Effectiveness of hypnosis in preventing anxiety during coronary angiography: HypCor study

PROTOCOL FOR EVALUATION OF ROUTINE CARE

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PROTOCOL UPDATE HISTORY

VERSION	DATE	REASON FOR THE UPDATE

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SUMMARY

LIST OF ABBREVIATIONS

ANSM	National Agency for the Safety of Medicines and Health Products
GCP	Good Clinical Practice
CCTIRS	Comité Consultatif sur le Traitement de l'Information en Matière de la Recherche dans le Domaine de la Santé
CNIL	National Commission for Information Technology and Civil Liberties
PPC	Committee for the Protection of Persons
CRF	Case Report Form (Observation Book)
EVA	Visual Analog Scale
ICH	International Conference on Harmonization
	State Registered Nurse
STAI-Y	State Trait Anxiety Inventory, Form Y
CST	Clinical Study Technician

1. SUMMARY OF THE RESEARCH

SPONSOR	CHR METZ THIONVILLE MERCY Hospital 1 allée du château CS 45001 57085 METZ cedex 03
PRINCIPAL INVESTIGATOR	Dr Nazmine GULER CHR METZ THIONVILLE MERCY Hospital Emergency Department 1 allée du château, CS 45001, 57085 METZ cedex 03
TITLE	HYPCOR study: Effectiveness of hypnosis in preventing anxiety during coronary angiography
STUDY CONTEXT	Coronary angiography is a medical imaging technique used in cardiology to visualize the coronary arteries in cases of suspected coronary artery disease. It is performed under local anesthesia by consensus of experts. Indeed, the procedure is in principle painless, apart from the initial arterial puncture. Moreover, it is necessary to know during the procedure if the patient feels chest pains, which allows to orientate towards the guilty coronary lesion. This is impossible if the patient is under general anesthesia. However, the absence of general anesthesia can be a source of anxiety for patients, and in practice the procedure can be made painful at several moments: at the time of the puncture, the mounting of the probes on tortuous, spastic or very calcified arteries, or at the time of the dilatation by inflation of the balloon thus obstructing the artery downstream. The evaluation of the effectiveness of the practice of hypnosis, carried out by INSERM in 2015, concludes that "the use of hypnosis during surgery or during an interventional medicine or radiology procedure allows for a reduction in the consumption of sedatives and/or analgesics during surgery." We hypothesize that hypnosis can contribute to a decrease in anxiety and pain in patients undergoing coronary angiography, and even reduce complications thanks to a better control of hemodynamics (heart rate and blood pressure). It is also possible that this will result in improved operator comfort during coronary angiography.
OBJECTIVES	The main objective is to compare state anxiety preceding scheduled coronary angiography in adult patients without a history of coronary angiography, according to whether or not they will have benefited from a hypnosis session before coronary angiography, with post-hypnotic suggestions of self-hypnosis to be performed during coronary angiography. The secondary objectives will be to compare, between the hypnosis group and the no-hypnosis group, the following criteria: - pain during and after coronary angiography, - hemodynamic parameters: non-invasive blood pressure and heart rate before coronary angiography and invasive during coronary angiography,

	-operator comfort, -the use of sedatives, analgesics or local anesthetics - the occurrence of major and minor complications.
STUDY DESIGN	Single-center, randomized, single-blind, routine care efficacy study (blinded coronary staff). Patients admitted to cardiology the day before a scheduled coronary angiography will be offered to participate in the study by their cardiologist. If they accept, an initial assessment of their anxiety (trait and condition) will then be performed. The next day, before leaving the department for the coronary angiography room, the patients will be randomized into two groups: a group of patients will benefit from a hypnosis session before leaving the department for the coronary angiography room, with post-hypnotic suggestions of self-hypnosis to be carried out during the coronary angiography; a prescription of anxiolytics could be carried out according to the clinical signs of anxiety presented by the patient -The other group will only be prescribed anxiolytics according to the clinical signs of anxiety presented. State anxiety will be measured after the patient is installed in the coronary angiography room, before the procedure is performed. Pain and hemodynamic parameters will be measured during and after coronary angiography. The comfort of the operator will also be evaluated. Patients will be contacted by telephone one month after coronary angiography to assess their satisfaction with their care.
INCLUSION CRITERIA	Patients will be included: - 18 years of age or older on the day of the pre-inclusion visit - who require scheduled coronary angiography with or without stenting during the procedure - affiliated to a social security system - having received complete, clear, oral and written information from their physician.
NON-INCLUSION CRITERIA	Patients will be excluded: - having already undergone coronary angiography in the past (in order not to induce an "experience" bias in the evaluation of anxiety related to coronary angiography) - not speaking or understanding the French language - with higher function disorders (dementia, disorientation, confusion, etc.) - with a known history of schizophrenia (contraindication to hypnosis) - deaf or hard of hearing (because it prevents the good realization of the hypnosis session) - patient under legal protection (guardianship, curatorship, safeguard of justice)
NATURE OF ROUTINE CARE EVALUATED IN THE RESEARCH	Management with hypnosis: a hypnosis session by a hypnotherapist before the installation in the coronary angiography room, with post-hypnotic suggestions of self-hypnosis to be carried out during the coronary angiography. The hypnosis session will be performed by a hypnotherapist (nurse or doctor) trained in an institute recognized by the French-speaking Confederation of Hypnosis and Brief Therapies (CFHTB) and having at least 2 years of experience in the practice of hypnosis), and will take place in the patient's room in the cardiology department at the patient's bed on the morning of the coronary angiography. The principles of the session are:

