Clinique CHC MONTLÉGIA
CLINICAL TRIAL CENTER NEUROLOGY

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING ONLY MINIMAL RISKS AND CONSTRAINTS

EMAIL

Evaluation of the predictive value of **M**icroemboli detected by robotic transcranial doppler for the occurrence of an **A**cute **I**schemic stroke or **L**eft ventricular thrombus in STEMI patients with left ventricular dysfunction

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PROTOCOL SIGNATURE PAGE

Study title and acronym : EMAIL
Evaluation of the predictive value of microemboli detected by robotic transcranial doppler for the occurrence of an acute ischemic stroke or left ventricular thrombus in STEMI patients with left ventricular dysfunction

Research code :

Protocol version no. *1.1* dated *15 May 2024*

This protocol has been read and approved on the date noted below.

Both parties undertake to conduct the research in accordance with the protocol, good clinical practice and the legislative and regulatory provisions in force.

FOR THE PROMOTER :

Dr François Delvoye — Date :
Neurology Department — Signature :
CHC MontLegia

***COORDINATING/PRINCIPAL* INVESTIGATOR :**

Dr Philippe Desfontaines — Date :
Neurology Department — Signature :
CHC MontLegia

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Abbreviations

ACC: American College of Cardiology

AF: Atrial Fibrillation

AHA: American Heart Association

AIS: Acute Ischemic Stroke

ASPECT: Alberta Stroke Program Early CT Score

CAD: Carotid Artery Disease

CMR: Cardiac Magnetic Resonance Imaging

DOAC: Direct Oral Anti-Coagulant

DW: Diffusion-weighted

ESUS: Embolic Stroke of Undetermined Source

FLAIR: FLuid Attenuated Inversion Recovery

PFO: Patent Foramen Ovale

HF: Heart Failure

ICU: Intensive Care Unit

LVD: Left Ventricular Dysfunction

LVT: Left Ventricular Thrombus

MES: Micro Embolic Signals

MI: Myocardial Infarction

MoCA: Montreal Cognitive Assesment

MRI/IRM: Magnetic Resonance Imaging

mRS: modified Rankin Scale/ score de Rankin Modifié

NIHSS: National Institutes of Health Stroke Scale

OR: Odds Ratio

PCI: Percutaneous Coronary Intervention

SAH: SubArachnoid Hemorrhage

STEMI: ST Elevation Myocardial Infarction

TCD: Trans-Cranial Doppler

TTE : Trans-Thoracic Echography

Synopsis

Title of research	Evaluation of the predictive value of microemboli detected by robotic transcranial doppler for the occurrence of an acute ischemic stroke or left ventricular thrombus in STEMI patients with left ventricular dysfunction
Acronym	**EMAIL**
Promoter	François Delvoye
Coordinating investigator	Philippe Desfontaines
Number of centers	3
Justification for the research	We speculate that detection of microembolic signals (MES) with trans-cranial doppler (TCD) could help to resolve the underdiagnosis of left ventricular thrombus (LVT) after ST-segment-elevation myocardial infarction followed by left ventricular dysfunction (LVD) and could help to better define a patients group at high risk of embolic acute ischemic stroke (AIS) due to LVT after STEMI. MES detection with TCD monitoring has become a broadly used technique with a high sensitivity and specificity (of 90% and above). MES detection is already used as a prognostic factor in a wide range of conditions. For example, it has been related to new silent AIS on diffusion-weighted magnetic resonance imaging (DWI-MRI) after pulmonary vein isolation and is shown to be more prevalent in cardiac catheterization. MES have been related to segmental left ventricular (LV) hypokinesis and have been shown to be more prevalent in patients with LVD presenting with an AIS in small retrospective series.
Objective and primary endpoint	<u>Objective</u> To define a correlation between the number of MES detected and the risk of occurrence of an AIS at 2 years or a LVT at 6 weeks in patients suffering from post-STEMI LVD. <u>Endpoint</u> Demonstration of a correlation between the number of MES detected and the 2-year risk of AIS or the occurrence of a LVT at 6 weeks in patients with post-STEMI LVD
Objectives and secondary endpoints	<u>Objectives</u> - To define a correlation between the number of MES detected and the secondary prevention treatment (single anti-aggregation, double anti-aggregation, anti-coagulation) in patients suffering from post-STEMI LVD - To establish a correlation between changes in the number of MES detected and changes in the treatment given (single anti-aggregation, double anti-aggregation, anti-coagulation) in patients suffering from post-STEMI LVD

