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Early point-of-care focused echocardiographic asystole as a predictive factor for absence of return of spontaneous circulatory in out-of-hospital cardiac arrests: a study protocol for a prospective, multicentre observational study

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ABSTRACT

Introduction Management of out-of-hospital cardiac arrests (OHCAs) in France is performed by a particular prehospital system based on medicalisation of mobile intensive care units composed of an emergency physician and a nurse with all the required devices for advanced care. It follows the European recommendations which advocate for the use of early point-of-care focused echocardiography (EPOCE) in the prehospital setting. An ability of EPOCE may be to predict the absence of return of spontaneous circulation (ROSC) in cases of absence of cardiac motion. We thus intended to investigate this predictive value with a prospective multicentre study. This paper describes the study protocol, while the first patients were recruited in December 2018.

Methods ACE is a prospective multicentre (n=8) prognostic study. Briefly, as soon as OHCA is diagnosed and advanced life support (ALS) is initiated, EPOCE will be performed during the automated external defibrillator' analysis period. The physician will assess detectable motion within the heart and reversible causes of OHCA. However, as the prognostic value of absence of cardiac motion is not currently validated, the results of EPOCE will not be used to withdraw ALS, and the decision to withdraw life support will be done following the European Resuscitation Council recommendations during our study.

Analysis The primary endpoint is the positive predictive value of absence of cardiac motion for the absence of final ROSC. The secondary endpoints are predictive characteristics of EPOCE asystole on morbimortality 30 days after OHCA, description of reversible cause and analysis of the EPOCE technique.

Ethics and dissemination ACE was approved by an ethical committee (2018-A01491-54). While ACE is adapted to the French prehospital system, its results will be translatable to other organisations if inter-rater variability is not found.

Strengths and limitations of this study

► The study has a broad inclusion criteria, which would allow extrapolation to rather all out-of-hospital cardiac arrests.
► The study plans to recruit a high number of patients.
► A previous pilot study has demonstrated the feasibility of this protocol.
► Cardiac massage interruption will be monitored in three out of eight centres.
► This is an observational not an interventional study.

Trial registration number NCT03494153.

INTRODUCTION

Out-of-hospital cardiac arrests (OHCAs) are a major cause of mortality in France (between 30 000 and 50 000 cases per year).[1 2] The prognosis is particularly poor, since only 5%–6% of patients will leave the hospital alive with satisfying neurological condition.[2–4] Their management in France is performed by a particular prehospital system based on medicalisation of both ambulance dispatch (SAMU) and mobile intensive care units (SMUR), and follows the European recommendations (cardiac massage, ventilation, cardiac rhythm analysis, drug administration and defibrillation if needed).[1 5] Based on published studies,[6–8] the 2015 European recommendations advocate for the use of point-of-care focused echocardiography (POCE) in the prehospital setting, in particular to identify reversible causes of OHCA.[1 6] Indeed, POCE can reveal various reversible

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causes such as tamponade, massive pulmonary embolism, deep hypovolaemia or suffocating pneumothorax.[6 7] Their identification allows the clinician to better adjust his therapeutic strategy and accordingly might improve the patient's prognosis.

Another ability of POCE is to predict the absence of return of spontaneous circulation (ROSC) at the end of an advanced life support (ALS) procedure in cases of absence of cardiac motion. ROSC was defined as a spontaneous cardiac rhythm accompanied by breathing, coughing, movements or fleeting palpated pulse, according to the recommendations of Utstein registries.[9] Several studies found a strong correlation between absence of cardiac motion and absence of ROSC.[6–8 10 11] This fact deeply impacts extracorporeal circulation indications and organ donation procedures. However, these studies, mainly performed in a hospital setting, included rather small populations and used different cardiac motion definitions and procedures. Furthermore, they cannot be extrapolated to OHCA because of differences in terms of delay, management and environment. In this context, the European Resuscitation Council (ERC) stated in 2015 that, while absence of cardiac motion is highly predictive of death, sensitivity and specificity have not been reported. Thus, usage of this ascertainment to determine premature termination of resuscitation is currently not recommended until publication of a pivotal study.

METHODS AND ANALYSIS
Objectives
The ACE French national trial fits precisely into this bibliographic gap, the uncertainty on the diagnostic value of absence of cardiac motion for the absence of final ROSC. Our objectives are multiple:

► The main objective is to assess the positive predictive value (PPV) of early point-of-care focused echocardiography (EPOCE) asystole for the absence of final ROSC.

