Introduction

Stroke is rapidly developing clinical symptoms and/or signs of focal, and at times global, disturbances of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin ***(Hatano, 1976)***.

It is a neurological emergency that requires rapid diagnostic workup and immediate treatment ***(Einhaupl, 1999)***.

The definition of stroke for clinical trials has required either symptoms lasting more than 24 hours or imaging of an acute clinically relevant brain lesion in patients with rapidly vanishing symptoms. The use of the term "brain attack" which may lack specificity has been championed by the educational campaigns of national health organizations to help inform the public about the urgency of stroke ***(Sacco, 2009)***.

Stroke continues to be a major health problem that ranks in the top three causes of death in most countries coming after ischemic heart disease and cancer. It is responsible for a large burden of the population of neurological disorders ***(Poungvarin, 1998).***

Stroke has multiple impacts on the patient's life and their families since around 15% to 30 % of survivors are disabled and dependent on others for their primary daily activities, they have also decreased life satisfaction after stroke with evidence of depression in 50%, high risk of dementia, and increased incidence of fracture ***(Bertson et al., 2004)***

Ischaemic stroke accounts for 75-85% of stroke incidence worldwide, causing substantial morbidity and mortality ***(Longmore, 2010)***.

Quatitative clinical scores such as national institute of health stroke scale (NIH), Barthel activity of daily living (ADL) and modified Rankin scale (mRS) have shown to have some degree of correlation with the clinical status,

and were used in many clinical trials, evaluating outcome of the patients ***(Greg et al., 2003)***.

Cardiac of sources of embolism has been estimated to be etiologic factor in up to 20% of ischemic stroke cases. Although there are large number of cardiac diseases reported to be a potential source of embolism to the brain, the majority of causes can be diagnosed by straightforward clinical examination, electrocardiography , chest X-ray along with non-invasive echocardiography ***(Sandercock et al., 1992).***

Among these numerous causes, some are much more threatening as prosthetic valves and rheumatic atrial fibrillation than others like mitral leaflet prolapse and patent foramen ovale ***(Warlow, 2001, Longmore et al., 2010).***

Cardiac emboli differ not only in their composition, but also in their size. Emboli may be formed of fibrin as those coming from fibrillating atrium, or mostly formed of platelet as those coming from prolapsed mitral valve or calcified material as those coming from calcified mitral annulus or infected vegetations in case of infective endocarditis. Their size may also vary from those large enough to occlude large arteries as middle cerebral artery or small enough to occlude small artery as the central retinal artery ***(Caplan, 1998).***

The neurologic outcome from an embolic stroke depends not only on the occluded vasucular territory but also on other factors; the presence of vasospasm, hemorrhagic transformation and the presence of hypoperfusion ***(Cordonnier et al., 2008, Rothwell et al., 2009)***

Different cardiac diseases have their own impact on severity, subtyping and prognosis of stroke ***(José et al., 2008).***

Aim of the Work

1- To assess the impact of cardiac diseases on stroke severity and short-term (1 month mortality).

2- To assess the role of left ventricular dysfunction as an independent risk factor for ischemic stroke.

Chapter (1)
Stroke Pathophysiology and Cardiac disorders with Potential Cardiogenic Stroke

Introduction

The two major mechanisms causing brain damage in stroke are ischemia and hemorrhage. In ischemic stroke, which represents about 80% of all strokes, decreased or absent circulating blood deprives neurons of necessary substrates. The effects of ischemia are fairly rapid because the brain does not store glucose, the chief energy substrate and is incapable of anaerobic metabolism ***(Jones et al., 1981).***

Non-traumatic intracerebral hemorrhage represents approximately 10% to 15% of all strokes. Intracerebral hemorrhage originates from deep penetrating vessels and causes injury to brain tissue by disrupting connecting pathways and causing localized pressure injury. In either case, destructive biochemical substances released from a variety of sources play an important role in tissue destruction ***(Rothwell et al., 2009).***

Focal Ischemic Injury

A thrombus or an embolus can occlude a cerebral artery and cause ischemia in the affected vascular territory. It is often not possible to distinguish between a lesion caused by a thrombus and one caused by an embolus. Thrombosis of a vessel can result in artery-to-artery embolism. At a gross tissue level, the vascular compromise leading to acute stroke is a dynamic process that evolves over time. The progression and the extent of ischemic injury are influenced by many factors such as:-

Rate of onset and duration: the brain better tolerates an ischemic event of short duration or one with slow onset.