	- To define a correlation between the number of MES and the grade of Heart failure according to the ACCF/AHA Heart Failure classification - To define a correlation between the number of MES detected and the risk of occurrence of an AIS at 2 years in patients suffering from LVD, classified by subgroup of cardiac decompensation according to the ACC/FAHA Heart Failure classification - Creation of a large, prospective follow-up database of patients suffering from LVD <u>Endpoints</u> - Demonstration of a correlation between the number of MES detected and the treatment given (single anti-aggregation, double anti-aggregation, anti-coagulation) in patients suffering from LVD - Demonstration of a correlation between the variation in the number of MES detected and the modification of the treatment administered (single anti-aggregation, double anti-aggregation, anti-coagulation) in patients suffering from LVD - Demonstration of a correlation between the number of MES and the LVD rate according to the ACCF/AHA Heart Failure classification - Demonstration of a correlation between the number of MES detected and the risk of occurrence of an AIS at 2 years or LVT at 6 weeks in patients suffering from LVD, classified by subgroup of cardiac decompensation according to the ACCF/AHA Heart Failure classification. - Creation of a large multicentric prospective follow-up database of patients suffering from LVD, whether symptomatic or not
Experimental design	Prospective, non-randomized, multicentric, interventional study in patients with proven post-STEMI LVD. Evaluation of the predictive value of MES for the occurrence of an AIS in LVD
Population concerned	Patients aged 18 or over with proven post-STEMI LVD within 72 hours of hospitalization for acute STEMI
Eligibility criteria	Inclusion criteria: - Patient aged 18 or over - Patient with proven post-STEMI LVD within 72 hours of hospitalization for acute STEMI - Ejection fraction less than 35% - Express consent to participate in the study - Member or beneficiary of a social security scheme Exclusion criteria: - Patient with known carotid stenosis greater than 50%. - Patient with a history of AIS - Patient with AF - Patient with mechanical valve - Pregnant or breast-feeding women - History of cardiorespiratory arrest - Patient benefiting from a legal protection measure - Life expectancy of <6 months

	Secondary exclusion criteria: - Withdrawal of consent to participate in the study
Trial procedures	- Assessment of the number of MES using a standardized detection protocol, carried out at inclusion, 6 weeks after a STEMI and within two weeks of a change in anti-thrombotic treatment. - Clinical evaluation at 1 year and 2 years
Practical conduct of the trial	Follow-up data (vital status and occurrence of an AIS) will be collected from the patient him/herself or, failing that, from his/her relatives or the caregivers looking after him/her at the time of the follow-up visits. These visits will be conducted by phone or face-to-face by one of the investigators, at 1 year and 2 years (+/- 15 days) following inclusion.
Number of patients	We estimate the number of patients at 116
Statistical method	Comparability to baseline between the experimental arm and the control arm will be assessed using a Student's t-test (or Mann-Whitney test if necessary) for continuous parameters and a Chi^2 test (or Fisher's exact test if necessary) for qualitative parameters. MES will be compared between patients with and without AIS using Student or Mann-Whitney tests depending on the distributions. The variables most strongly associated ($P < 0.20$) with the incidence rate of stroke recurrence will be included in a Cox proportional regression model. The MES will be correlated with the AIS using graphical representations and the calculation of Pearson or Spearman correlation coefficients (and tests).
Provisional timetable	Duration of inclusion period : 1 year Duration of participation for each subject : 2 years Total duration of the study : 3 years

EMAIL

Evaluation of the predictive value of microemboli detected by robotic transcranial doppler for the occurrence of an acute ischemic stroke or left ventricular thrombus in ST-segment-elevation myocardial infarction patients with left ventricular dysfunction

Introduction - background

Acute ischemic stroke (AIS) is an infrequent yet severe complication of acute myocardial infarction (MI). AIS burdens around 0.5% of MI patients within 1 month and 2.1 to 3 % within a year after an acute MI with a doubled 1-year mortality compared with those not complicated with stroke[1].