	-The patient must be comfortable, -To feel the environment with the five senses (sight, hearing, smell, kinesthesia, taste), -Deepening of the hypnotic state by counting from 1 to 10 with catalepsy of the arm, -work on the painful part of the body and the healthy parts, -suggestion from the therapist that the suffering part of the body is recovering, -anchoring with a color or a gesture (which allows the patient to return spontaneously without help to this state of trance where he/she will be able to heal himself/herself), -suggestion to perform the same session independently in the coronary angiography room with the possibility of answering questions from the cardiologist, -train the patient gradually to the state of full consciousness by counting down, -Make sure the patient is okay.
EVALUATION CRITERIA	Primary end point: state anxiety measured with the STAI-Y A questionnaire just before coronary angiography. Secondary endpoints: Anxiety trait (STAI-Y B questionnaire) Anxiety on the eve of coronary angiography Pain before and during coronary angiography: visual analog scale (VAS) Heart rate and blood pressure before and during coronary angiography Comfort of the arteriography operator: 5-point Likert scale (1: worst comfort, 5: best possible comfort) Dose of sedatives, analgesics and local anesthetics administered during coronary angiography Occurrence of major complications during coronary angiography (death, stroke, tamponade, hemorrhagic shock, anaphylactic shock to the contrast medium, ventricular tachycardia or ventricular fibrillation, severe bradycardia) or minor complications (vagal malaise, puncture site hematoma, skin allergy)
NUMBER OF PATIENTS	Assuming a mean STAI-Y A score of 50 (standard deviation 10) in the control group, and a clinically relevant difference from 5 points, it is necessary to include 85 patients in each group, for a total of 170 patients.
EXPECTED NUMBER OF CENTERS	One center.
DURATION OF THE RESEARCH	Duration of the inclusion period: 12 months - Duration of participation per patient: 1 month - Total duration of research: 18 months (including data analysis and writing of results)
STATISTICAL ANALYSIS OF DATA	Primary objective: comparison of mean STAI-Y A scores between the two groups (Student's t-test), with adjustment if necessary for possible confounding factors (multiple linear regression) Secondary objectives: comparison of quantitative (Student's t-tests) and qualitative (Fischer's exact tests) criteria between the two groups.
EXPECTED BENEFITS	Coronary angiography is an invasive procedure that affects a noble organ without general anesthesia and is therefore an anxiety-provoking and even traumatic procedure on the psychological level. The fact that it is not performed under general anesthesia removes the possible risks incurred by the patient, but there is anxiety, discomfort and pain; we therefore believe that hypnosis will promote the management of the patient in his psychological and physical dimension, whatever the invasive procedure. Thus we will have less or no need for sedatives and analgesics, thus

	reducing their potential iatrogenicity, and will gain in improvement of the management of the procedure by the surgeon in front of a more serene, less painful, more hemodynamically stable patient. By introducing hypnosis in as many areas of the hospital as possible, the population and the caregivers will benefit from a more serene and calm work environment and the possibility for the patient population to have recourse to an alternative recognized by the Academy of Medicine as being complementary.

1. SCIENTIFIC JUSTIFICATION

1.1. Current state of knowledge

1.1.1. ON THE PATHOLOGY

Coronary angiography is a medical imaging technique used in cardiology to visualize the coronary arteries. It is the reference examination in case of suspected coronary artery disease: angina, myocardial infarction or silent myocardial ischemia.
It is a complementary invasive medical examination that uses the X-ray technique and the injection of an iodinated contrast product. It can be completed by different complementary techniques, in particular a coronary angioplasty which can be done in the wake of a coronary stenosis. Coronary angioplasty is the procedure that consists of treating a narrowed coronary artery, for example in the case of coronary artery disease, by dilating it with a catheter equipped with an inflatable balloon at its tip.

Coronary angiography is a technique that has grown dramatically over the last 30 years [1]. This interventional procedure is increasingly replacing standard surgical treatments. Thus, approximately 250,000 coronary angiographies were performed in France and no less than 116,000 angioplasties in 2009.
Endoluminal revascularization techniques have emerged as a major treatment for acute and chronic coronary insufficiency [2,3].

Coronary angiography is performed by puncturing the radial or femoral artery. The puncture is usually done on the right. During a radial puncture, a mixture of heparin 2500ui and verapamil is injected into the arterial desilet in order to eliminate any problem of spasticity or thrombosis. The patient is always provided with a peripheral venous infusion, usually on the left side of the body so as not to interfere with the procedure.

Two specific probes, one for the left coronary artery, one for the right coronary artery are mounted against the blood flow under scopic control and directed with a guide called "J-guide" in reference to its distal end, with a diameter of 0.35mm made of Teflon.

Coronary images are obtained by injecting 10 centiliters of iodinated contrast medium under fluoroscopy, so-called subtractive images. Several incidences are performed in order to best determine a coronary lesion.

If a lesion is defined and the operator decides to treat it, then it will be necessary to use catheters and also dedicated equipment for angioplasty.

These techniques generally do not exceed one hour and are performed with permanent measurement of the heart rate, a surface electrocardiogram with peripheral leads. A non-invasive blood pressure measurement is performed systematically before any procedure, and then the blood pressure figures are given continuously in an invasive manner. Oxygen saturation is not mandatory and is performed if clinical signs point to an oxygenation problem.

