Extracorporeal life support (ECLS) has been initially limited to hypothermic cardiopulmonary resuscitation (CPR) in refractory cardiac arrests and to cardiac arrest occurring during the peri-operative period of cardiothoracic surgery [1, 2]. Recently, the ease of use of more miniaturized ECLS devices has permitted a more widespread use of the technique in cardiac surgery departments and ICUs. Encouraging results have been published recently by several teams in single centre retrospective and prospective cohorts, in which most cardiac arrests were from toxic or cardiac causes and occurred in hospital [3–5]. In these highly selected cohorts, survival with good neurological outcome has been observed in up to 20-30% of cases [3–5]. Nevertheless, the preliminary results of the use of ECLS in out-of-hospital cardiac arrest have been described as very poor, with < 1% survival [6].

In addition to therapeutic ECLS performed for the benefit of the patient, this technique has also been developed as a tool to optimize organ homeostasis before organ retrieval in patients determined as dead by cardio-circulatory criteria. These technical advances obviously raise new medical and ethical questions that will be summarized here. In patients suffering from out-of hospital cardiac arrest, it is mandatory to distinguish the indications of therapeutic ECLS, performed for the benefit of the patient him/herself, to the situations where, in case of a deceased individual, the technique is established to optimize the quality of organs to be harvested and transplanted for the benefit of another patient after transplantation.

Finally, distinct to this latter situation of uncontrolled cardiac death, some have proposed that the quality of the organs removed could be improved in a setting of controlled cardiac death, during which patients are declared dead in the hospital after withdrawal of active life-support. This point will not be covered by this refresher course lecture.

**Indications for ECLS in out-of hospital cardiac arrest for the benefit of the patient**

In ECLS performed in out-of hospital cardiac arrest, the time delay for starting the procedure was far greater than that previously reported in in-hospital cardiac arrest [7]. The associated contrasting results observed questioned the indications and contra-indications of ECLS in these conditions. Accordingly, important questions should be considered in these special setting:

- an ‘uncontrolled’ development of ECLS in out-of-hospital cardiac arrest may lead to its abandonment because of very poor outcome
- ECLS in these settings may lead to the survival of patients with poor neurological recovery and the associated considerable suffering for the patient and its relatives (although further evolution to brain death has been observed in most of these surviving patients with poor neurological outcome) [3–5]
- heterogeneous criteria may be applied for the use of ECLS in case of refractory cardiac arrest because of the lack of any published data on its indications and contra-indications.

In France, medical scientific societies under the auspices of the French Ministry of Health selected a group of experts to propose guidelines that could help physicians performing CPR for refractory cardiac arrest in deciding whether ECLS should be used or not [8]. We present here the consensus obtained by these experts (from different scientific and medical backgrounds), although it should be noted that the views expressed are very likely to be modified in the near future in a rapidly evolving topic. These indications and contra-indications of ECLS in refractory cardiac arrest occurring both in and out of the hospital should also be considered provisional, since this rarely performed technique does not yet have proven benefit and is not widely available.
What is refractory cardiac arrest? Definition and important elements leading to a changing paradigm

Refractory cardiac arrest is usually defined as the lack of return of spontaneous circulation (ROSC) within a period of at least 30 min of CPR under medical direction in the absence of preexisting hypothermia [9, 10]. This definition is mainly used to authorize CPR teams to stop resuscitation in a situation without any hope of survival. The concept of lack of any hope of survival has been largely demonstrated in the literature and is supported by the absence of the likelihood of restoring cardiac activity following cardiac arrest requiring more than 30 min of unsuccessful CPR, and the low probability of obtaining good neurological recovery in these conditions.

However, the new possibility of using ECLS diminishes the importance of the first of these two points, at least initially. If ECLS is used, the issue of spontaneous cardiac activity should be considered only after starting the technique, since it is possible to observe spontaneous cardiac recovery (for example, following the elimination of a toxic drug or recovery from myocarditis). Further considerations are the use of further therapeutic options that can reverse cardiac failure (re-warming during deep hypothermia, coronary artery bypass, or coronary angioplasty) or replacing the failing heart (artificial heart, cardiac transplantation). Thus, we are facing a change in paradigm, since refractory cardiac arrest might be now defined only by considering the possibility of obtaining a good neurological recovery, which might become the key factor.