Left ventricular thrombus (LVT) after ST-segment-elevation MI (STEMI) are considered the prevailing cause of MI-associated AIS, resulting from LV regional wall akinesia and dyskinesia leading to blood stasis as well as inflammatory changes and hypercoagulability during acute MI[2]. Other causes of post-STEMI AIS include atrial fibrillation (AF), iatrogenic percutaneous coronary intervention (PCI) related stroke and a general state of hypercoagulability in the post-MI phase.

The incidence of LVT after MI treated with PCI has been recorded at 15% in patients with STEMI and more than 25% in anterior STEMI with LVD[3-5].

Two unresolved issues hinder the optimal patient selection for anticoagulant therapy in STEMI patients at risk for embolic AIS due to LVT:

1. Underdiagnosis of LVT: transthoracic echocardiogram (TTE) is now commonly used for screening, but this technique is limited by low sensitivity for LVT detection. When compared to more sensitive, but less accessible techniques like cardiac magnetic resonance imaging (CMR), only a quarter of all LVT are detected by TTE, leading to important underdiagnosis of this condition[5].
2. Inability to clearly define a high-risk group for embolic AIS due to LVT. For the minority of STEMI patients where LVT is diagnosed, expert consensus papers recommend oral anticoagulant therapy. But for the remainder of the STEMI patients, the large majority where no LVT is diagnosed, recommendations are less clear. Since routine anticoagulation in this group is contraindicated, experts suggest a patient tailored approach with consideration of the pros and cons of prophylactic anticoagulant therapy, depending on a multitude of factors[6-7].

Microembolic signals (MES) detection with trans-cranial doppler (TCD) monitoring has become a broadly used technique with a high sensitivity and specificity (of 90% and above)[8].

MES detection is already used as a prognostic factor in a wide range of conditions. It has been related to new silent AIS on diffusion-weighted magnetic resonance imaging (DW-MRI) after pulmonary vein isolation[9] and is shown to be more prevalent in cardiac catheterization[10].

Moreover, MES have been related to segmental left ventricular (LV) hypokinesis[11] and have been shown to be more prevalent in patients with left ventricular dysfunction (LVD) presenting with an AIS in small retrospective series[12].

In MI patients, MES have been correlated with stroke, LVD and LVT as detected with TTE[13].

In view of these data, we speculate that detection of MES with TCD could help to resolve the underdiagnosis of LVT and could help to better define a patient group at high risk of embolic stroke due to LVT after STEMI.

The recent advent of robotic TCD has lowered the threshold for this technique to be routinely applied to an all-comer STEMI population, due to ease of use and lower personnel costs.

We thus propose to investigate the prognostic value of MES as detected by robotic TCD for the occurrence of AIS post-STEMI.

Research objectives

Hypothesis tested

MES detected by robotic TCD using a standardized protocol are prognostic for the occurrence of an AIS or LVT in patients with a diagnosed LVD (defined as an ejection fraction of less than 35%) in the acute phase of a STEMI. The number of MES is modified by changes in anti-thrombotic treatment (from double to single anti-aggregation, from anti-platelet to anti-coagulant, and vice versa).

Main objective

To define a correlation between the number of MES detected and the risk of occurrence of an AIS at 2 years or a LVT at 6 weeks in patients suffering from post-STEMI LVD.

Secondary objectives

- To define a correlation between the number of MES detected and the treatment administered (single anti-aggregation, double anti-aggregation, anti-coagulation) in patients suffering from post-STEMI LVD.
- To establish a correlation between changes in the number of MES detected and changes in the treatment given (single anti-aggregation, double anti-aggregation, anti-coagulation) in patients suffering from post-STEMI LVD.
- To define a correlation between the number of MES and the grade of Heart failure according to the ACCF/AHA Heart Failure classification.
- To define a correlation between the number of MES detected and the risk of occurrence of an AIS at 2 years in patients suffering from LVD, classified by subgroup of cardiac decompensation according to the ACCF/AHA Heart Failure classification.
- Creation of a large, prospective follow-up database of patients suffering from LVD.

Assessment criteria

Primary endpoint

- Demonstration of a correlation between the number of MES detected and the 2-year risk of AIS or the occurrence of a LVT at 6 weeks in patients with post-STEMI LVD.