Coronary angiography is performed under local anesthesia. In fact, the procedure is usually painless, except for the initial arterial puncture. Moreover, it is necessary to know during the procedure if the patient feels chest pains, which allows to orientate towards the guilty coronary lesion. This is impossible if the patient is under general anesthesia.
However, the absence of general anesthesia can be a source of anxiety for patients, and in practice the procedure can be made painful at several moments: at the time of the puncture, the mounting of the probes on tortuous, spastic or very calcified arteries, or at the time of the dilatation by inflation of the balloon thus obstructing the artery downstream.

Coronary artery disease and coronary angiography, an invasive procedure performed under local anesthesia, cause significant anxiety in patients [4]. 4] This anxiety may itself be the cause of adverse events [5].

Moreover, it is currently well demonstrated that there is a strong relationship between coronary disease and the occurrence of a depressive syndrome [6], especially as many patients undergo coronary angiography, thus increasing the level of anxiety that can lead to a state of post-traumatic stress and consequently to depression. Better management of anxiety during coronary angiography could limit this risk.

It is therefore important to control this state of anxiety for the patient but also for the operator and thus perform the examination in the best possible technical conditions.

Several treatments have already been evaluated to reduce patient anxiety before and during coronary angiography: massage [7], music therapy [8], aromatherapy [9]. However, no study has been performed to evaluate the effectiveness of hypnosis in this context.

1.1.2. ON THE STRATEGIES/PROCEDURES UNDER CONSIDERATION

The American Psychological Association (APA) defines the hypnotic state as "a state of consciousness involving focused attention and decreased sensitivity to the environment, characterized by an increased capacity to respond to suggestion" [10]. The term hypnosis is used to define the hypnotic process of inducing this state.

Although it is the subject of numerous neuroscientific studies to explain its mechanism, this state of modified consciousness is without risk for the patient because it is above all a physiological state. This is why hypnosis is at least an adjunctive measure in various clinical applications.

For example, hypnoanalgesia is an analgesic method. Its application can be found in dental care, especially for children [11], as well as in pain management during childbirth [12]. Hypnosedation, of which Prof. FEYMONVILLE is a pioneer, is a sedative method that has been proven to be effective in surgical interventions [13-15]. In my clinical practice, in the Emergency Department, hypnosis is regularly associated with invasive procedures (sutures in children and adults, insertion of peripheral venous lines, chest drains, lumbar punctures) or not (reduction of dislocation, pain management). Our observation is an improvement in management, resulting in better patient compliance, a decrease in the use of analgesics and sedatives, and an improvement in management conditions for the teams. A Cochrane review mentions hypnosis as a treatment for pain and distress during invasive procedures [16].

As mentioned, whether it is an emergency or a planned procedure, there is an emotional distress, the preoperative anxiety [17]. This psychological state can condition the success of the procedure [18]. Thus hypnosis appears to be a non-medicinal alternative to reduce the patient's anxiety and therefore has repercussions on the success of the procedure.

The evaluation of the effectiveness of the practice of hypnosis [19], carried out by INSERM, concludes that "the use of hypnosis during surgery or during a medical or radiological intervention reduces the consumption of sedatives and/or analgesics during surgery. These results seem to provide a solid foundation; nevertheless further studies would be welcome."

To date, no study has been carried out to evaluate the effectiveness of hypnosis as a complement to local anesthesia during coronary angiography. A study was carried out in 2004 concerning coronary angioplasties only, and comparing hypnosis and drug sedation [20].

1.2. Research Hypotheses

We hypothesize that hypnosis can contribute to a decrease in anxiety and pain in patients undergoing coronary angiography, and even reduce complications thanks to a better control of hemodynamics (heart rate and blood pressure).

It is also expected to result in improved operator comfort in coronary angiography, related to better control of pain and anxiety by patients.

1.3. Nature of routine care evaluated in the research

The use of hypnosis has been described for many medical interventions
Its application can be found in dental care, especially for children [11], as well as in pain management during childbirth [12]. Hypnosedation, pioneered by Prof. Feymonville, is a sedative method that has been proven to be effective in surgical procedures [14]. In clinical practice, in the emergency department, hypnosis is regularly associated with invasive procedures (sutures in children and adults, insertion of peripheral venous lines, chest drains, lumbar punctures) or not (reduction of dislocation, pain management). Our observation is an improvement in management, resulting in better patient compliance, a decrease in the use of analgesics and sedatives, and an improvement in management conditions for the teams. A Cochrane review mentions hypnosis as a treatment for pain and distress during invasive procedures [16].

The evaluation of the effectiveness of the practice of hypnosis, carried out by INSERM in 2015 [19], concludes that "the use of hypnosis during a surgical procedure or during an interventional medicine or radiology act allows for a reduction in the consumption of sedatives and/or analgesics in the intraoperative period".

Adverse effects related to hypnosis are more related to repetitive and extensive hypnosis practices [21, 22]. However, these effects can rarely appear even during a simple session like the one carried out in this research:

- Persistence of a residual hypnotic state at the end of the treatment,
- Anxiety or dysphoria, or "abreaction",
- Decompensation of schizophrenic disorders

1.4. Justification of the methodological choices

A two-group parallel comparison study with single-blind randomization (the coronary angiography operator will be kept blinded to the group during the study) is proposed to minimize potential confounders.