Collateral circulation: the impact of ischemic injury is greatly influenced by the state of collateral circulation in the affected area of the brain. A good collateral circulation is associated with a better outcome.

Health of systemic circulation: Constant cerebral perfusion pressure depends on adequate systemic blood pressure. Systemic hypotension from any reason can result in global cerebral ischemia.

Hematological factors: a hypercoagulable state increases the progression and extent of microscopic thrombi, exacerbating vascular occlusion.

Temperature**:** elevated body temperature is associated with greater cerebral ischemic injury.

Glucose metabolism**:** hyper- or hypoglycemia can adversely influence the size of an infarct ***(Schwab et al., 1997).***

Cerebral Blood Flow

Normal cerebral blood flow (CBF) is approximately 50- to 60 ml/100g/ minute and varies in different parts of the brain. In response to ischemia, the cerebral autoregulatory mechanisms compensate for a reduction in CBF by local vasodilatation, opening the collaterals, and increasing the extraction of oxygen and glucose from the blood. However, when the CBF is reduced to below 20 ml/100g/minute, an electrical silence ensues and synaptic activity is greatly diminished in an attempt to preserve energy stores. Cerebral blood flow of less than 10ml/100g/minute results in irreversible neuronal injury ***(David, 2006).***

Mechanisms of neuronal injury

Formation of microscopic thrombi responsible for impairment of microcirculation in the cerebral arterioles and capillaries is a complex phenomenon. Formation of a microthrombus is triggered by ischemia-induced activation of destructive vasoactive enzymes that are released by endothelium, leucocytes, platelets and other neuronal cells. Mechanical "plugging" by leucocytes, erythrocytes, platelets and fibrin ensues ***(Tudor et al., 2008).***

At a molecular level, the development of hypoxic-ischemic neuronal injury is greatly influenced by "overreaction" of certain neurotransmitters, primarily glutamate and aspartate. This process called "excito-toxicity" is triggered by depletion of cellular energy stores. Glutamate, which is normally stored inside the synaptic terminals, is cleared from the extracellular space by an energy dependent process. The greatly increased concentration of glutamate and aspartate in the extracellular space in an energy-depleted state result in the opening of calcium channels associated with N-methyl-D-asapartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxanole propionate (AMPA) receptors. Persistent

membrane depolarization causes influx of calcium, sodium, and chloride ions and efflux of potassium ions ***(José et al., 2008).***

Intracellular calcium is responsible for activation of a series of destructive enzymes such as proteases, lipases, and endonucleases that allow release of cytokines and other mediators, resulting in the loss of cellular integrity ***(Rothman et al., 1987).***

Inflammatory response to tissue injury is initiated by the rapid production of many different inflammatory mediators, tumor necrosis factor being one of the key agents. Leukocyte recruitment to the ischemic areas occurs as early as thirty minutes after ischemia. In addition to contributing to mechanical obstruction of microcirculation, the leucocytes also activate vasoactive substances such as oxygen free radicals, arachidonic acid metabolites (cytokines), and nitric acid. The cellular effects of these mediators include vasodilatation, vasoconstriction, increased permeability, increased platelets aggregation, increased leukocyte adherence to the endothelial wall, and immunoregulation ***(Fisher et al., 2003).***

Endothelial cells are one of the first cell types to respond to hypoxia. This response occurs at morphological, biochemical and immunological levels, causing a variety of physiological and pharmacological effects. Morphologically, endothelial cells swell and form "microvilli" at the luminal surface of the cell. This results in a reduction in the luminal patency of the capillary vessel. Mechanical plugging by erythrocytes, leukocytes, and platelets ensues. At a biochemical level, endothelial cells mediate the effects of vasoactive agents such as endothelin peptides, eicosanoids, and smooth muscle relaxant (probably nitric acid), which in part modulate the vascular tone of the microcirculation. Activation of endothelial adhesion molecules promotes

leukocyte adherence to the endothelial wall, a key process in the initiation of the inflammatory process ***(Schneck et al., 2005).***

Ischemic Penumbra (IP)

Following vessel occlusion, the main factors ultimately determining tissue outcome are regional CBF and duration of vessel occlusion. A decrease in regional CBF leads to diminished tissue perfusion. In persistent large vessel occlusion, local perfusion pressure, which is the main factor influencing the eventual outcome of tissue, depends on several factors such as the presence and extent of collaterals and systemic arterial pressure (brain autoregulatory capacity). It is inversely correlated to the local tissue pressure (which is increased by ischemic edema) ***(Schneck et al., 2005).***

Cerebral Blood Flow Thresholds in Acute Cerebral Ischemia

The difference in tissue outcome following arterial occlusion is based on the concept that CBF thresholds exist, below which neuronal integrity and function are differentially affected ***(Fig.1)***.