Secondary endpoints

- Demonstration of a correlation between the number of MES detected and the treatment administered (single anti-aggregation, double anti-aggregation, anti-coagulation) in patients suffering from LVD.
- Demonstration of a correlation between the variation in the number of MES detected and the modification of the treatment administered (single anti-aggregation, double anti-aggregation, anti-coagulation) in patients suffering from LVD.
- Demonstration of a correlation between the number of MES and the LVD rate according to the ACCF/AHA Heart Failure classification.
- Demonstration of a correlation between the number of MES detected and the risk of occurrence of an AIS at 2 years or LVT at 6 weeks in patients suffering from LVD, classified by subgroup of cardiac decompensation according to the ACCF/AHA Heart Failure classification.
- Creation of a large multicentric prospective follow-up database of patients suffering from LVD, whether symptomatic or not.

Clinical evaluation at 1 year and 2 years

Assessment of the number of MES using a standardized detection protocol, carried out at inclusion, 6 weeks after the inclusion and within two weeks of a change in anti-thrombotic treatment.

The classifications used are presented in the appendix.

Follow-up data (vital status and occurrence of an AIS) will be collected from the patient him/herself or, failing that, from his/her relatives or the caregivers looking after him/her at the time of the follow-up visits. These visits will be conducted by telephone or face-to-face by one of the investigators at 1 year and 2 years (+/- 15 days) following inclusion.

Selecting and excluding people from research

Inclusion criteria

Patient aged 18 or over
Patient with proven post-STEMI LVD within 72 hours of hospitalization for acute STEMI
Ejection fraction less than 35%
Express consent to participate in the study
Member or beneficiary of a social security scheme

Exclusion criteria

Patient with known carotid stenosis greater than 50%.
Patient with a history of AIS
Patient with AF
Patient with mechanical valve
Patient benefiting from a legal protection measure
Pregnant or breast-feeding women.
History of cardiorespiratory arrest
Life expectancy of <6 months

Secondary exclusion criteria

Withdrawal of consent to participate in the study

Description of the study

Type of study
This is a prospective, non-randomized, multicentric, interventional study.

Research process
Investigating centers

- CHC MontLegia
- Universitair Ziekenhuis Brussel (UZBrussel)
- Academic Erasme hospital (ULB)

Recruitment procedures
The target patients for this study are all patients admitted to the investigating centers with post-STEMI LVD, as defined by an ejection fraction of less than 35% on a TTE performed within 72 hours of admission. The inclusion visit must take place within 14 days following the myocardial infarction.

Informing patients and obtaining their consent
Once the inclusion and non-inclusion criteria have been checked, the principal investigator or one of his colleagues (listed on the delegation form) will explain the aims and schedule of the study to the patient, using an information form, and will seek for the patient's consent.

Patient care procedures
If the patient meets the inclusion criteria and agrees to take part in the study, a TCD with MES detection will be performed the day of the inclusion.
Another TCD will be performed at 6 weeks of the inclusion.
They will then receive telephone follow-up at one year, followed by a final visit two years after inclusion, blinded to the results of the TCD.
In the event of an AIS during the study period, the characteristics of the AIS (admission NIHSS, infarcted territory, level of occlusion, volume of AIS assessed by the ASPECT or pc-ASPECT score, etiology according to the TOAST classification) will be recorded in the file.

A change in management as a result of the patient's participation in the study.
The main changes are the introduction of a TCD, as well as the initiation and closure visits, and the telephone visit at one year.

Procedures for study termination and participation in another clinical study
Stopping a patient's participation in research

Patients may withdraw their consent and ask to leave the study at any time for any reason. The data collected during the patient's participation in the study will be kept unless the patient objects.

The investigator may temporarily or permanently discontinue a patient's participation in the study for any reason that is in the best interests of the patient, particularly in the event of adverse events.

In the event of premature discharge, the investigator must document the reasons as fully as possible.

The patient who has withdrawn his consent will be replaced numerically.

If a patient is lost to follow-up, the investigator will make every effort to contact the patient to find out why he/she has left the trial and his/her state of health. The observation book must be completed up to the last visit made.

Follow-up of patients who have left the study

If a patient is discharged from the study programme, this will in no way change the way in which the disease is managed.

Permanent or temporary cessation of research

The sponsor may suspend or terminate the research prematurely, in particular:

- In the event of new information requiring a reassessment of the benefit/risk ratio,

- If it turns out that the inclusion targets are unlikely to be met.

In the event of premature termination of the research, the decision and justification will be sent by the promoter within 15 days to the Ethical Board. The investigator will also be notified.