► The secondary objectives are the following:

1. Assess the prognostic value of EPOCE asystole (ie, within the first 12 min of ALS initiation) on survival at hospital admission and on morbimortality at day 30 after OHCA (D30).
2. Assess the prognostic performance of EPOCE asystole for the absence of final ROSC.
3. Assess the prognostic value of EPOCE asystole according to timing of initiation after ALS initiation (by 2 min increment).
4. Assess the relationship between EPOCE findings and ECG rhythms.
5. Describe the frequency and typology of reversible causes (tamponade, massive pulmonary embolism, deep hypovolaemia or suffocating pneumothorax) in the context of OHCA.
6. Describe the characteristics of EPOCE: timing and quality assessed by the operator and by an expert committee.
7. Assess the prognostic performance of EPOCE in patients with ventricular tachycardia.
8. Create a multifactorial score with EPOCE combined with other clinical parameters (composite prognostic tool combining myocardial and/or electrical activity, capnography, no/low flow duration, and clinical profile including sex and age) for the absence of final ROSC.
9. Measure the cardiac massage interruption associated with EPOCE realisation by video recording in three centres (Nantes, La Roche-sur-Yon and Bobigny).

Design
ACE was designed as a prospective, multicentre prognostic study. It is based on a rigorous methodology (prospective observational study with a unique protocol), has a high proof-level design and will recruit a large sample of patients (n=624). The Standard Protocol Items: Recommendations for Interventional Trials checklist is shown in the online supplementary file. Recruiting centres include both rural and urban community and university hospitals. This pragmatic approach intends to validate the performance of EPOCE in the prediction of the absence of a final ROSC in cases of absence of cardiac motion in the out-of-hospital setting. If this hypothesis is validated, it will allow for shorter delays before extracorporeal membrane oxygenation (ECMO) or organ donation processes.

Echographic or EPOCE asystole is defined by the complete absence of cardiac motion (coordinated or fibrillation) and the absence of valve movements.

Methods
Patients
The inclusion criteria were all patients >18 years old presenting with an OHCA for whom an EPOCE has been initiated in less than 12 min after ALS initiation.

Non-inclusion criteria include a do not resuscitate order, ROSC prior to EPOCE, ALS not performed by the prehospital team, pregnancy, breastfeeding women and inmates.

Procedures
After verification of inclusion and exclusion criteria, ALS intervention will replace basic life support with an overlap period, as usual (figure 1). ALS will be performed according to the latest ERC regulations, including realisation of an ECG. Once standard ALS interventions are done according to the focused echocardiographic evaluation in life support (FEEL) protocol and ERC recommendations.[4 5] The echography will be performed. The FEEL protocol was designed and evaluated in a prospective observational study using an ALS-compliant focused echocardiography. Briefly, once on the scene, if the patient was in cardiac arrest, cardiopulmonary resuscitation was started, an ECG was performed and a clinical diagnosis was established. A focused echocardiography was then performed. Outcome, defined as survival to admission, was better when cardiac motion was present regardless of
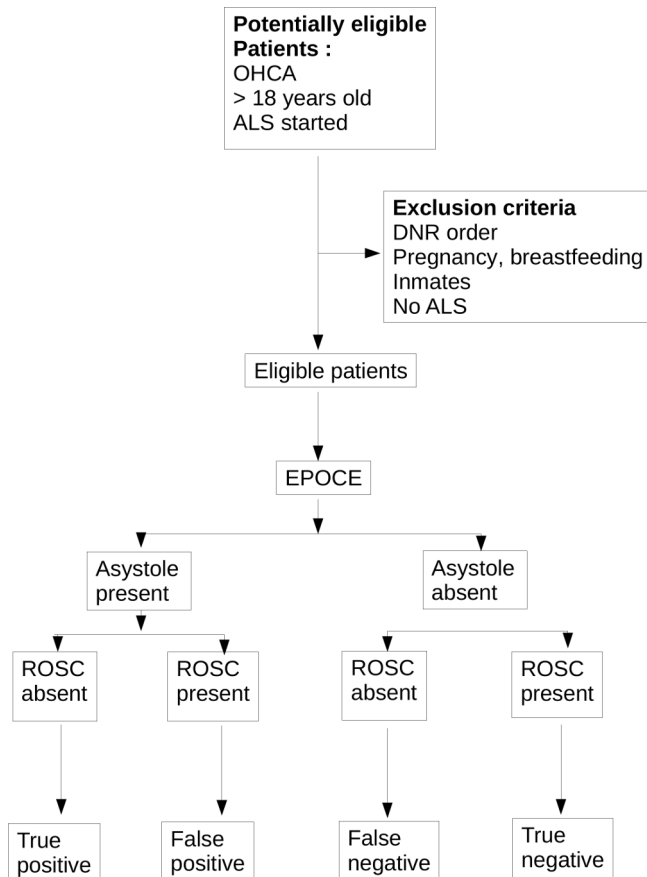
Figure 1 Patient's flow chart in the ACE trial. ALS, advanced life support; DNR, do not resuscitate; EPOCE, early point-of-care focused echocardiography; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.