The main criterion of judgment was state anxiety, evaluated by the STAI-Y A questionnaire. This questionnaire has been validated to evaluate state anxiety in adult populations [23,24] and has already been used in studies evaluating the effect of hypnosis on anxiety [25]. It also has the advantage of a short administration time (about 10 minutes).

As the constraints of the coronary angiography technical platform do not easily allow a hypnosis session to be performed during the procedure, the session will be performed in the morning in the cardiology department, before the patient is transported to the coronary angiography room. During this session, the hypnotherapist will make post-hypnotic suggestions of self-hypnosis during the coronary angiography. This is a model that can easily be transposed to other establishments, regardless of the organization of the technical platforms.

For these same organizational constraints, only patients scheduled for coronary angiography will be included (emergencies will be excluded).

2. OBJECTIVES

2.1. MAIN OBJECTIVE

The main objective is to compare state anxiety preceding scheduled coronary angiography in adult patients without a history of coronary angiography, according to whether or not they will have benefited from a hypnosis session before coronary angiography, with post-hypnotic suggestions of self-hypnosis to be performed during coronary angiography.

2.2. Secondary objectives

The secondary objectives will be to compare, between the hypnosis group and the no-hypnosis group, the following criteria:
- pain during and after coronary angiography,
- hemodynamic parameters: non-invasive blood pressure and heart rate before coronary angiography and invasive during coronary angiography,
-operator comfort,
-the use of sedatives, analgesics or local anesthetics
- the occurrence of major and minor complications.

3. RESEARCH DESIGN

3.1. SCHEME/METHODS

This is a single-center, randomized, single-blind, comparative, routine care study (coronary angiography tray staff) in 2 parallel groups, ratio 1:1.

Patients admitted to cardiology the day before a scheduled coronary angiography will be offered to participate in the study by their cardiologist. If they accept, an initial assessment of their anxiety (trait and condition) will then be performed. The next day, before leaving the department for the coronary angiography room, the patients will be randomized into two groups:

- a group of patients will benefit from a hypnosis session before leaving the department for the coronary angiography room, with post-hypnotic suggestions of self-hypnosis to be carried out during the coronary angiography; a prescription of anxiolytics could be carried out according to the clinical signs of anxiety presented by the patient
- the other group will be prescribed only anxiolytics according to the clinical signs of anxiety presented.

State anxiety will be measured after the patient is installed in the coronary angiography room, before the procedure is performed. Pain and hemodynamic parameters will be measured during and after coronary angiography. The comfort of the operator will also be evaluated.

Patients will be contacted by telephone one month after coronary angiography to assess their satisfaction with their care.

3.2. Randomization

Randomization will be performed in the cardiology department before the patient is transported to the coronary angiography suite. The hypnotherapist opens a sealed envelope with the patient's inclusion number.

The randomization list will be established by drawing lots without stratification.

The randomization list will be established for 200 patients by the methodologist of the Clinical Research Support Platform of the CHR Metz-Thionville. It will be kept in a protected computer file at the Clinical Research Support Platform of the CHR Metz-Thionville.

4. ELIGIBILITY CRITERIA

4.1. INCLUSION CRITERIA

Patients will be included:

- 18 years of age or older on the day of the pre-inclusion visit
- who require scheduled coronary angiography with or without stenting during the procedure
- affiliated to a social security system
- having received complete, clear, oral and written information about the study from the cardiologist.

4.2. Non-inclusion criteria

Patients will be excluded:

- having already undergone coronary angiography in the past (in order not to induce an "experience" bias in the evaluation of anxiety related to coronary angiography)
- not speaking or understanding French
- with higher function disorders (dementia, disorientation, confusion, etc.)
- with a known history or notion of a history of psychotic disorders (according to the interrogation, the medical file or the referral letter from the attending physician). All psychotic disorders will be considered, although only schizophrenic disorders can be decompensated by hypnosis, in order not to misunderstand a schizophrenic disorder which would have been only qualified as psychotic.
- deaf or hard of hearing (because it prevents the good realization of the hypnosis session)
- patient under legal protection (guardianship, curatorship, safeguard of justice)

4.3. Recruitment procedures

The recruitment will be carried out in the cardiology department of the CHR of Metz-Thionville, Mercy Hospital.

The study will be proposed to patients when they are admitted to the cardiology department, by their cardiologist, the day before their scheduled coronary angiography. Inclusions will be targeted on half-days identified in advance on a schedule, according to the availability of the 3 hypnotherapists participating in the research. One to three half-days will be identified each week.

Inclusions will take place over 12 months to reach a total of 170 patients (85 per group). On average, there are about 2000 scheduled coronary angiographies per year in the department.

The patient may simultaneously participate in any other biomedical research, with the exception of protocols that may impact pain and/or anxiety the day before and/or the day of the coronary angiography procedure.

5. NATURE OF ROUTINE CARE EVALUATED IN THE RESEARCH

5.1. Act(s) under consideration

The hypnosis session will be performed by a hypnotherapist (nurse or doctor) trained in an institute recognized by the French-speaking Confederation of Hypnosis and Brief Therapies (CFHTB) and having at least 2 years of experience in the practice of hypnosis), and will take place in the patient's room in the cardiology department at the patient's bed on the morning of the coronary angiography.