Participation in another study

Patient participation in the study does not preclude participation in other clinical studies. There is no exclusion period.

Data collection

The confidentiality and anonymization of study data will be ensured by the law of July 30, 2018 relating to the protection of privacy, the law of August 22, 2002 relating to patient rights and GDPR. Data will be collected in an electronic case report form (e-CRF) using Datacapt© software, which offers secure data hosting and is ISO/IEC 27001 certified. All data will be entered into the e-CRF by the study investigation team. A unique identification number will be allocated to each patient, allowing data to be pseudonymised. For each patient, directly identifying data will not be entered into the e-CRF (i.e. only the inclusion number, inclusion date, first letter of the surname, first letter of the first name, month and year of birth will be collected). A correspondence file making the link between the pseudonymised database and the identity of the patients will be kept in the investigator's file.

The e-CRF will be created, tested and validated before data capture begins. The data required to meet the primary and secondary endpoints will be monitored at regular intervals throughout the trial. Data will be monitored using predefined data management rules and queries will be automatically generated. Every reasonable effort should be made to complete the data as soon as possible. The principal investigator is responsible for the accuracy and completeness of the data recorded in the case report form. After checking and validation, the database will be frozen and exported for analysis.

Summary table of the progress of the study

Examinations marked S are carried out as part standard of care, and those marked R are added as part of research.

	Inclusion ***D0***	**Visit N°2 (D0 + 6 weeks)**	**Visit N°3 (D0 + one year)**	**Visit N°4**	**Visit N°5** ***(D0 + 2 years)***
How the visit is organised	*Consultation*	*Consultation*	*By phone*	*Consultation (optional)*	*Consultation on site or by phone*
Information	R				
Checking inclusion and non-inclusion criteria	R				
Obtaining consent	R				
TTE	S				
Occurrence of AIS, vital status	S		R	S	R
TCD	R	R		R	R
CMR		S			
File closure					R

* optional, in the month following the change in anti-thrombotic treatment. AIS = Acute Ischemic Stroke; CMR = Cardiac Magnetic Resonance imaging; TCD = Trans-Cranial Doppler; TTE = Trans-Thoracic Echography.

Study timetable

Number of patients expected	116
Inclusion period	1 year
Maximum participation time per patient	2 years
Expected time to response to primary endpoint	2 years
Total duration of the study	3 years

Benefits, risks and constraints for patients taking part in research

Benefits

There is no direct benefit for the patient, and the results of this research will not change patient management in the short term.

Risks

The risk to the patient is minimal, corresponding to the performance of a TCD. Participation in this study will not change the therapeutic decision or the treatment modalities undertaken.
TCD ultrasound does not involve any deterministic or stochastic risk.

Constraints

The only constraints linked to the patient's participation in the study are the need to undergo TCD specifically for research purposes.

Description of the study

Echocardiography and grading of heart failure

TTE will be performed within 72 hours of admission for STEMI.
If this demonstrates an ejection fraction of less than 35%, the patient will be offered inclusion in the study.

Transcranial Doppler ultrasound and quantification of embolic micro-signals

A portable TCD device (Novaguide, NeuraSignal, Los Angeles, USA) will be placed between the lateral edge of the orbit and the ear, above the zygomatic arch. Low-power 2 MHz pulsed wave transducers, 1.7 cm in diameter, will be used with TCD-8 software (version 8.00 K) at a pulse repetition rate of 6,500 Hz and a programmable high-pass filter from 50 to 600 Hz. The transducers will be attached bilaterally to a headset to monitor both middle cerebral arteries at 45-60 mm. All patients will be initially assessed by two independent neurologists for the presence of a temporal acoustic window by TCD. Patients with a temporal window will have a TCD examination for approximately 30 minutes. The investigators will be single-blinded when monitoring the risk stratification of patients. The TCD examination will be performed without perfusion.
To assess the presence and number of MES, the following characteristics will be taken into account according to the consensus on the detection of MES:
- Random occurrence during the cardiac cycle
- Short duration (< 0.1 s)
- High intensity (3 to 9 dB) above the wave spectrum and characteristic audible sound.

We will use the Novaguide device to identify arteries and facilitate the identification of MES (Fig. 1). The monitoring time will be 30 minutes. Automatic detection of MES by Novaguide will be used in combination with visual and audible detection of MES. All tests will be independently reviewed by two blinded investigators to identify MES. The presence or absence of MES will be recorded, as well as the number of MES for each patient.

