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Ischemia as Superimposed Previous Ischemic Events Centered on Microcirculatory Failure

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Abstract: A clear delineation of events in the production of an ischemic lesion that evolves in terms of previous episodes of similar ischemia might implicate episodes of superimposition of various cellular injuries. Central to such events there would evolve a micro-circulatory failure that precipitates crescendo-type pathways of progressive injury to cells and also to vessels supplying the area concerned. It is perhaps with regard to such micro-circulatory events that evolve as regional and focally regional sites of injury to vessels that there would in turn become superimposed a proximal pathway of progressive luminal stenosis and occlusion of parent vessels such as the epicardial coronary arteries. One might indeed view superimposed episodes of ischemia to tissues and cells a source of propagated injury determining both microcirculatory failure and also an influence in progression of proximal vascular pathology related to impaired hemodynamics. Proximal parent vascular stenosis would progress hand in hand with microcirculatory failure in determining the acute critical precipitation of ischemia affecting cardiac myofibers in acute myocardial infarction and crescendo angina and in the evolution of progressive neuronal ischemia and necrosis of liquefactive type.

Key words: Ischemia, microcirculatory, vessels, injury

INTRODUCTION

The effects of ischemia may include not only hypoxia but also a lack of inadequate supply of nutrients such as glucose and also impaired removal of waste products. Blood lactate concentrations are a highly sensitive index of tissue oxygen deprivation[1]. *Adenosine,* extracellularly derived from CD73, may activate platelets and participate in leukocyte-endothelial interactions and modulate coronary vascular tone[2].

These forms of disturbed cellular homeostasis are probably intimately related and include also inflammation in further inducing ischemic injury[3]. The main effect of ischemia is lack of oxygen especially in cases of acuteness of many of the cases of vascular insufficiency affecting organs. This is true particularly since infarction is the main significant pathologic lesion induced by ischemia. Tissue infarction constitutes a radically dramatic evolution of changes and events that contribute mainly to clinical significance and manifestations. In fact, infarction of tissues is the direct cause of the patient's presenting symptoms and signs and even more so forms the basis for the pathology resulting from ischemia of organs and tissues.

Primary vascular disorders mainly translate in terms of compromise of the vascular lumen, thus potentiating the development of infarction.

p21-activated kinase regulation of vascular permeability induced by growth factors and cytokines may be exerted via an effect on cell contractility[4].

Infarction is a fundamental transformation in the clinical and pathobiologic state of the patient and is the main concern clinically.

Ischemia in the absence of infarction is particularly significant clinically in terms of required measures in prevention of the ischemic effects being translated into infarction. Ischemic preconditioning protects the heart by phosphorylating the pro-survival kinases Akt and Erk1/2 at the time of reperfusion[5]. Ischemic hypoxia is closely tied up with the two other basic requirements compromised by ischemia. When significant ischemic hypoxia develops, the disturbed utilization of any available glucose and the impaired excretion of any endproducts of cellular metabolism are less significant in that there is not sufficient oxygen to metabolize the glucose or other nutrients.

Significant ischemic hypoxia so dominates the pathologic milieu of the cell that a failure of delivery of adequate nutrients or of the elimination of waste products assumes a very secondary form of disturbance, particularly when one considers the acuteness of episodes of ischemia leading to infarction.

Evidence indicates that oxidative injury is significant after ischemia-reperfusion of tissues[6].

Regarding actual tissue organ infarction in cases where longstanding significant ischemia has been present, as with progressive stenosis of the vascular lumen by atherosclerosis, the progressive long-term

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inadequacy of glucose and of other nutrients would be important in actually precipitating acute infarction at that particular point in time. Mitochondria consume ATP during ischemia by reversing ATP synthetase activity, which compromises cellular membrane potential by consuming ATP[7].

It is important clinically to recognize certain pathobiologic factors or parameters that may precipitate the acute episode of infarction. The infarction process is generally an acute one and hence there must exist a given set of usual circumstances and parameters that tend to precipitate the acute episode of infarction.

Much pathogenic significance has been attached to the complicated atheromatous plaque particularly in terms of surface plaque ulceration with superimposed thrombotic occlusion of the lumen, or of acute hemorrhage within the plaque causing severe stenosis or luminal occlusion. A degree of narrowing is often reached, short however of complete occlusion of the lumen, that would precipitate acute infarction.

Endogenous monocyte chemoattractant protein appears implicated in inducing neovascularization after ischemia by recruiting macrophages that activate Tumor Necrosis Factor-alpha and Vascular Endothelial Growth Factor (VEGF) induction[8].

One possible set of circumstances would represent a sudden need for more oxygen as induced by physical exertion or tachycardia. Arrhythmias are a recognized effect of myocardial ischemia and such induced arrhythmias may further lead to functional demand for oxygen to cardiac myofibers.

Arrhythmias may very well be particularly induced in patients who have suffered from significant myocardial ischemia for a number of months or years due to stenosis of a coronary vessel but in the absence of complete luminal occlusion.

