Global Ischaemic Injury and Neuroprotection

a report by

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Neurological disease remains, without doubt, one of the leading causes of both death and disability in modern society. In the majority of afflicted patients, the neurological sequelae are a result of cardiovascular disease (CVD). Consequently, prophylaxis of this disease can also be expected to have beneficial effects on the incidence of neurological disability. For example, such effects have been demonstrated for arterial hypertension (AH). For those affected by CVD and its complications, however, treatment is often a prerequisite, not only for continued life, but also for the secondary goal of limiting the magnitude of suffering and costs that would otherwise impact the family and/or society.

CVD is one of the major causes of death in the Western world, and it annually affects approximately 100 per 100 000 population. In Sweden, with a population of nine million, approximately 15,000 people die each year due to CVD, two-thirds of whom suffer a cardiac arrest outside of a hospital. Approximately 2,000 of these out-of-hospital patients undergo cardiopulmonary resuscitation (CPR), which is administered by ambulance staff when they arrive on the scene. Upon arrival at the hospital, 15–50% of these patients are still alive, while one month after their cardiac arrest, only 5% are still alive. In spite of major efforts to improve these results, little has happened over the past 25 years.

The question is why, despite intense research and in-depth education of both ambulance and hospital crews, the final decades of the 20th century did not bring about improved results in the resuscitation of cardiac arrest victims. Part of the explanation was recently revealed when two research groups monitored the efficacy of CPR, as practiced in both ambulances and the hospital. This group observed that for practical reasons, efficient resuscitation could only be delivered for less than half of the resuscitation process. This resulted in coronary perfusion pressure and a blood flow that was too low, which is known to result in a low incidence of restoration of spontaneous circulation (ROSC), i.e. death.

Furthermore, insufficient systemic blood flow secondarily involves a risk of increased neurological injury. However, this knowledge has already led to improvements in education and training and, above all, development of automated technical aids that ensure continuous resuscitative efforts of improved

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quality, resulting in better circulation as a basis for successful resuscitation.

The 1990s ended in a rather pessimistic way regarding the possibilities of inducing neuroprotection by means of pharmacological agents. Although several hundred chemical compounds were tested and efficacy was experimentally verified in small animals, very few of the successful results were obtained with candidate drugs in larger animals when administered after the ischaemic event. This was even more the case in the clinical setting. However, there were also exceptions, where more positive results were achieved. Therefore, it was not a total surprise when Bernard et al.5,6 published the successful results of their clinical investigations where cardiac arrest victims were subjected to mild hypothermia (32°C to 34°C) during 24 hours after ROSC. A rather significant improvement in neurological outcome was demonstrated.

In the new guidelines issued by the American Heart Association (AHA), the European Resuscitation Council (ERC) and the International Liaison Committee on Resuscitation (ILCOR),7 this therapeutic success has been introduced as a recommended treatment after ROSC.8 This rather recent progress has been regarded as quite promising, although the mechanisms of the effect are not yet fully understood. Obviously, the decreasing cerebral oxygen metabolic uptake, which has been known for a long time, cannot account for the entire clinical effect. In the experimental setting, mild hypothermia seems to reduce neuronal injury.9 New information must be secured if the promising development of hypothermia is to be used scientifically when undertaking the next step in this hopefully successful future therapeutic hierarchy.

It is conceivable that such an advance was recently achieved when it was found that methylthionine chloride (methylene blue), a blue dye that has been known for over a century, not only increases porcine survival after a 12-minute untreated cardiac arrest and eight minutes of CPR, but also attenuates the myocardial and cerebral ischaemic injury. This is probably due to the ability of this dye to lower nitric oxide (NO) production as well as its effects.

These findings are currently being further investigated through the use of molecular biology and microarrays to assess gene activation and immunostaining of slides from the above-mentioned tissues after an experimental porcine cardiac arrest. By comparing the differences on a subcellular level between drug candidates known to exert at least experimental therapeutic effects, there seem to be good possibilities for elucidating major mechanisms of action.

Both the author’s and other research groups have increasingly come to realise that the chances of finding a single complete solution to the problem

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of neuroprotection in connection with ischaemia are not good. Thus, the possibilities of finding a single agent that can elicit sufficient neuroprotective effects after a long ischaemic event (20 minutes or more) seem to be minimal. Instead, it is thought that a combination of different effects is needed, and effects of so-called ‘dirty drugs’ are consequently becoming increasingly attractive.

The question is what chances there are of achieving real neuroprotective effects that can be used for practical purposes on a patient after a cardiac arrest. From the investigations conducted by Jørgensen,\textsuperscript{10,11} it is already clear that during ischaemia, the brain does not die immediately. In addition, it will probably be possible to induce a sort of hibernating state in the brain for a period of time during which at least some parts of this organ are allowed to recover. This resting state cannot easily be induced in the heart, as it must perform hydromechanical work on a more or less constant basis unless it is ‘uncoupled’ from the systemic circulation by the patient being put on cardiopulmonary bypass. This therapeutic approach can also be used to gain time for the brain when myocardial function is not sufficient.

The Future

In the author’s opinion, the progress that has been made would favour relatively rapid improvements in therapy. Therapeutic mild hypothermia is already here. Hopefully, a necessary lesson has been learnt regarding the need to improve the practical and industrious performance of efficient central systemic circulation during CPR. Rheological improvements have been available for a few years. Interesting and promising pharmaceuticals are awaiting finalised stage II–III trials; proof of concept is available for others. Before long, the chances of surviving a cardiac arrest with good neurological function will be much better.

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