Statistical analysis

Calculating the number of subjects

Assuming a 20% difference in the occurrence of AIS or LVT in patients with MES compared with those without MES we estimate the number of patients at 116, with a power of 90% and a two-sided alpha risk of 5%.

Description of the statistical analyses used

Choosing the people to be included in the analyses

All patients included will be analyzed.

Descriptive statistics

A descriptive analysis of the data will be carried out. This analysis will include point estimates, numbers and percentages for qualitative variables, mean, standard deviation, median and range for quantitative variables. The normality of continuous variables will be assessed graphically and using a normality test (e.g. Shapiro-Wilk). Missing data for each variable (number and percentage) will be described.

Group comparisons at baseline

Comparability to baseline between the experimental arm and the control arm will be assessed using a Student's t-test (or Mann-Whitney test if necessary) for continuous parameters and a Chi^2 test (or Fisher's exact test if necessary) for qualitative parameters.

Analysis of primary endpoint

- MES will be compared between patients with and without AIS and with or without LVT using Student or Mann-Whitney tests depending on the distributions.
- The relationship between the occurrence of an AIS and the identification of MES (presence or absence and number per patient) during follow-up will be assessed using a univariate analysis of potential confounding factors, such as age, sex, race, hypertension, smoking, obesity, diabetes and dyslipidemia.
- The variables most strongly associated ($P < 0.20$) with the incidence rate of stroke recurrence will be included in a Cox proportional regression model.
- The MES will be correlated with the AIS using graphical representations and the calculation of Pearson or Spearman correlation coefficients (and tests).
- The strength of the association between the number of MES and the occurrence of an AIS will be demonstrated by calculating the Odds Ratio (OR) with their 95% confidence intervals, for all patients and by ACC/AHA Heart Failure classification subgroup.

Analysis of secondary endpoints

The number of MES detected will be correlated with the anti-thrombotic treatment given (single anti-aggregation, double anti-aggregation, anti-coagulation) using graphical representations and the calculation of Pearson or Spearman correlation coefficients (and tests).
The variation in the number of MES detected will be correlated with the change in treatment given (single anti-aggregation, double anti-aggregation, anti-coagulation) using graphical representations and the calculation of Pearson's or Spearman's correlation coefficients (and tests).

The number of MES detected will be correlated with the grade of LVD according to the ACC/AHA Heart Failure classification using graphical representations and calculation of Pearson's or Spearman's correlation coefficients (and test).
The number of MES detected will be correlated with the risk of occurrence of an AIS at 2 years in patients suffering from LVD, classified by sub-group of cardiac decompensation according to the ACC/AHA Heart Failure classification, using graphical representations and calculation of Pearson's or Spearman's correlation coefficients (and test).

Level of statistical significance
Alpha risk set at 5%. A Benjamini-Hochberg correction will be applied to take into account the number of tests performed.

Statistical criteria for discontinuing research
No interim analysis included in the protocol.

How missing, unused or invalid data are taken into account
Analyses will be carried out on complete cases. Missing data will not be replaced.

Managing changes to the initial statistical plan
Modifications to the initial strategy may be made as the study progresses and will be included in the statistical analysis plan, which will be drawn up just before the database is frozen. Any changes to be made to the statistical analysis plan will be proposed by the study methodologist and validated by consensus with the statistician and the principal investigator.

Safety assessment
- Undesirable events / adverse reactions / incidents must be reported to the various health vigilance circuits applicable to each product or practice concerned (care vigilance, pharmacovigilance, material vigilance, hemovigilance, etc.) in accordance with the ongoing regulations.
-The investigator can either follow the vigilance provisions applicable within his health establishment (by specifying the clinical trial concerned) or report them directly via the national reporting system.
- The sponsor must be informed of any new safety data that could affect the conduct of the research, as well as any errors or misuse, so that corrective measures can be taken if necessary.

Regulatory provisions
CHC MontLegia is the sponsor of this interventional research involving humans, which involves only minimal risks and constraints.

Request for an opinion from the Ethical Board
This research is subject to the opinion of the Ethical Board, without which it cannot begin. The opinion of this committee will be notified to the competent authority by the sponsor before the start of the research, and the summary of the research will be sent to it. The coordinating investigator will inform the sponsor of any proposed changes to the protocol. Any substantial modification to the protocol will be submitted by the research sponsor to the sponsor for its opinion.