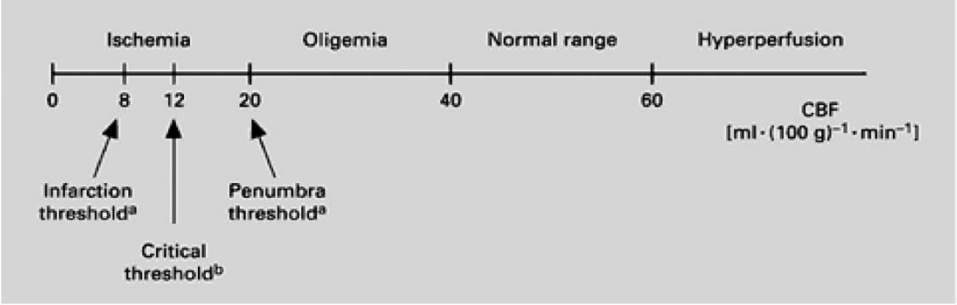

Fig. (1): Schematic drawing of the different cerebral blood flow thresholds in man ***(Tudor et al., 2008).***

Early human studies performed in the 1950s during carotid artery clamping for carotid endarterectomy using

intracarotid xenon 133 injections reported that hemiparesis occurred when regional CBF fell below 50% to 30% of normal, and permanent neurologic deficit occurred if mean CBF fell below 30% of normal ***(Boysen, 1971).***

Evidence also indicated that development of permanent neurologic sequelae is a time-dependent process; for any given blood flow level, low CBF values are tolerated only for a short period of time, while higher CBF values require longer time for infarction to occur. Two hours of continuous middle cerebral artery (MCA) occlusion in awake macaque monkeys required CBF values of 5mL/100g/min to produce infarction, while 3 hours of continuous occlusion resulted in infarction if CBF values were around 12 mL/100 mg/min. Permanent occlusion resulted in infarction if flows were 18 mL/100 mg/min or less. It should be noted that 30 minutes of occlusion did not result in infarction even at CBF values below 5 mL/100 mg/min ***(Tudor et al., 2008).***

The notion that in acute stroke, depending on the extent and duration of hypoperfusion, the tissue supplied by the occluded artery is compartmentalized into areas of irreversibly damaged brain tissue and areas of brain tissue that are hypoperfused but viable led to the concept of ischemic core and ischemic penumbra ***(Astrup et al., 1981)***.

The ischemic core represents tissue that is irreversibly damaged. Positron emission tomography scan (PET) studies in humans suggest that the ischemic core corresponds to CBF values of 7 to 12 mL/100 mg/min (***Heiss, 2004).***

The ischemic penumbra represents tissue that is functionally impaired but structurally intact and, as such, potentially salvageable. Salvaging this tissue by restoring its flow to nonischemic levels is the aim of acute stroke therapy. Another compartment, termed area of oligemia, represents mildly hypoperfused tissue from the normal range down to

around 22 mL/100 mg/min. It is believed that under normal circumstances this tissue is not at risk of infarction ***(Tudor et al., 2008)***.

It is conceivable, however, that under certain circumstances, such as hypotension, fever, or acidosis, oligemic tissue can be incorporated into penumbra and subsequently undergo infarction. Evidence in the literature suggests that there is temporal evolution of the core, which grows at the expense of penumbra if vessel occlusion persists. ***(Hossmann, 2006).***

Alternatively, it may return to a normal state following vessel recanalization or possibly neuroprotective interventions. It thus appears that the ischemic penumbra represents a transitional state between evolution into permanent ischemia as one possibility and transformation into normal tissue as the other possibility ***(José et al., 2008).***

Restriction of acute stroke therapy aimed at vessel recanalization to 4.5 hours from onset of symptoms for IV thrombolysis and 6 hours for intra-arterial thrombolysis is based on the concept that the ischemic penumbra has a short lifespan, being rapidly incorporated into the core within hours of the ictus ***(Rothwel et al., 2009).*** However, recent evidence suggests that penumbral brain tissue of significant extent is present even beyond 6 hours of stroke onset. PET studies using quantitative CBF assessment or markers of tissue hypoxia such as 18F fluoromisonidazole to assess penumbra, included patients studied within 6 hours to as late as 51 hours after stroke onset and reported the existence of penumbra comprising 30% to 45% of the total ischemic tissue at risk ***(Tudor et al., 2008).***