From a patho-physiological point of view, two points are essential for the decision whether or not to continue CPR: the duration of cardiac arrest without cardiac output (no-flow) before CPR and the duration of cardiac arrest with low cardiac output (low-flow) during CPR. These two points contribute equally to the usual definition of refractory cardiac arrest. Knowing the duration of no-flow presupposes that the cardiac arrest was witnessed. A zero no-flow duration implies that CPR was immediately performed by witnesses and cardiac arrest without no-flow is probably the ideal target for ECLS. The no-flow duration is obviously of paramount importance as it is the main variable that determines the neurological prognosis [11]. Nevertheless, in some circumstances, this no-flow duration may lose its importance, for example, in cases of a pre-existing hypothermia before the cardiac arrest that would protect the cerebral nervous system from ischaemia. Good neurological recovery has been reported after prolonged duration of no-flow in deeply hypothermic patients. In other cases, the determination of the no-flow duration may not be accurate, particularly when loss of circulation does not coincide with loss of consciousness. Therefore, when vital signs (spontaneous movements, lack of pupil dilation or persisting pupils reactivity or even the presence of inspiratory gasps - although these probably suggest poor neurological outcome) are observed during CPR, the no-flow duration is questionable. Equally, certain cardiac dysrhythmias (such as ventricular tachycardia, ventricular fibrillation, torsades de pointes) should also lead the physician to question the value of no-flow duration.

Although its importance is probably less, the low-flow duration should also be considered. Low-flow duration has been linked to mortality rate, with < 10% survival after more than 100 min of CPR [5], a value similar to that observed without ECLS. Prolonged low-flow duration is an independent risk of poor neurological outcome and contributes to the multiple organ failure syndrome observed after cardiac arrest. This issue should be taken into account for out-of hospital cardiac arrest since the duration of transportation from the scene to the ECLS centre is usually known by the emergency team. In the case of poisoning with cardiac drugs, a prolonged duration of CPR should not be considered as a contra-indication to ECLS because survival with good neurological recovery has been reported [3]. Thus, in the case of cardiac drug intoxication, CPR should not be continued on scene for 30 min, but, instead, the patient should be transported rapidly to an ECLS centre, as described by an existing recommendation for ECLS [12]. The rapid spread in the use of automatic cardiac massage devices by pre-hospital emergency teams (although their efficiency and safety have not been demonstrated [6]), should not modify the maximum recommended delay to the commencement of ECLS. Finally, monitoring end-tidal CO₂ (ETCO₂) reflects cardiac output produced during CPR, and an ETCO₂ value of less than 10 mmHg (measured after 20 min of CPR under medical supervision) is known to be associated with a poor neurological outcome [13].
ECLS should not be used in patients with certain co-morbidities. These are clinical situations that preclude administration of invasive treatment (for example, admission into ICU, major surgery, coronary angioplasty). Age should not be a limitation since it is not a sufficient reason to limit admission to ICU. It should be emphasized that the present guidelines provided by the French Expert group on the use of ECLS in refractory cardiac arrest should not modify the scientific basis for normal CPR that should be followed for most refractory cardiac arrest, since these are based on considerable clinical evidence as well as regularly updated guidelines [9, 10]. Modification of the definition of refractory cardiac arrest that enables physicians to stop futile resuscitation when the duration of unsuccessful CPR is > 30 min in the absence of ECLS is not required. In contrast, when ECLS can be used, it is not necessary to wait for 30 min to decide to perform ECLS. It should be noted that, particularly in out-of-hospital cardiac arrest, the delay in starting ECLS will usually be greater than 30 min. However, it is not appropriate to consider ECLS when CPR has lasted < 15 min.

An algorithm for indications of ECLS use

A simple algorithm that could be used in emergency situations has been proposed by the French Expert Group [8] (Figure 1). Because of the easy use of miniaturized ECLS devices, there is some temptation to consider that this technique could be applied more widely. However, care of a patient receiving ECLS requires strict co-operation between pre-hospital and hospital teams. Management of therapeutic measures needed to reverse cardiac dysfunction or replace cardiac function, and management of their related complications, requires highly trained multidisciplinary teams. Direct surgical access to femoral vessels is recommended and requires the skills of a trained surgeon. Management of ECLS also requires a team trained in critical care. The preparation and maintenance of ECLS device is ideally performed by a bypass-pump technician, although this can be performed by other trained personnel.

Figure 1

A suggested algorithm to decide whether extracorporeal life support (ECLS) could be used in treating refractory cardiac arrest (cardiac arrest), CPR: cardiopulmonary resuscitation; VT: ventricular tachycardia; VF: ventricular fibrillation; TP: torsades de pointes; ETCO$_2$: end-tidal CO$_2$ (measured 20 min after the onset of medical CPR). *: CPR duration > 100 min could be accepted in case of poisoning with cardiac drugs. y: indications accepted by ILCOR [13]. Co-morbidities are those which should contra-indicate invasive care (admission into ICU, major surgery, coronary angioplasty for example). The low-flow duration encompasses basic CPR (witness and/or paramedics) and medical CPR. From Riou et al [8].
In case of hypothermic cardiac arrest, it is not possible to estimate neurological injury during the no-flow and low-flow periods. However, even highly trained teams using ECLS in these circumstances (drowning, avalanches) have also limited their indications of ECLS to cases with favourable prognosis criteria (for example, patients found buried in snow surrounded by an air cavity) or have used some biological variables, such as the serum potassium level to help in deciding whether or not to use ECLS.