Information note and consent form

An information note specifying the information to be provided in accordance with Article 13 of the European Union's General Data Protection Regulation (GDPR) and submitted to the ethical board beforehand, will be explained and given to patients, who may refuse to take part in the research, as specified in the document. Details of the information procedure are given earlier in this protocol.

The information given to patients and their consent must be recorded and dated in the patient's medical file. In the event of refusal to participate, the patient will receive the usual care. Once the research has been completed, the person taking part in the research may be informed of the overall results in the manner specified in the information document. Information relating to the rights of persons taking part in this research (right of access and rectification, right to object to the transmission of data covered by professional secrecy which may be used as part of this research) is included in the information notes.

Commitment to responsibility

The research will be supervised in accordance with the sponsor's standard operating procedures. The research will be carried out in the investigating center and patients will be managed in accordance with the protocol, Good Clinical Practice and current legislation. A copy of the undertaking of responsibility, dated and signed by the investigators, will be given to the sponsor's representative.

Right of access to source data and documents

The sponsor ensures that each person taking part in the research has not objected to access to his/her personal data. Each patient's medical data will only be transmitted to the organization to which the person responsible for the research is attached, or to any person duly authorized by the latter, under conditions guaranteeing confidentiality. Where appropriate, the organization to which the person responsible is attached may request direct access to the medical file in order to verify the procedures and/or data relating to the research, without breaching confidentiality and within the limits authorized by the laws and regulations.

In the event of withdrawal of consent and a request for deletion of the data, the data collected prior to withdrawal of consent may not be deleted and may continue to be processed under the conditions provided for by the research, if deletion of the data is likely to make it impossible or seriously compromise the achievement of the research objectives.

Participants have the right to limit the processing of their personal data.

During the research and at its conclusion, the data collected on the persons involved and transmitted to the sponsor by the investigator (or any other research collaborator) will be coded. Under no circumstances must the names of the persons concerned, their addresses or any other information enabling direct identification appear in clear text. A list of the names of the patients included, with the corresponding patient number, will be kept in the investigator's file and destroyed 15 years after the end of the study.

Conservation of research documents and data

Documents and data relating to this research will be archived by the investigator and the sponsor for a period of 15 years after the end of the research.

This indexed archiving includes:

- Copies of the EB opinion
- Successive versions of the protocol (identified by version number and version date)
- Correspondence with the promoter
- The completed and validated observation booklet for each subject included
- All appendices specific to the study
- The final report on the statistical analysis and quality control of the study (duplicate sent to the sponsor)
- Certificates of any audits carried out in the course of the research
- The database used for the statistical analysis must also be archived by the person responsible for the analysis (on paper or electronically)

Insurance and financing

Insurance

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Financing

This research is granted by the CHC MontLegia innovation fund.

Publication rules and final report

Final report

The final study report will be drawn up and signed by the sponsor and the investigator. A summary of the report will be sent to the ethical board within two years of the end of the study, i.e. at the end of the participation of the last person involved in the research.

Communication and publication of results

No written or oral comment may be made on trials without the joint agreement of the investigator and the sponsor.

CHC MontLegia Hospital, the study promoter, is the owner of the study data and results. No use or transmission to a third party may be made without its prior agreement. Any findings resulting from the trial will automatically become the exclusive property of the sponsor, who may use this information in any way it sees fit.

Communications and publications of the results of the study will be the responsibility of the coordinating investigator, with the agreement of the responsible investigators and the other associated co-authors. They must describe all aspects of the study in an honest and balanced way, without taking into account other interests, particularly non-scientific interests. The co-authors of the publications will be the investigators and clinicians involved (in proportion to their contribution), the methodologist and biostatistician responsible for the study, and the associated researchers (to be defined according to the case). Other members of staff in the clinical research department who played an active role in the design and implementation of the protocol and the drafting of results should also be mentioned. Publication rules will follow the recommendations of the EQUATOR network (https://www.equator-network.org/reporting-guidelines/). CHC MontLegia will be mentioned as the research promoter. It is responsible for the first publication.

Any request to hide results, change or attenuate the content of the final report or publications will be systematically rejected by the sponsor. The investigator will send a copy of the publications to the sponsor.