Several investigators have estimated the penumbra based on diffusion/perfusion MRI (diffusion-weighted imaging [DWI]/perfusion-weighted imaging [PWI]) mismatch

in acute stroke. Since the diffusion abnormalities are presumed to represent an approximation of the irreversible ischemic lesion and the perfusion abnormalities are presumed to represent the brain territory at risk, the area of mismatch between DWI and PWI is considered a territory still viable but at risk of undergoing infarction and corresponds theoretically to the concept of ischemic penumbra. The major shortcoming of this concept derives from the lack of quantitative data provided by MRI imaging. It has been shown that the DWI lesion is not precise in distinguishing between irreversible and reversible ischemia, it incorporates both types of ischemia and therefore cannot be considered equivalent to the ischemic core ***(Guadagno et al., 2005).***

Additionally, the PWI lesion has been shown to incorporate both imminently threatened brain and brain that will not undergo infarction as a consequence of persistent vessel occlusion. Since, by definition, penumbra represents tissue that will undergo infarction with continuous vessel occlusion, assessment of penumbral extent based on perfusion MRI is also not precise ***(Heiss et al., 2004).***

Cellular mechanisms of ischemic neuronal injury in acute stroke

At a cellular level, the biochemical and electrophysiologic mechanisms involved in the ischemic brain injury vary according to the extent of cerebral ischemia. Neuronal cell death occurs as a result of two main mechanisms: necrosis and apoptosis ***(Bhardwaj et al. 2003*)**.

Necrosis is a process that is not regulated or programmed and is the predominant mechanism that follows acute permanent focal vascular occlusion. It occurs mainly as a consequence of disruption of cellular homeostasis due to energy failure and is accompanied by cellular swelling, membrane lysis, inflammation, vascular damage, and edema