The principles of the session are:
-The patient must be comfortable,
-To feel the environment with the five senses (sight, hearing, smell, kinesthesia, taste),
-Deepening of the hypnotic state by counting from 1 to 10 with catalepsy of the arm,

-work on the painful part of the body and the healthy parts,
-suggestion from the therapist that the suffering part of the body is recovering,
-anchoring with a color or a gesture (which allows the patient to return spontaneously without help to this state of trance where he/she will be able to heal himself/herself),
-suggestion to perform the same session independently in the coronary angiography room with the possibility of answering questions from the cardiologist,
-train the patient gradually to the state of full consciousness by counting down,
-Make sure the patient is okay.

The only contraindication to performing the hypnosis session was the presence of schizophrenic disorder, which was a factor for non-inclusion in the study.

In accordance with the usual management, the cardiologist may prescribe hypnovel for anxiolytic purposes, depending on the patient's clinical signs of anxiety.

5.2. ACT(S) OF COMPARISON

The group without hypnosis session will benefit from the management of their anxiety by the nursing staff of the cardiology department: attitudes and usual speech to prepare and reassure the patients before the intervention.
In accordance with the usual management, the cardiologist may prescribe hypnovel for anxiolytic purposes, depending on the patient's clinical signs of anxiety.

5.3. BLINDING

The patients will not be able to be unaware of the realization of the hypnosis session, only the personnel of the technical platform of realization of the coronarography will be.

The hypnosis session is performed - or not, depending on the patient's randomization group - in the cardiology department, before the patient is transferred to the coronary angiography room. The patient and the staff of the department will be instructed not to disclose whether they have performed this session to the staff present in the coronary angiography room.

The vigilance unit will have a duplicate of the randomization list in case of need for unblinding.

If the blind is unintentionally lifted during the study, the reasons and precise timing of the lifting will be documented by the investigative site and/or the sponsor.

A "sponsor" blind will be systematically removed at the level of the vigilance unit in the event of a suspected serious unexpected adverse reaction before it is reported to the competent authorities and on an annual basis when the annual safety reports are drawn up.

6. EVALUATION CRITERIA

6.1. Primary endpoint

The primary endpoint is state anxiety (state of anxiety at the time of measurement), measured using the Spielberger Anxiety Inventory (STAI), in its Y form [23,24].
The STAI-Y is a self-administered questionnaire designed to assess momentary and habitual anxiety.
It consists of 2 scales of 20 items each:

- The State Anxiety Scale (STAI-Y A) assesses the feelings of apprehension, tension, nervousness and worry that the subject feels at the time of the consultation. It is an indicator of transient changes in anxiety caused by therapeutic or aversive situations.
- The Anxiety-Trait Scale (STAI-Y B) assesses the feelings of apprehension, tension, nervousness and worry that the subject usually experiences. This scale is intended to identify anxiety as a stable disposition.

The patients' treatment anxiety and condition will be assessed the day before the coronary angiography. The cardiology department's nurse will give the two questionnaires to the patient, who may ask the nurse or the department's physician if he or she has any difficulty in filling them out.
State anxiety will be measured again the next day using the STAI-Y A, just after the patient has been placed on the coronary angiography table, before the coronary angiography is performed. The questionnaire will be handed out by the coronary angiography IDE, who will be available to the patient if he/she encounters difficulties in filling it out. The coronary angiography team will be blinded to the patient's group (with or without hypnosis) and will therefore not be able to influence the answers to the questionnaire, nor the patient's condition in general.

6.2. Secondary endpoints

Pain assessment:
Assessed with a visual analog scale (VAS)
- ➔ During the installation of the patient on the coronary angiography table, by the nurse of the coronary angiography tray
- ➔ At the end of the procedure, by the NURSE of the coronary angiography platform
- ➔ In the "post-coronary" room, by the room's nurse, about 5 minutes after the end of the procedure
- ➔ After the patient's return to the cardiology department, by the department's nurse, approximately 30 minutes after the end of the procedure.

Heart rate and blood pressure:
Heart rate and blood pressure will be measured non-invasively:
- on admission of the patient to the cardiology department the day before the coronary angiography by the department's nurse,
- in the cardiology department on the day of the coronary angiography by the department's nurse, before transfer to the examination room,
- on arrival in the coronary angiography room by the room's nurse,
- at the end of the coronary angiography by the NURSE of the room (in the "post-coronary angiography" room),
- and in the cardiology department, upon the patient's return, by the department's nurse.

In addition, during the coronary angiography procedure, heart rate and blood pressure are continuously monitored invasively. Mean, minimum and maximum values will be collected for the study.

Arteriography operator comfort:
Evaluated using a 5-point Likert scale (1: worst comfort, 5: best possible comfort), collected from the cardiologist at the end of the coronary angiography, by the NURSE of the coronary angiography platform

Dose of sedatives, analgesics and local anesthetics administered during coronary angiography:
Retrospective collection in the patient file.

Occurrence of major or minor complications:
Major Complications:
- Deaths
- Stroke
- Tamponade
- Hemorrhagic shock
- Anaphylactic shock to contrast medium
- Ventricular tachycardia or ventricular fibrillation

- Severe bradycardia

Minor complication:

- Vagal discomfort
- Hematoma at the puncture site
- Skin allergy

Patient views of hypnosis:

"Do you think hypnosis is a technique that works, in general?
"Do you think hypnosis works for you?

