Commentary

**Effect of myocardial ischaemia & reperfusion on brain**

Very primitive man has witnessed rapid loss of life by asphyxiation and drowning, and strangulation as a means of exterminating enemies has been used since antiquity. Curville credited Ibu Sina (Avicenna Ca 954 AD) as the first physician to associate clinical manifestations of asphyxiation with effect of oxygen deprivation and its detrimental effects on the brain. Francis Bacon in 1848 and Schank in 1644 recognized that death from drowning may only be apparent and some individuals can be revived. William Harvey discovered the phenomenon of circulation in human body and French chemist Lavoisier demonstrated the effect of oxygen and respiration leading to oxidative reaction. The advent of the use of anaesthetics, open chest-cardiac surgery, high altitude flying have offered new avenues to understand the terms - hypoxia-anoxia-reperfusion and their effect on the nervous system. In 1911, Sand observed degeneration of cerebral cortex in a boy who died following anaesthesia. He had respiratory and cardiac arrest and survived for 9 days. This forms a prototype for cardiac arrest - global ischaemia - reperfusion and anoxic encephalopathy. Patients who are febrile, undernourished in hypovolaemic shock due to trauma or surgery are vulnerable to ischaemic damage of different systems. Cardiac arrest during anaesthesia is common in children under 1 yr of age manifesting with periventricular leucomalasia. When the cardiac function is restored by open or closed cardiac massage, damage to the myocardium by hypoxia or mechanical trauma may impair the haemodynamics and contribute to additional cerebral damage.

In a critical care setting, hypoxic-ischaemic encephalopathy can occur secondary to myocardial infarction, cardiac arrest, shock, carbon monoxide poisoning and cyanide poisoning. With hypoxaemia that occurs following circulatory arrest, consciousness is lost soon. With restoration of circulation within 3-5 min, full recovery may occur, but if hypoxia-ischaemia lasts beyond 3-5 min, some degree of permanent cerebral damage is bound to occur. It is difficult to judge the precise degree of ischaemia and some patients make relatively complete recovery even after 8-10 min of global ischaemia. A distinction between pure hypoxia and hypoxia-ischaemia is essential, since $pO_2$ of 20 mm Hg (2.7 KPa) can be well tolerated if the event evolves gradually and normal blood pressure is maintained, but short spell of very low or absent cerebral circulation may result in permanent impairment. The ischaemic pathology affecting the cerebral cortical ribbon, CA1 subfield of the hippocampus, basal ganglia, hypothalamus and brain stem explains the amnesia, myoclonic seizures and persistent vegetative state.

Sequential imaging studies of human brain in patients remaining in a persistent vegetative state following resuscitation after cardiac arrest and following hypoglycaemic injury revealed specific lesions in bilateral basal ganglia, cerebral cortex, substantia nigra and hippocampus, suggesting particular vulnerability of these anatomical areas. The hypoglycaemic lesions usually do not reveal haemorrhage, while ischaemia-reperfusion lesions consistently have haemorrhagic component due to
rupture of end arteries supplying the cortex, basal ganglia and thalamus.

In premature infants periventricular leukomalacia is probably the brain tissue response to ischaemia and reperfusion, with impaired regulation of cerebral blood flow. Injury to developing oligodendroglia by ischaemia related free radical/oxidative/nitrative stress following reperfusion is the probable pathogenic mechanism, finally manifesting hypomyelination in long term survivors. Perinatal insults like hypoxia-ischaemia, hypoglycaemia, stroke and trauma are associated with excessive release of glutamate, an excitatory aminoacid. The activation of glutamate receptors present on neurons, astrocytes and oligodendrocytes may lead to a cascade of intracellular events, calcium flooding and apoptosis/necrosis. These intracellular pathways are sexually dimorphic. Selective vulnerability of neuroanatomical areas at different gestational ages is modulated by different forms of glutamate receptors. Selective injury to putamen, thalamus and cerebral cortex due to ischaemia in infants is related to excessive stimulation of neuronal N-methyl-D-aspartic acid (NMDA) and α-Amino-3-hydroxy-5-methylisoxazole-4-riopionic acid (AMPA) glutamate receptors, while brain stem injury is related to neuronal AMPA/kainate receptors on immature oligodendroglia. In premature infants and experimental neonatal mice, following ischaemic insult and reperfusion, the thrombin in the blood is found to participate in precipitating periventricular haemorrhages. The ischaemic injury to the periventricular subplate neurons may be the central component of perinatal injury leading to developmental consequences.