formation ***(Bhardwaj et al., 2003)*** (***Fig. 2).***

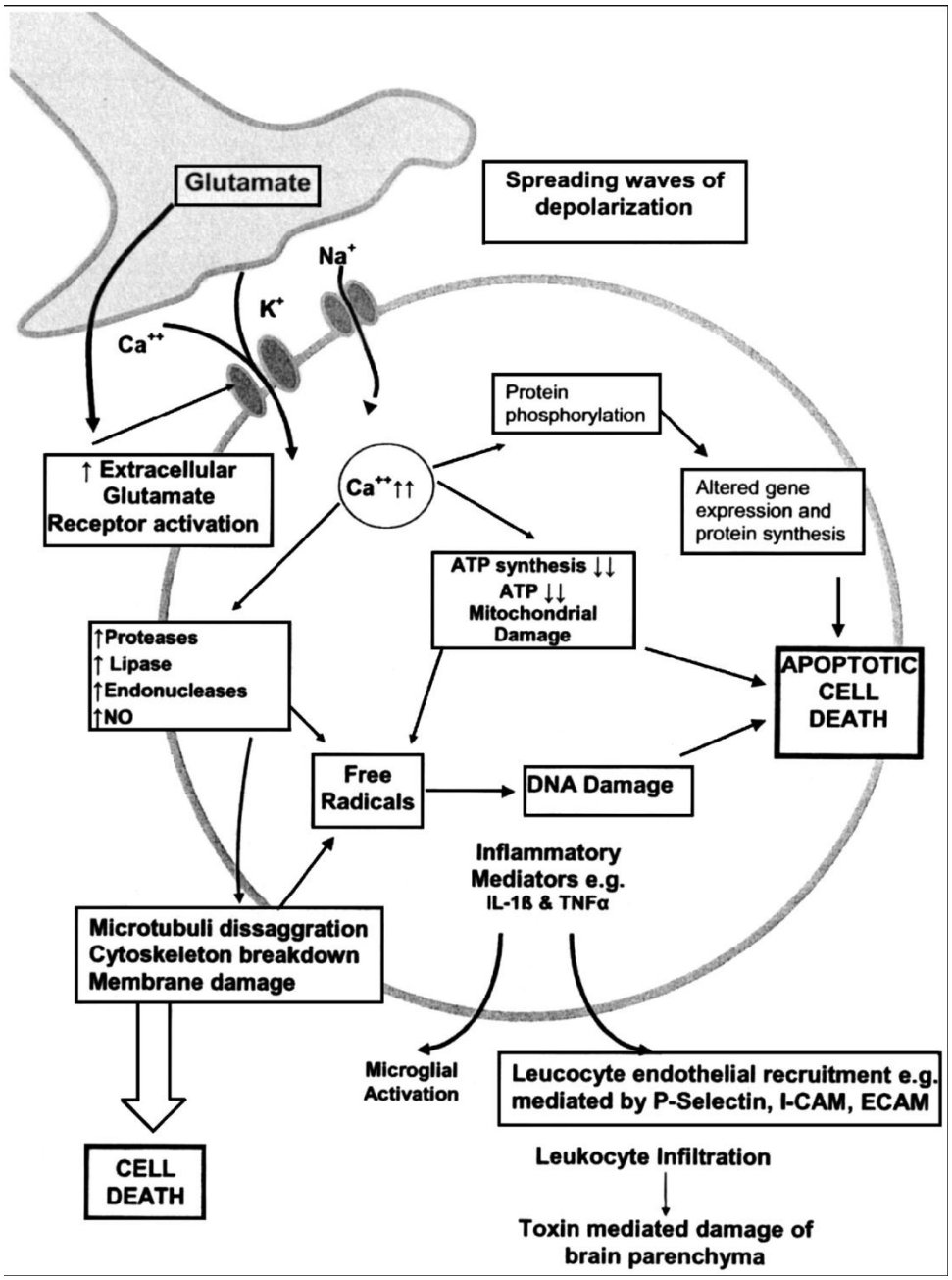

Fig. (2): Cellular mechanisms of ischemic neuronal injury in acute stroke. IL-1b = interleukin 1b; TNF = tumor necrosis factor; ICAM = intercellular adhesion molecule; ECAM = endothelial cell adhesion molecule ***(Tudor et al., 2008)***

Apoptosis, or programmed cell death, is characterized by cell shrinkage, chromatin clumping, and cytoplasmic blebbing and is not associated with inflammation or secondary injury to surrounding brain ***(Graham et al., 2001) (Fig. 3).***