**Perspectives**

The use of this algorithm by physicians who care for patients with refractory cardiac arrest has been proposed to enable standardization of ECLS clinical practice in France, while providing an appropriate response from medical and ethical points of view. In addition, development of ECLS should be associated with thinking about access to care and quality of care. It should be emphasized that the indications of ECLS should only be considered as provisional since this complex technique is not yet widely and consistently available, mainly because it requires highly trained and equipped teams. Moreover, the present recommendations are based on the results of highly selected cohorts originating from single centre studies performed with highly trained and equipped teams caring mainly in-hospital refractory cardiac arrest.

There is a need to develop registries in the future to validate these recommendations and to define further the indications and contraindications of ECLS in refractory cardiac arrest. Lastly, it should be emphasized that the indications of ECLS should only be considered as provisional since this complex technique is not yet widely and consistently available, mainly because it requires highly trained and equipped teams. Moreover, the present recommendations are based on the results of highly selected cohorts originating from single centre studies performed with highly trained and equipped teams caring mainly in-hospital refractory cardiac arrest.

**Organ donation after uncontrolled cardiac death**

Medical progress in organ preservation during cardiopulmonary resuscitation now allows organs for transplantation to be obtained from patients suffering from a cardiac arrest. The different cardiac arrest situations have been summarized in an international classification (Maastricht classification). The different categories encompass:

- **Maastricht I** (dead on arrival): cardiopulmonary function ceased spontaneously in absence of advanced life support
- **Maastricht II** (unsuccessful resuscitation): cardiopulmonary function ceased spontaneously in presence of advanced life support
- **Maastricht III** (awaiting cardiac arrest): cardiopulmonary function ceased after a decision to withdraw life-sustaining therapy from a hospitalized patient
- **Maastricht IV** (cardiac arrest when brain dead): cardiopulmonary function ceased spontaneously in a brain-dead donor.

The fact that patients dying after a phase of withholding or withdrawing active therapy in ICU (Maastricht class III) are specifically excluded in France from this process is seen as an ethical safeguard for the public and health-care providers. Ethically, in cardiac arrest patients, there is a desire to maintain a clear distinction between the care of the patient for the benefit of the patient (that cannot lead to an organ withdrawal except for the specific case of evolution towards brain death) and for pursuit of therapeutic manoeuvres in order to obtain organs for transplantation.

In uncontrolled non-heart beating donors (NHBD) after sudden out-of-hospital refractory cardiac arrest, promising results have been found in 122 potential NHBD after a mean resuscitation attempt of 35 min [14]. In these patients, transported to hospital with mechanical lung ventilation and external cardiac massage, kidney protection was performed in 56 (at the hospital) by insertion of an intra-aortic double-balloon catheter with perfusion of a hypothermic solution. Kidney retrieval and kidney preservation with a hypothermic pulsatile perfusion machine allowed assessment of the quality of the organs in 27 out of these patients. Finally, out of the 54 kidneys procured, 31 kidneys (57%) were transplanted. As expected, there was a high rate of delayed graft function (92%), but creatinine clearance and graft survival rate was good at six months.
These advances in medical technology must be ethically sound. According to the ‘dead donor rule’ donation should not cause or hasten death [15]. The issue of ‘in-situ preservation in uncontrolled death’ vs harvesting organs after ‘controlled’ death represents ‘another matter of life and death’ [16]. In this setting, a new understanding of the ‘irreversible’ nature of a cardiac arrest becomes essential. As carefully described in a recent review [16]: “Is cardiac arrest “irreversible” if circulation could be restored but no resuscitation efforts are going to occur? Or is cardiac arrest only “irreversible” when circulatory function cannot be restored, even if resuscitation efforts are undertaken?”.

Advances in ECLS in out-of-hospital cardiac arrest raise new medical and ethical challenges for physicians. As the concepts of brain-death and cardiac death may be differently understood by professionals and by the public, society’s acceptance of these changes is mandatory. This is key to preventing any potential negative impact of these new techniques on organ procurement from brain dead donors.

Key learning points

- The ease of use of more miniaturized extracorporeal life support (ECLS) devices now permits a more widespread use of this technique in cardiac surgery departments, ICUs, and out-of-hospital situations
- The preliminary results of ECLS systems in out-of-hospital cardiac arrest remain very poor, with < 1% survival
- The more efficient methods to increase survival in cardiac arrest remain those that permit the reduction of the no-flow period (such as training in basic life support in the general population, automatic defibrillation)
- In out-of hospital cardiac arrests, it is mandatory to distinguish the indications of therapeutic ECLS, performed for the benefit of the patient himself, to a deceased individual with the technique established to optimize the quality of organs to be harvested and transplanted for the benefit of another patient after transplantation
- Kidneys harvested in uncontrolled non-heart beating donors (NHBD) after sudden out-of-hospital refractory cardiac arrest have shown promising results, with a high rate of delayed graft function, but respectable creatinine clearance and graft survival rate at six months

References