Editorial

The role of the gray-to-white matter ratio to predict the prognosis of cardiac arrest treated with ECMO

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Outcome of patients who have suffered a cardiac arrest (CA), has improved in the past years. However, survival and good neurological outcome rates are still low (1).

After CA, patient's outcome depends on many factors, one of the most important one being the site of arrest. Out-of-hospital CA (OHCA) has clearly worst results due to the longer periods until resuscitation is started, time to advanced cardiopulmonary resuscitation (CPR) initiation and complications in transfer to hospitals (2). Other factors influencing prognosis are the cause of arrest (traumatic CA have worst outcomes), initial rhythm (asystole is the rhythm with poorer results in contrast with shockable rhythms), CPR duration and complications after return of spontaneous circulation (ROSC) (3).

A significant percentage of patients who attain ROSC, die within days or weeks, most of them from brain death or multiorgan failure, and a significant percentage of survivors are left with important neurological sequelae (4).

Ischemia and tissular hypoxia during CA and CPR are mainly responsible of death and neurological injuries. Other physiopathological factors contributing to tisular damage are hyperemia and hyperoxia after reperfusion and the systemic inflammatory response after ROSC. Therefore, efforts to improve the prognosis of cardiac arrest should be directed to try to reduce the factors that influence mortality and neurological outcome. It is not only important to achieve greater survival rates after CA, but it is essential to reduce brain damage in survivors. In order to reduce the time from CA to the initiation of CPR it is essential to first prevent, diagnose and quickly treat CA with CPR training programs for healthcare workers and general population (5). Campaigns to promote access to semiautomatic defibrillators in public places and healthcare centers are essential in the early treatment of ventricular arrhythmias (5). Training in quality CPR is necessary to diminish ischemia and hypoxia during resuscitation (5). Haemodynamic and respiratory stabilities after ROSC should be procured in order to avoid hyperemia, ischemia, hyperoxia, hypoxia, hypocapnia and hypercapnia, and thus decrease neurological damage (6). In the past years, certain controversy has been created over the role of hypothermia in preventing neurological damage after CA. Initial studies found out that moderate hypothermia improved outcome in adult patients after CA, mostly in those with a shockable rhythm at the time of arrest (7). However, further studies have not found any differences in outcome of patients treated with hypothermia when compared to those in whom normothermia was assured (8).

Extracorporeal membrane oxygenation (ECMO) can rescue some of the patients after CA in whom ROSC is not achieved with CPR (9). On the other hand, ECMO helps in keeping a good organ (and brain) perfusion and oxygenation, decreasing damage after ROSC. Various studies have demonstrated that ECMO, when used early and by an experienced team increases survival after CA and achieves a good neurological outcome (10).

However, to establish ECMO as a CPR measure some requirements are needed. Being CPR duration one of the most important factors influencing survival, it is centers with an ECMO program have to be able to start ECMO-CPR early. This requires maintaining an ECMO team on alert, its early activation and ECMO circuits purged and ready to use (11). For this reason, at the present time the ability to perform ECMO during CPR is only available in some hospitals.

When ROSC is achieved after CA, whether using usual cardiopulmonary resuscitation or ECMO-CPR, it is very important to try to early predict the prognosis and neurological long-term outcome.

In assessing CA outcome, methods used must be able to predict the prognosis early and with a high specificity to accurately distinguish patients who will die or be left with a bad neurological status, in order to help decide the maintenance of life supporting measures.

Several studies have examined the power of clinical examination methods, monitors, biochemical markers, electroencephalography, evoked potentials, imaging, etc. to predict neurologic outcome of patients after recovery from cardiac arrest (12,13). Patients who have suffered a CA are frequently treated with sedation or hypothermia, and these can interfere with the clinical evaluation and interpretation of various tests. Moreover hemodynamic instability, often present in these patients, or treatment devices and monitors needed in their management, in many cases prevent performing some diagnostic tests such as MRI or cerebral gammagraphy. At present there is no method that, by itself, can early predict the outcome and neurological prognosis of patients who have suffered a CA (12,13).

Moreover, patients treated with ECMO have special characteristics that prevent MRI test, or alter other tests. For instance, the assessment of cerebral blood flow is more complex because blood flow when in ECMO is not pulsatile and thus, it is difficult to differentiate between the patient´s spontaneous cerebral blood flow and that due to the ECMO. Furthermore, keeping a patient in ECMO is both complex and expensive, therefore it is important to assess when this technique should be discontinued.

What is the role of imaging test in assessing the prognosis of patients who have suffered a cardiac arrest? What parameters can be measured in the CT to assess brain alterations after CA?

One of the first changes that occur in the brain due to the ischemia-reperfusion process is brain edema. Both CT and MRI can assess qualitatively the existence of cerebral edema.

The earliest post-ischaemic MRI change is hyperintensity in cortical areas or basal ganglia on diffusion weighted imaging sequences. Advantages of MRI over brain CT include a better spatial definition and a high sensitivity for identifying ischaemic brain injury. However, its use can be problematic in the most clinically unstable patients (14).

CT scan has great advantages over MRI in these patients. It's easy and quick to perform, is accessible in a large number of hospitals 24 hours a day and is not incompatible with any kind of instrumentation (pumps, respirators, ECMO, etc.). Cerebral oedema is characterized by less attenuation in the grey matter and a lower GWR. A system to assess and quantify the cerebral edema by studying the grey-to-white matter ratio (GWR) in the CT has been proposed (15). Several brain slices at the level of the basal ganglia (BG) and two levels of the superior cortex (CO) are performed in the CT. At the BG level values were recorded for caudate nucleus, putamen, corpus callosum and posterior limb of the internal capsule; at the cortex values for centrum semiovale and high convexity area were registered. Several index GWR-BG (basal ganglia), GWR-CO (cortex), GWR-SI (simplified) and GWR-SA (average) were calculated (16,17).

