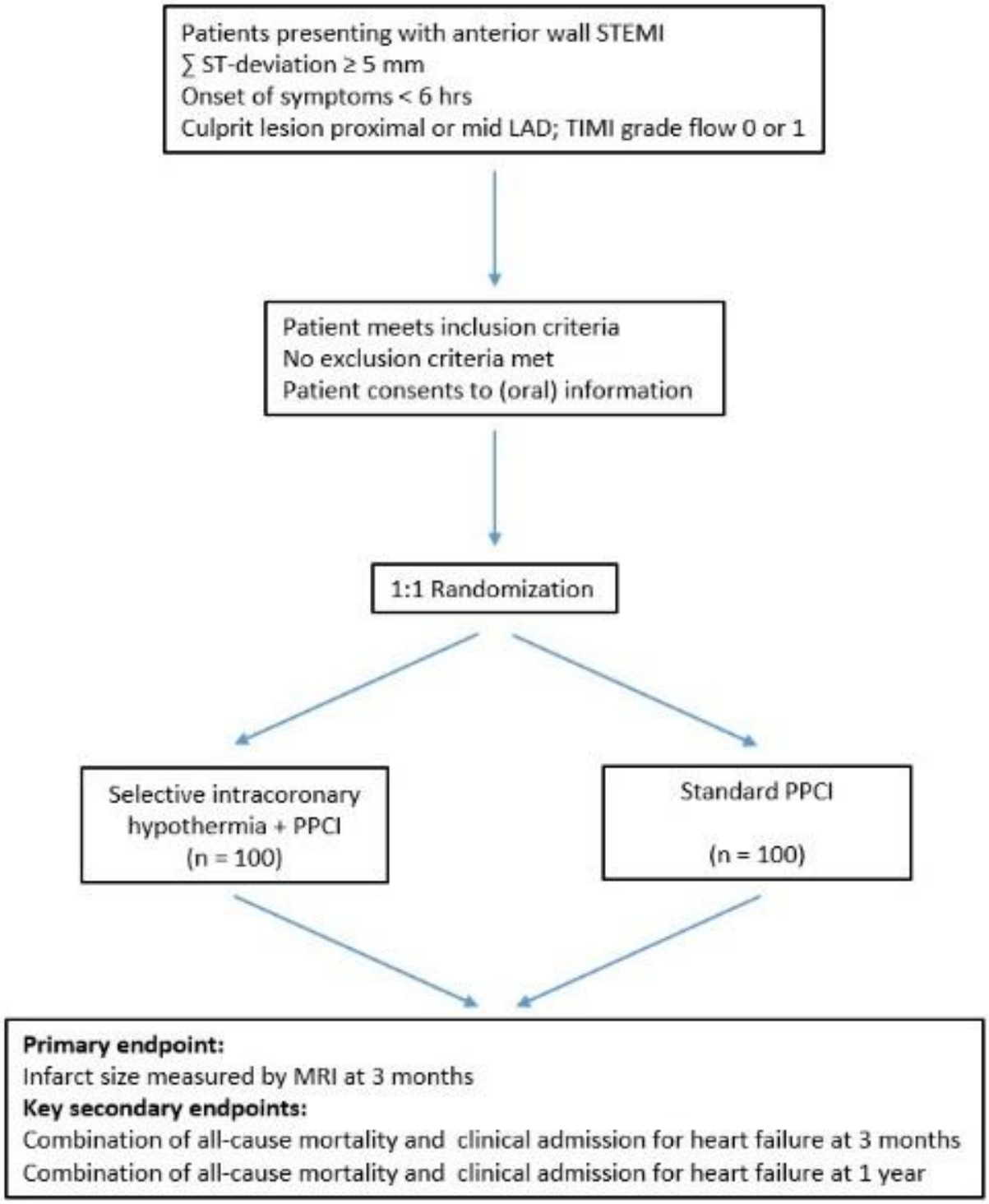
Co-principal investigators: Luuk C. Otterspoor, Catharina Hospital, Eindhoven, the Netherlands; Pim A.L. Tonino, Catharina Hospital, Eindhoven, the Netherlands; Marcel van 't Veer, Catharina Hospital, Eindhoven, the Netherlands; Bernard De Bruyne, Cardiovascular Center Aalst, OLV Clinic, Aalst, Belgium; Keith G. Oldroyd, Golden Jubilee National Hospital, Glasgow, United Kingdom; Colin Berry, Golden Jubilee National Hospital, Glasgow, United Kingdom; Thomas Engstrøm, Rigshospitalet, Copenhagen, Denmark; Faculty of Health, University of Lund, Lund, Sweden; Zsolt Piroth, Hungarian Institute of Cardiology, Budapest, Hungary; Ole Fröbert, Örebro University, Faculty of Health, Örebro, Sweden; Grigoris V. Karamasis, Essex Cardiothoracic Centre, Basildon, United Kingdom; Gabor G. Toth, Medical University of Graz, Graz, Austria.

MRI Core Laboratory: Colin Berry and Kenneth Mangion, Glasgow Imaging Core Laboratory, Glasgow, United Kingdom. The reviewers of the MRI Core Laboratory are blinded to the randomisation code of the patients.

Data Safety and Monitoring Board: Nils P. Johnson (Chair), Division of Cardiology, Department of Medicine, Weatherhead PET Center, McGovern Medical School, UTHealth and Memorial Hermann Hospital, Houston, TX, USA; Emanuele Barbato, Cardiovascular Center Aalst, OLV-Clinic, Aalst, Belgium; Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy; Jaques J. Koolen, Amsterdam, the Netherlands.

Supplementary Appendix 5. Advantages of selective intracoronary hypothermia versus systemic cooling

Applying selective intracoronary hypothermia overcomes several limitations of systemic cooling. First, hypothermia is directed selectively to the area at risk, which guarantees rapid and sufficient cooling within 100 seconds, hence achieving the target temperature before reperfusion. This point has proven to be crucial in reducing reperfusion injury in previous animal studies. Second, because hypothermia is achieved locally, systemic side effects such as shivering and volume overload are avoided. In addition, we showed that temperature change is negligible in the adjacent healthy myocardium. Third, the pressure/temperature wire in the coronary artery allows continuous monitoring of the distal pressure and precise control and adjustment of the target coronary temperature to enhance the precision and safety of the procedure. Fourth, the intracoronary method requires a coronary angiogram prior to the decision to treat with hypothermia. Therefore, unnecessary cooling is avoided in cases with existing TIMI flow grade 2 or 3, where cooling is not effective anymore. Fifth and finally, selective intracoronary hypothermia reaches the infarct area directly. This is in contrast to many negative studies in humans to reduce reperfusion injury in which the protective agents were administered intravenously most of the time and hence not able to reach the target area because of the occlusion in the culprit artery.



Supplementary Figure 1. Study flow chart of the EURO-ICE trial.

Supplementary Table 1. Inclusion and exclusion criteria.

Inclusion criteria
Age 18-80 years
STEMI anterior wall, ∑ ST-deviation ≥5 mm
Onset of symptoms <6 hours
Culprit lesion in proximal (segment 6) or mid (segment 7) LAD artery
TIMI flow grade should be 0 or 1
Exclusion criteria
Age <18 or >80 years
Cardiogenic shock or haemodynamic instability
Severe conduction disturbances necessitating implantation of a temporary pacemaker
History of previous anterior wall myocardial infarction or bypass surgery
Very tortuous or calcified coronary arteries, i.e., complex coronary anatomy
Severe comorbidity with life expectancy of less than 1 year
Inability to understand and give informed consent
Contraindication for MRI
Pregnancy