Despite the wealth of knowledge related to over activation of multiple receptor systems and changes in ionic gradients in experimental models following ischaemia and traumatic injury and ‘reperfusion’ as a compensatory reaction in both, knowledge of molecular genetic events associated with the pathophysiology is limited. Lipid peroxidation, oxidative stress and nitric oxide mediated nitration participate in the membrane damage, aberrant cell signaling pathways, subsequently reflecting acute genomic responses. The immediate early genes c-fos, c-jun and jun B which are transcription factors regulating the expression of a variety of target genes controlling trophic factors, cytoskeletal proteins and metabolic enzymes and the stress proteins known as heat shock proteins (HSPs), are activated as a protective cellular response. These factors rapidly rise and fall following the injury, probably corresponding to the early ‘golden hours’ in clinical setting when resuscitative efforts can be effective. The expression of fos and jun has been associated with synaptic plasticity and programmed cell death observed in both ischaemic and traumatic injury. It appears that after these initial events, delayed and relatively irreversible cell dysfunction may occur following ionic fluxes and free radical/superoxide mediated membrane damage. The level of these insults will influence the gene expression, protein regulation, ultimately leading to cell death or repair in an attempt at functional restitution. These responses are universal though well studied in brain and heart because of their central role controlling the survival of the system and their interdependence.

Focal cerebral ischaemia results in expression of varied classes of heat shock proteins, with a temporal sequential expression. The HSPs (HSP 27, 70, 90α) act as molecular chaperones and are crucial for cytoprotection and repair of tissues. A further alteration in the expression of HSPs indicates pathology. HSPs are also known to play a role in activation of immune system, inflammatory response and also in neuronal differentiation. In addition, HSP 27 is known to stabilize actin microfilaments and is regulated by MAP kinases. HSP 90 and 70 are associated with a number of signaling molecules including steroid receptors. Very importantly, these HSPs inhibit caspase activation and prevent apoptosis of the cells. The HSP 70 can suppress both necrosis and apoptosis induced by various injuries in vivo and in vitro. In the brain, overexpression of HSP 70 significantly protects astrocytes from 4 h oxygen-glucose deprivation and 24 h reperfusion. In the
infracted areas, zones expressing HSP 70 survive the sublethal metabolic stress during reperfusion after focal ischaemia. hsp 70 mRNA expression can be found in cortical penumbra, where as c-fos and jun B mRNA expression increases both in penumbra and in cortical areas away from the site of infarction, reflecting the molecular response of the brain away from the site of insult. Alterations in the expression of heat shock proteins and immediate early genes in ischaemic/reperfusion conditions are mainly studied in greater detail from animal studies and data from humans are very limited.

In this issue, Wang et al have probed the molecular genetic expresional events of c-fos and heat shock proteins (HSPs) in the brain following myocardial ischaemia and reperfusion. This provides insight into the effect of ‘reparative reperfusion’ on the events, unlike the immediate response to ischaemic insult. This reperfusion event closely mimics traumatic brain injury and repair mechanisms induced during the initial phases of post injury period. The interesting feature of this study is recording the response of the brain to cardiac ischaemia, thus causing vasomotor and haemodynamic alterations. The alterations in cerebral blood flow are obviously secondary to reduced ventricular ejection and fall in mean arterial pressure. The changes observed are rather anticipated, but offered an insight into cerebral changes following myocardial ischaemia and reperfusion while the haemodynamic changes being within the threshold of autoregulatory changes. Single hypovolaemia as recorded in this experiment could be encountered following transient syncope and during obstetric and surgical practice and may have sub-clinical effect on cerebral function, probably manifesting with mood changes which is usually neglected.

We are aware that translating the animal studies to human physiology and psychology is hazardous, but cannot escape from the fact of various mild symptoms for which one does not have explanations. Accordingly, observations of Wang et al on alterations in differential expression of heat shock proteins and associated cerebral blood flow changes in the discrete brain regions following myocardial ischaemia/reperfusion is significant. However, further studies are warranted to provide molecular basis of stroke/ischaemia and reperfusion conditions in both animal and humans.

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References