7. PROCESS OF THE RESEARCH

7.1. Research schedule

Start of inclusions: April 2016
Inclusion period: 1 year
Duration of participation of each patient: 1 month
Total duration of research: 18 months (including data analysis and final report)

7.2. Summary table of patient follow-up

	Pre-inclusion (the day before the intervention) j-1	Inclusion (on the day of the procedure, in the room) J0	In the pre-catheterization room J0	In the catheterization room J0	In the post-catheterization room J0	In the room J0	24-hour visit J+1	1 month call J+30
Patient information	X							
Non-invasive BP AND HR measurement	X	X	X		X	X	X	
Measurement of BP AND invasive HR				X				
EVA	X	X	X	X	X	X	X	
Spielberger TRAIT questionnaire (20 questions)	X							
Spielberger STATE Questionnaire (20 questions)	X		X					
Major Complications				X	X	X	X	
Minor Complications				X	X	X	X	
Use of Hypnovel				X				
Perfalgan use				X				
Use of subcutaneous xylocaine				X				
Likert Patient Satisfaction Scale from 1 to 5								X

Patient's views on hypnosis	X							X
Likert Cardiologist Satisfaction Scale 1 to 5					X			
Question to cardiologist: Do you think the patient benefited from a hypnosis session?					X			

7.3. PRE-INCLUSION VISIT (D-1)

During the pre-inclusion visit, the day before the scheduled coronary angiography and before any research-related examination, the cardiologist will offer the patient to participate in this research and inform him or her:

-the objective, the nature of the constraints,

-of the computerized treatment of the data concerning him which will be collected during this research and also specifies to him his rights of access, opposition and rectification to these data.

The cardiologist checks the inclusion and exclusion criteria.

An information note and a no objection form will be given to the patient.

The nurse of the service (having benefited from a specific training within the framework of this study) will be in charge of:

- record hemodynamic parameters (blood pressure and heart rate)
-Assess the pain with a self-evaluation scale VAS (Visual Analog Scale),
- Give the patient the Spielberger State and Trait Anxiety Inventory (STAI-Y A and B) to complete in its entirety (40 questions).

7.4. INCLUSION VISIT (D0)

On the morning before coronary angiography, in the cardiology department, no-objection forms are collected from pre-included patients.

A unique inclusion number is assigned to the patient and socio-demographic information as well as the patient's opinions about hypnosis (see 7.2) are collected by the department's nurse.

A random draw is performed to assign each patient to one of two groups (with or without hypnosis). The result of the randomization will be communicated to the patient and the hypnotherapist, but not to the cardiologists.

For patients in the "with hypnosis" group, the hypnotherapist performs the hypnosis session in the patient's bed. Before starting the session, the hypnotherapist will explain to the patient what hypnosis is and what the session will consist of. The patient will be advised not to reveal his or her group to the staff of the department and the coronary angiography room. The session will last an average of 15 minutes and during the hypnosis session, post-hypnotic suggestions of self-hypnosis in the coronary room will be made. The hypnosis session will be the same for all selected patients.

In the coronary angiography room, the nurse welcoming the patient and trained for the study will perform in order:

- taking hemodynamic parameters (blood pressure, heart rate)
- measurement of the pain scale by the VAS
- Spielberger questionnaire STAI-Y A.

At the end of tabletop coronary angiography, the nurse does in order:

- monitoring of invasive hemodynamic parameters (blood pressure, heart rate)
- measurement of the pain scale by the VAS.
- Likert satisfaction scale (from 1 to 5), collected from the operator concerning his comfort in performing the procedure, and the operator's feeling (do you think the patient had a YES or NO session)

In the post-coronary room, the nurse does in order:

-Measurement of hemodynamic parameters (blood pressure, heart rate)
-measurement of the pain scale by the VAS
- notes minor complications
And at the same time, the cardiologist notes the major complications

Back on the ward, the NURSE does in order:
- taking hemodynamic parameters (blood pressure, heart rate)
- measurement of the pain scale by the VAS
- monitoring for the development of major or minor complications

7.5. FOLLOW-UP VISIT / END OF STUDY (D30 TO D40)

Telephone call between D30 and D40:
Upon return home, between D30 and D40, a phone call will be made to the patient and he/she will be asked the following questions:
- "On a scale of 1 to 5 (1 the worst, 5 the best), how satisfied are you with your management for coronary angiography?"
- Do you think hypnosis is a technique that works, in general?
- Do you think hypnosis works for you?
This call will also look for possible late-onset adverse events related to the research.

7.6. Specific monitoring procedures

The realization of the hypnosis session and the collection of data related to the study do not lengthen either the duration of the intervention or the duration of the hospitalization. The only constraint for the patients is the completion of the STAI-Y A anxiety questionnaire (about 10 minutes) on two occasions during hospitalization, and then the response to a telephone interview of about 10 minutes, 30 to 40 days after the intervention.

7.7. Rules for stopping the search

Reasons for patient discharge from the study will be as follows:

False inclusion: discovery after inclusion (before or after the intervention) of a non-inclusion criterion

-Withdrawal of patient consent

-Failure to perform coronary angiography

In the event of premature termination, exclusion, loss of sight, withdrawal of consent, abandonment or major deviations, the patient will be returned to his or her usual care pathway.
The end of the research is the last phone call to the last patient included in the study.

8. MANAGEMENT OF SERIOUS INDIRECT EVENTS

Serious adverse effects and events of medicines or medical devices will be reported to the regional pharmacovigilance center and the local materialovigilance correspondent respectively, according to the procedures in force in the establishment.