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Appendices

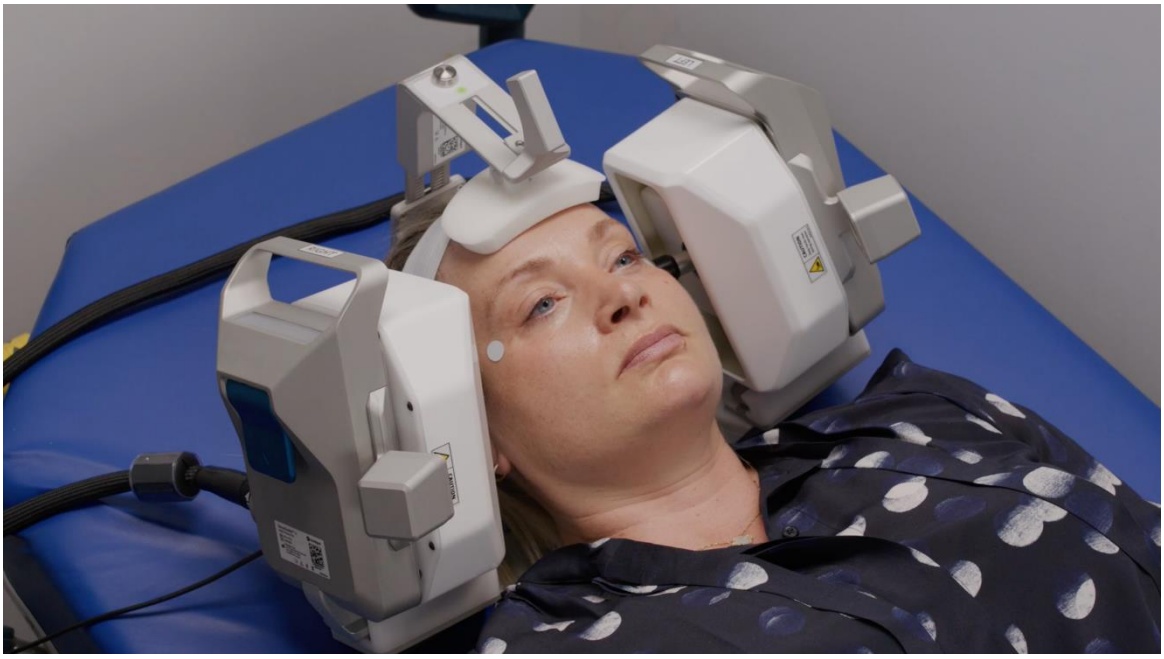


Fig. 1. : NovaGuide setup

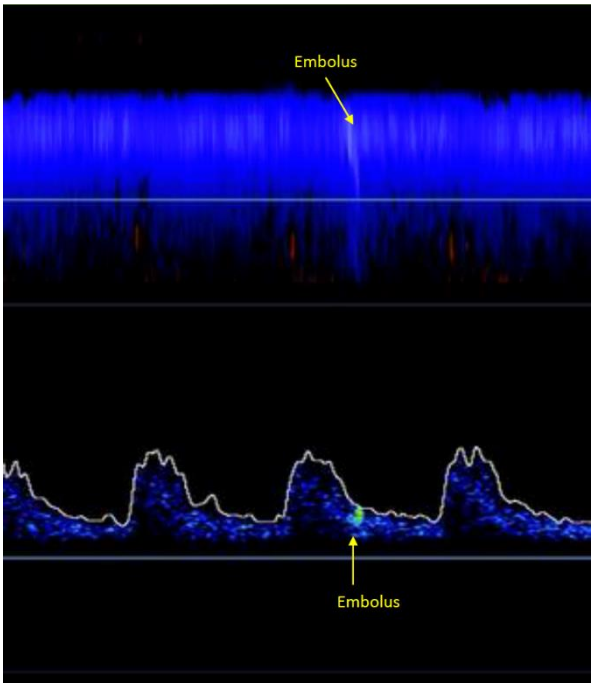


Fig. 2: MES detection with robotic TCD

ACCF/AHA stages of HF	
A	At high risk for HF but without structural heart disease or symptoms of HF
B	Structural heart disease but without signs or symptoms of HF
C	Structural heart disease with prior or current symptoms of HF
D	Refractory HF requiring specialized interventions

Table 1: ACCF/AHA stages of heart failure