the initial rhythm. In our study, the physician will perform EPOCE during the defibrillator's analysis period, thus in less than 10 s. It will be done using a phased array probe with a subcostal view. It has to be done as early as possible and always before 12 min after ALS initiation. The physician will observe for cardiac motion or lack thereof and will look for reversible causes. Video clips will be stored in the echographic device and secondarily uploaded in the electronic case report file (eCRF) for random review by an expert committee. The entire ALS procedure will be closely monitored to assess for diagnostic and therapeutic delays (defined as the interval between arrival time on the scene and therapeutic initiations). ALS will be terminated following the ERC rules, and the results of EPOCE will not be used for that purpose. For the study purpose, the presence or absence of ROSC will be assessed after ALS termination. In the case of ROSC, the hospital course (intensive care unit, medicine ward) will be described. At D30, the vital status of all patients will be assessed by either a hospital file consult or a phone call if the patient is still alive. For these patients, autonomy will be assessed using the Glasgow Outcome Scale. These two events (dead or alive and Glasgow Outcome Scale score) define morbimortality. They will be assessed by

the research team of Nantes Hospital. In three centres, the entire resuscitation procedure will be monitored via a mobile video recorder. Video clips will be uploaded and analysed to measure the duration of cardiac massage interruptions.

Endpoints
Primary endpoint
► Predictive prognostic value of EPOCE asystole (ie, within the first 12 min of ALS initiation) on resuscitation failure (absence of ROSC). We have chosen PPV as the primary endpoint because we want to isolate a population without ROSC with EPOCE asystole.

Secondary endpoints
► Predictive prognostic value of EPOCE asystole (ie, within the first 12 min of ALS initiation) on hospital admission and on morbimortality (defined as dead or alive and Glasgow Outcome Scale score) evaluated at 30 days.
► Sensitivity, specificity and negative predictive value (NPV) of EPOCE asystole for the absence of final ROSC.
► Sensitivity, specificity, PPV and NPV of EPOCE asystole for the absence of final ROSC according to their timing of initiation after ALS initiation (by 2 min).
► Association between the ultrasound asystole rate according to the cardiac electrical activity (pulseless activity, asystole, ventricular fibrillation and ventricular tachycardia).
► Description of reversible causes (tamponade, massive pulmonary embolism, deep hypovolaemia or suffocating pneumothorax), diagnostic (time between ALS onset and diagnosis) and therapeutic delays (time between ALS onset and specific therapeutic intervention), and the effectiveness of implemented curative strategies defined by the association with ROSC and 30-day morbimortality.
► Analysis of the EPOCE technique during OHCA resuscitation: duration, whole quality of the video clips assessed by the operator on a predetermined scale (from 0=impossible to 10=excellent) and an expert committee reviewing a 10% random sample.
► Sensitivity, specificity, PPV and NPV of EPOCE asystole to predict ROSC absence in the subgroup of patients with ventricular fibrillation on the ECG.
► Main determinants of death (age, sex, comorbidities, suspected aetiology, no/low flow duration, initial treatment, electrical activity and cardiac motion) associated with the absence of ROSC to determine a score with 100% PPV.
► Measure of duration of cardiac massage interruption in seconds during EPOCE, using a portable video recorder (three centres: Nantes, La Roche-sur-Yon and Bobigny).

Recruiting centres

The recruiting centres will be university hospitals (Nantes, Brest, Tours, Angers and Bobigny) and community hospitals (Saint-Nazaire, La Roche-sur-Yon and Chateaubriant).