Some studies have evaluated the utility of measuring the grey-to-white matter ratio (GWR) in a CT to predict the neurological outcome of patients who have suffered a CA. In these studies, the loss of the differentiation between grey matter and white matter on the brain CT was a marker of cerebral oedema in patients after cardiac arrest (18-21).

Scheel *et al.* studied 98 cardiac arrest patients treated with hypothermia (18). These authors found a strong association of a low GWR with poor outcome following cardiac arrest. Determination of the GWR increases the sensitivity in a multi-parameter approach for prediction of poor outcome after cardiac arrest (18).

Torbey *et al.* studied 25 patients in a coma after a CA. GWR was lower in comatose patients than in normal controls, and in those who died than in survivors (19). Inamasu studied 39 CA survivors. 31 with impaired GWR died, while 5 of the remaining survived (20).

In another study of 224 patients, Lee found that combining brain CT and serum neuron specific enolase improves the prognostic performance when compared to either alone in predicting poor neurologic outcome in cardiac arrest patients treated with hypothermia (21).

Gentsch found that a simpler method using only four different regions of interest (putamen and internal capsule bilaterally) had the same prognostic value compared with the standard method using 16 regions (22).

The study "*The prognostic value of the grey-to-white matter ratio in cardiac arrest patients treated with extracorporeal membrane oxygenation*" recently published by in Resuscitation (23) is the first to evaluate if this method can be of use in patients in ECMO.

The authors carried out a retrospective single center study, in which patients who had suffered an OHCA and were resuscitated with ECMO in the emergency department (ED) were included. Out of 38 patients who were treated with ECMO, eight died in the ED because of ECMO pump failure. A CT was carried out in the remaining 30 patients one hour after initiating the ECMO and before their transfer to the ICU. Twenty two patients died after that in the ICU (10 from brain death). Out of the eight survivors, five patients had good neurologic outcome (CPC one or two) and three patients had poor neurologic outcome (CPC of 4). The median GWR-BG (basal ganglia), GWR-CO (cortex), GWR-SI (simplified) and GWR-SA (average) were significantly lower in the three patients with worst outcome when compared to the five with good neurological outcome. The authors used a ROC curve to determine the cut-off points with a 100% specificity (23).

The CT findings were related to the MRI performed later during evolution. None of the five patients with good neurological outcome had abnormalities on MRI in contrast with the three patients with poor neurological outcome, who showed various cortical and gray matter lesions (23).

It is important to highlight that with such a small number of cases (only eight patients) there were statistically significant differences in all GWR parameters between patients with good and poor neurological outcome. This fact, on the one hand supports the prognostic value of this diagnostic method in patients with ECMO after CA, but should also make us be cautious in assessing this technique until there are no studies with larger numbers of patients. The authors could perhaps have included the 10 patients who died in the ICU because of brain death in the poor neurological prognosis group, which would increase the number of patients analyzed and could give more reliable results. In this study the time between the CA and the start of ECMO was statistically longer in patients with poor neurological outcome than in those who had good prognosis (23). Unfortunately other markers of neurological prognosis (clinical examination, biomarkers, electroencephalogram, evoked potentials) were not analyzed and therefore it is not possible to compare the predictive efficacy of CT with other parameters.

Another important limitation of this study is that the GWR cutoffs found to differentiate patients with good and poor prognosis were higher than those reported in other studies in patients treated with conventional CPR (23). The authors suggest some possible explanations (their patients were younger, the effect of ECMO, hypothermia and other treatments) but the reason is not clear, and therefore, cutoffs must be interpreted only as indicative parameters and never as definitive limits. Larger studies comparing normal GWR at different ages and assessing the effect of different therapeutic measures are needed.

With the results of this work and those of other authors should we encouraged to perform an urgent CT in patients who achieve ROSC after CA, to predict prognosis, inform relatives and adapt therapeutic measures?

In my opinion at this time a general recommendation to that effect cannot be made. The fact that the realization of an urgent CT in these patients is not possible in many centers and it is not without risks should not be forgotten. After ROSC patients often have hemodynamic and respiratory disorders, which may worsen during transport to radiology or during the performance of the CT, where they cannot be treated as in an ICU. In addition, in patients with ECMO the risk of complications, both technical and medical, during transfers increases. Therefore, each center should assess the risk-benefit ratio, and establish whether the capacity and preparation of staff and equipment allows to safely perform an urgent CT after ROSC or the establishment of ECMO, or if it is safer for the patient to be directly transferred to the ICU and to delay this test image.

In conclusion, the GWR measurement in a brain CT can be a good diagnostic method that helps the early establishment of a prognosis in patients who have recovered from a CA, treated or not with ECMO. But at the present time, it does not identify specific cut-off points that may determine using only this diagnostic tool the neurological outcome of patients with certainty.

For the time being, a multimodal approach in which clinical evaluation methods, evoked potentials, EEG and imaging studies are used is what can help the clinician to establish a prognosis after ROSC (24). The development of simple, continuous, easily replicated and safe methods that can be performed without moving the patient is necessary. Perhaps in the near future, with technological development of portable CT, its use could be generalized and the role of the GWR could be redefined as an early prognostic method in patients recovering from cardiac arrest.

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Footnote

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