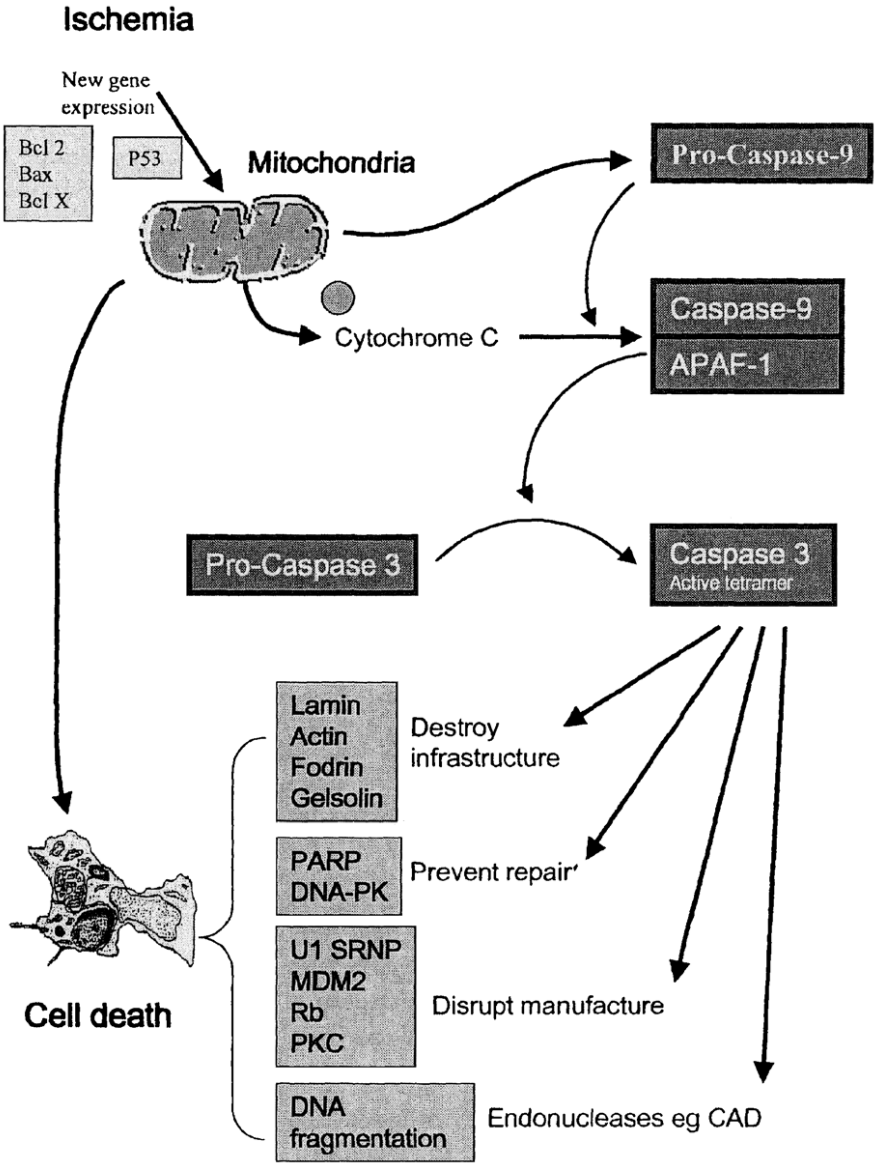

Fig. (3): Overview of molecular events involved in apoptosis. CAD = caspase activated DNAas, PARP: Poly –ADP ribosyl polymerase, PK: protein kinase, SNRP: Stress non-response period, PKC protein kinase-C; ***(Tudor et al., 2008)***

These two distinct types of neuronal death appear to represent opposite poles of a spectrum that coexist within the ischemic brain, with necrosis being the main mechanism of neuronal injury in the ischemic core and apoptosis being the main mechanism of neuronal injury in the penumbra where, because of the milder degree of ischemia, sufficient energy is produced to allow for expression of new proteins that mediate apoptosis ***(Bhardwaj et al., 2003).***

Acute vascular occlusion triggers a complex sequence of pathophysiologic events that evolve over time and space. Major pathogenic mechanisms of the ischemic cascade leading to neuronal injury constitute active targets for various neuroprotective strategies and include cytotoxicity, peri-infarct depolarization, inflammation, tissue acidosis, nitric oxide, and free radical production, as well as, at a later stage, apoptosis ***(Doyle et al., 2008).***

Excitotoxicity, Peri-infarct Depolarizations, Acidosis, and Inflammation

The reduction in regional CBF through insufficient delivery of the neuron main energy substrates, oxygen and glucose, results in inadequate production of energy required to maintain ionic gradients ***(Martin et al., 1994).***

Since the transport of calcium from the cell into the extracellular space is an energy-dependent process, this leads to intracellular accumulation of calcium. Calcium influx is further enhanced by impairment in the energy-dependent reuptake of excitatory amino acids, especially glutamate, and by release of excitatory amino acids into the extracellular space. An increase in extracellular glutamate leads to increased calcium influx, through increased stimulation of the NMDA or non-NMDA (mainly α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid [AMPA]) receptor. At the same time, sodium and chloride enter the neuron via channels

for monovalent ions ***(Tyson et al., 1996).***

Water follows osmotic gradients, leading to edema, which is predominantly cytotoxic and can further diminish perfusion in regions surrounding the core, leading to recruitment of penumbral areas into the core (***Hossmann, 2006).***

Effects of delayed edema formation (at this stage predominantly vasogenic) include increased intracranial pressure, shift and displacement of brain structures, vascular compression, and herniation ***(Hossmann, 2006).***

The accumulation of intracellular calcium leads to a series of events at both the cytoplasmic and nuclear levels that result in cell death through several mechanisms (Fig. 2): activation of enzymes that degrade cytoskeletal proteins, activation of lipoxygenase and cyclooxygenase, xanthine oxidase and nitric oxide synthase with resultant accumulation of highly cytotoxic oxygen free radicals oxygen (O2), hydrogen peroxide (H_2O_2), hydroxyl (OH) and nitric oxide (NO). These reactions occur both in the cytoplasm and in the mitochondria ***(Tudor et al., 2008).***

Mitochondria are an important source of reactive oxygen species. As a consequence of free radical–mediated disruption of the inner mitochondrial membrane and the oxidation of the proteins that mediate electron transport ***(Dugan, 1994),*** the mitochondrial membrane becomes leaky through the formation of a so called mitochondrial permeability transition pore in the mitochondrial membrane. This results in mitochondrial swelling, intra-mitochondrial calcium accumulation, impaired energy production, and reactive oxygen species production ***(Kristian et al., 1998).***

Another consequence of disrupted mitochondrial permeability is the release of proapoptotic molecules, such as