Sample size calculation

The principal objective is the PPV of absence of cardiac motion (asystole) for the absence of final ROSC. To specify the width of the CI at ±3% with 95% PPV, 203 patients without cardiac motion are required. Based on 37.5% ultrasound asystole rate,[10] a total of 542 patients are required. Taking into account a +15% attrition rate (incomplete data, too poor quality of the ultrasound for interpretation and so on), the required population will finally be 624 patients.

Recruitment

Chosen prehospital teams were recruited because they are highly skilled in clinical ultrasound and already use this technique in their emergency department. A monthly newsletter will be published with individual and global recruitment trends. Patients will be followed up until D30, and defined gradually as survival without neurological deficit, survival with neurological deficit or death.

Data management

eCRFs will be used via a web-based interface and video clips will be uploaded. All data will be stored in Nantes University Hospital's secured databases. The data management team will be responsible for the entire process. Data will be anonymised with an incremental number assigned to each patient. The final database will be available only to the steering committee. Subjects with missing data for the primary endpoint will not be analysed (+15% subjects in sample size calculation).

Monitoring

Monitoring will be performed both by electronic surveillance of recruitment and data quality. It will be done by the Clinical Research Department of Nantes University Hospital.

Statistical analysis

Sensibility, specificity, PPV, NPV and likelihood ratio of EPOCE asystole on resuscitation failure (absence of ROSC) and on morbimortality will be estimated with 95% CI. Logistic model regression and receiver operating characteristic curve will be estimated to analyse the time of EPOCE initiation that allows the best prognostic performance for the absence of final ROSC. χ^2 and Fisher's test will be used to analyse the association between ultrasound diagnosis and ECG electrical patterns. Reversible causes, diagnostic and therapeutic delays, and the effectiveness of implemented curative strategies will be described. The EPOCE technique during the OHCA resuscitation and the duration and quality of the video clips will be described. χ^2 and Student's t-tests will be used to test the association between the quality and duration of the videos. Prognostic performance of EPOCE to predict ROSC absence in patients with ventricular fibrillation without cardiac motion will be estimated. A multifactorial composite prognostic score associated with the absence of ROSC will be constructed with a logistic regression model. Parameters that will be taken into account will be myocardial and/or electrical activity, capnography, no/low flow duration, and clinical profile including sex and age. Measure of mean duration of cardiac massage interruption during EPOCE will be estimated. P values less than 0.05 will be considered statistically significant. All analyses will be performed using SAS V.9.4.

ETHICS AND DISSEMINATION

In accordance with the recommendations of Comité de Protection des Personnes 'Ile de France II' France, patient and/or legal authority consent will be requested only for survivors. Furthermore, with regard to the inclusion criteria, it will be impossible to seek for relatives' consent. With regard to the very low survival rate of patients with OHCA (5%), anonymised database and family-induced traumatism, we have asked for a derogation to surrogate information for deceased patients. Consent will be requested for surviving patients. We intend to publish ACE results in a major journal of emergency medicine, and raw data will be available on reasonable request.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public had no involvement in the design or planning of the study.

DISCUSSION

There is a strong rationale on the interest on early diagnosis of ROSC absence in OHCA. It might allow premature initiation of ECMO indications or organ donation procedures without waiting for a median time of 30 min after ALS onset. Conversely, in cases of cardiac motion visualisation, a far better prognosis is likely and prehospital teams might search for reversible causes.

Hard evidence is currently missing in the literature since the majority of published studies included small series of patients, in the hospital, and used different protocols.[6–8 10] A multicentre study was performed, but EPOCE was performed in the emergency department even if the cardiac arrest occurred out of hospital.[12] This was stated by the ERC in its 2015 recommendations.[1] ACE is adapted to the particularities of the French prehospital system, but its results will be translatable to other organisations such as European or American organisations.

ACE has the potential to provide a definitive response to this question. Furthermore, it will answer the question on the frequency of reversible causes and their management, which also needs hard evidence. ACE has the potential to provide this evidence since it will include 624 non-selected patients with OHCA.

POCE has been associated with delays in chest compressions[13] which would alter prognosis. However, the training of physicians in POCE in this previous study was not reported.[13 14] The study was performed in the USA, and it might be assumed that the training was in line with established residency training requirements. This potential flaw has to be addressed; in ACE, physicians will be trained before the trial's onset, and cardiac massage interruption will be recorded and measured in a subgroup of patients.

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