9. STATISTICAL ASPECTS

9.1. Calculation of the number of patients needed = sample size

The literature allows us to estimate an expected STAI-Y A score of 50 (standard deviation 10) for the control group and a clinically relevant difference of 5 points or more between the two groups [26, 27], it is necessary to include 85 patients per group, i.e. 170 in total (alpha risk 5%, beta risk 10%).

9.2. STATISTICAL METHODS USED

The primary analysis will consist of:

1. Description of the socio-demographic and clinical characteristics of the sample
2. Verification of the inclusion criteria and the representativeness of the final sample,
3. Comparison of the mean anxiety scores (STAI-Y A) between the two groups using a Student's t-test. For this analysis, a possible investigator effect (hypnotherapist) and a possible operator effect (cardiologist) will be sought. An adjustment on the trait anxiety level (STAI-Y B) will be performed if it is not homogeneous in the two groups.
4. Comparison of secondary endpoints between the two groups: pain before and during coronary angiography (VAS), hemodynamic parameters: blood pressure and heart rate before and during coronary arteriography, operator comfort (5-point Likert scale) using Student's t-tests; use of sedatives, analgesics, and local anesthetic (yes/no), occurrence of major (yes/no) or minor (yes/no) complications using Fischer exact tests.

No intermediate analysis will be performed.
The risk α is set at 5%.
The analysis will be performed on an intention-to-treat basis.

According to the rules for using the STAI-Y (Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press.), the scores of patients who failed to respond to one or two items will be imputed based on responses to the remaining items (imputed score = calculated score * total number of items / number of items completed). Data from patients who missed more than two STAI-Y items will not be used for the main analysis, but their characteristics will be compared with those of other patients.

A detailed analysis plan will be defined and will be validated by the study's scientific board. Subsequent modifications will have to be made before the database is unblinded and will be systematically validated by the scientific council.

10. OVERSIGHT OF RESEARCH

A steering committee will consist of the clinical initiators of the project, the biostatistician in charge of the project, and representatives of the promoter.
He will define the general organization and the course of the research and will coordinate the information. He will initially determine the methodology and will decide during the course of the research what to do in unforeseen cases, and will monitor the progress of the research, particularly in terms of tolerance and adverse events.

11. ACCESS RIGHTS TO SOURCE DATA AND DOCUMENTS

11.1. Data access

The manager is responsible for obtaining the agreement of all parties involved in the research to ensure direct access to all research locations, source data, source documents and reports for quality control and audit purposes.
The persons directing and supervising the research will make the documents and individual data strictly necessary for the monitoring, quality control and auditing of the research available to the persons having access to these documents in accordance with the legal and regulatory provisions in force.

11.2. Source data

Any original document or object that proves the existence or accuracy of a data or fact recorded during the research is defined as a source document.

It is the patient's file concerning his stay in cardiology and the coronary angiography, as well as the data from the Cardioreport® software, a computerized technical file used for the coronary angiography.

11.3. Data privacy

In accordance with the legislative provisions in force, the persons having direct access to the source data will take all the necessary precautions to ensure the confidentiality of the information relating to the research, to the persons who take part in it and in particular as regards their identity as well as the results obtained. These persons, as well as the persons who direct and supervise the research, are subject to professional secrecy.

During the research or at its conclusion, the data collected on the persons who lend themselves to it and transmitted to the manager by the persons who direct and supervise the research (or any other specialized actors) will be coded. Under no circumstances should the names of the persons concerned or their addresses be shown in clear text.

Patient coding rule: an identifying number corresponding to the chronological order of inclusion of the patient in the study will be assigned at inclusion. .
This code will be the only information that will appear on the observation book (CRF) and will allow the CRF to be linked to the patient afterwards.
The person in charge of the research is also required to code the patient data on all the documents that he/she may have in his/her possession (reports of imaging or biological examinations, etc.) that are attached to the CRF.

The manager will ensure that each person who takes part in the research has been informed of the access to individual data concerning him or her and strictly necessary for the quality control of the research.

12. QUALITY CONTROL AND ASSURANCE

12.1. Instructions for data collection

A paper CRF will be created for each patient. All information required by the protocol must be provided in the CRF and an explanation must be provided for any missing data. It should include the data needed to confirm compliance with the protocol and all data needed for statistical analysis, and to identify major deviations from the protocol. Data should be collected as they are obtained, and transcribed into these notebooks in a neat and legible manner.

Erroneous data found on the observation books will be clearly crossed out and the new data will be copied, next to the crossed out information, accompanied by initials, date and possibly a justification by the person directing and supervising the research or the authorized person who made the correction.

The person(s) responsible for filling in the CRFs (investigator, CRA, etc.) must be defined and is/are identified in the delegation of responsibilities table for each center (kept in the investigator's folder).

12.2. Research follow-up

The research will be monitored by a clinical research technician. He/she will be responsible, along with the person directing and monitoring the research, for:

- research logistics and monitoring,
- reporting on its progress,
- Checking that the observation book is up to date (requesting additional information, corrections, etc.),
- the sending of the samples.

He/she will work in accordance with standard operating procedures, in collaboration with the Clinical Research Associate delegated by the Manager.

12.3. Quality control

A clinical research officer mandated by the manager visits each center on a regular basis, when the research is set up, once or several times during the research, depending on the rate of inclusion, and at the end of the research. During these visits, the following elements will be reviewed:

- compliance with the research protocol, the procedures defined therein and the regulatory texts in force,
- quality of data collected in the observation book: accuracy, missing data, consistency of data with source documents (medical records, appointment books, original laboratory results, etc.),

A written monitoring report will be prepared for each visit.

12.4. Data management

Data processing will be carried out under the responsibility of the Clinical Research Support Platform of the CHR Metz-Thionville.
The data will be entered and proofread in an MS ACCESS® input mask.

The data validation and freezing processes will be carried out according to the procedures in force at the Clinical Research Support Platform of the CHR Metz-Thionville.

12.5. Audit and inspection

An audit may be carried out at any time by persons mandated by the manager and independent of those responsible for the research. The objective is to ensure the quality of the research, the validity of its results and the respect of the law and the regulations in force.

Persons conducting and supervising the research agree to comply with the requirements of the manager and the appropriate authority with respect to an audit or inspection of the research.

The audit may be applied to all stages of the research, from protocol development to publication of results and classification of data used or generated in the research.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Compliance with reference texts

The techniques and methods used during this research are usually carried out, and it may fall within the scope of **research aimed at evaluating routine care** as defined by law n°2004-806 of August 9, 2004 (article L1121-1, 2° paragraph and article R1121-3 of the public health code).

The manager and the person(s) directing and supervising the research undertake to ensure that this research is carried out in accordance with the law n°2004-806 of August 9, 2004, as well as in accordance with Good Clinical Practice (I.C.H. version 4 of ^{er}May 1, 1996) and the Declaration of Helsinki (which can be found in its integral version on the site http://www.wma.net/en/30publications/10policies/b3/).

The research will be conducted in accordance with this protocol. Except in emergency situations requiring specific therapeutic procedures, the person(s) conducting and supervising the research agrees to comply with the protocol in all respects.

This research has received the favorable opinion of the Comité de Protection des Personnes (CPP) of *name of the CPP*. This research is covered by the civil liability insurance of *name of the institution responsible for the care.*

The data recorded on the occasion of this research are the subject of a computerized treatment in the *name of the structure responsible for the treatment of the data* in the respect of the law n°78-17 of January 6, 1978 relating to data processing, the files and freedoms modified by the law 2004-801 of August 6, 2004. The *name of the manager* will send a request for an opinion to the Advisory Committee on Information Processing in Health Research (CCTIRS) and a request for authorization to the National Commission for Information Technology and Civil Liberties (CNIL).

This search is recorded on http://clinicaltrials.gov/.

13.2. Amendment to the protocol

Any substantial modification, i.e. any modification likely to have a significant impact on the protection of individuals, on the conditions of validity and on the results of the research, on the interpretation of the scientific documents that support the conduct of the research or on the methods of conducting the research, is the subject of a written amendment that is submitted to the manager and to the Centre de Méthodologie et de Gestion des données, if applicable, and, prior to its implementation, must obtain a favourable opinion from the CPP.

Non-substantive changes, i.e., those that do not have a significant impact on any aspect of the research, are communicated to the PPC for information purposes.

All amendments are validated by the manager, and by all the research stakeholders concerned by the amendment, before submission to the PPC. This validation may require a meeting of the SC and/or the ISC.

All amendments to the protocol must be made known to all health professionals participating in the research and who agree to abide by its content.

14. RETENTION OF RESEARCH DOCUMENTS AND DATA

The following documents related to this research are archived in accordance with Good Clinical Practice:

- By physician investigators:
  - ***for a period of 15 years following the end of the research***
    - The protocol and any amendments to the protocol
    - Observation books (copies)
    - Source records of participants who have signed a consent
    - All other documents and correspondence related to the research
  - ***for a period of 30 years following the end of the research***
    - Original signed informed consents from participants

  All of these documents are the responsibility of the investigator for the duration of the regulatory archiving period.

- By Manager:
  - ***for a period of 15 years following the end of the research (***
    - The protocol and any amendments to the protocol
    - The original observation books
    - All other documents and correspondence related to the research
  - ***for a period of 30 years following the end of the research***
    - A copy of the signed informed consents of the participants
    - Documents related to serious adverse events

All these documents are under the responsibility of the manager during the regulatory archiving period.

No removal or destruction can be carried out without the manager's agreement. At the end of the regulatory archiving period, the promoter will be consulted for destruction. All data, documents and reports may be subject to audit or inspection.

15. PUBLICATION RULES

15.1. Scientific communications

The analysis of the data provided by the investigating centers is carried out by the Clinical Research Support Platform of the CHR Metz-Thionville. This analysis gives rise to a written report which is submitted to the promoter, who will transmit it to the Committee for the Protection of Individuals and to the competent authority.

Any written or oral communication of the results of the research must have the prior approval of the coordinating investigator and, if applicable, any committee established for the research.

The publication of the main results mentions the name of the sponsor, all the investigators who included or followed patients in the research, the methodologists, biostatisticians and data managers who participated in the research, the members of the committee(s) set up for the research and the source of funding. The international rules for writing and publishing (*The Uniform Requirements for Manuscripts* of the ICMJE, April 2010) will be taken into account.

The CHR Metz-Thionville is the owner of the data and no use or transmission to a third party may be made without its prior agreement.

The CHR Metz-Thionville must be mentioned as the promoter of the biomedical research and as a financial supporter if applicable.

15.2. Communication of results to patients

In accordance with the law n°2002-303 of March 4, 2002, patients are informed, at their request, of the overall results of the research.

15.3. Transfer of data

The collection and management of the data are ensured by *name of the structure*. The conditions of transfer of all or part of the research database are decided by the research manager and are the subject of a written contract.

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