Such a possible train of events would account for many cases of sudden cardiac death even in the absence of complete occlusion of the lumen of any of the three main epicardial coronary vessels.

These cases of sudden cardiac death due to myocardial ischemia would be precipitated only by the sudden onset of a serious arrhythmia, itself induced by a long period of previously established tissue ischemia.

Chronic myocardial ischemia may be a very significant pathobiologic state that tends to progressively promote the likelihood of development of a serious arrhythmia.

One significant effect of chronic ischemia of the myocardium would involve increased excitability of these affected myofibers promoting further progression of arrhythmia, increased oxygen demand and hence a much greater risk of myocardial infarction.

Serious arrhythmia may not only result as a possible complication of an acute myocardial infarct, but theoretically might precipitate also acute myocardial infarction in many patients suffering from a long history of chronic myocardial ischemia.

Chronic ischemia may be significant in promoting the development of arrhythmias not only by inducing a chronic state of insufficiency of oxygen but also by a relative inadequacy of nutrients such as glucose or electrolytes such as potassium to the affected myocardium.

Is ischemia equivalent to ischemic hypoxia?: So essential is an adequate oxygen supply to tissues and cells that ischemia is generally considered essentially equivalent to ischemic hypoxia in its pathogenicity. An abrupt occlusion of a vessel such as a complicated atheromatous plaque with superimposed thrombosis appears to lead to myocardial infarction largely because of a failure to deliver oxygen to the involved area.

There is a tendency to equate infarction as a basic phenomenon with necrosis due to lack of oxygen supply.

However, there are probably other mechanisms that constitute an integral part in the production of a myocardial infarct. In aged individuals, there is evidence of reduced anti-oxidative protection of cardiomyocytes after ischemia-reperfusion, with resultant enhanced oxidative stress and inflammatory responses[9]. The effective lack of delivery of blood to a region of the left ventricular myocardium would implicate a very important element of hypoxia.

Subendocardial infarction in contrast to regional or transmural infarction is essentially diffuse and classically associated with severe diffuse stenosis of most of the coronary vessels in the absence of complete occlusion of their lumen. Hypotension associated with diffuse coronary vessel stenosis appears particularly prone to precipitate subendocardial infarction. This has been interpreted as a manifestation of a significantly decreased blood flow reaching particularly the subendocardium.

However, it would appear that in these cases some blood perfusion of the myocardium does occur. In fact, subendocardial infarction would imply some persistent blood flow to the involved myocardium, including possibly also the subendocardium.

Presumably, total occlusion of a coronary vessel that is already diffusely and severely stenosed by atherosclerosis would not result in subendocardial infarction but often in a fatal arrhythmia or in sudden cardiac death. On the other hand, a recognizable transmural infarct would occur mainly where there are focal occlusions of severe atherosclerotic vessels without any severe diffuse stenosis of the coronary vasculature.

Molecular chaperones actively participate in cytoprotection of cardiomyocytes. In addition, repeated brief episodes of ischemia tend to induce tolerance to ischemia[10].

The manifestations clinically, pathophysiologically and morphologically would depend considerably on the pattern of distribution of the atherosclerotic process, a process that is traditionally considered largely capricious in distribution.

The distribution pattern of atherosclerosis appears to be either focal (even if multiple lesions are present) or else diffuse and stenosing. One might postulate that the rate of blood flow in a vessel is a particularly important parameter that is distinct from the actual degree of delivery of oxygen to the area concerned.

This might even possibly imply an essential primary failure of the micro-circulation of the myocardium as an important lesion contributing to the onset and progression of a myocardial infarct.

Abrupt cessation of blood flow results in rapid membrane depolarization and increased reactive oxygen species in microvascular endothelial cells[11].

It might prove true to consider a failure of the microcirculation as a distinct entity in its own right towards the development of many or most myocardial infarcts, particularly with subendocardial infarction. Even in cases of regional or transmural infarction, there may possibly develop a situation whereby a cascade-like series of mechanisms primarily affect the myocardial micro-circulation inducing possible development of that infarct. Such mechanisms might operate in conjunction with terminal complement components C5a and the membrane attack complex in pathogenesis of ischemia-reperfusion injury of many organs[12].

Ischemia might inflict its damage and promote the development of an infarct by two main mechanisms: one due to actual ischemic hypoxia and another series of mechanisms that are due to a primary failure of the micro-circulation as a result of decreased perfusion pressure of blood. Coronary microvessels are functionally coupled to the myocardial metabolic state. Hypercholesterolemia effects functionality of the microvasculature[13].

Myocardial infarction might arise directly both from ischemic hypoxia and also from markedly diminished perfusion pressure as such, leading to hypoxia from coronary stenosis or occlusion and also microcirculatory failure.

This latter phenomenon would resemble the pathophysiologic events responsible for the shock state in systemic hypovolemia. It would tend to self-propagate in terms of a genesis and a progression that are unclear in nature.

Primary injury to the microvasculature might be due to a whole host of possible mechanisms and agents besides hypoxia, as for example, failed perfusion head pressure of blood, spasm and thrombosis centered on arterioles, capillaries and venules. Like natural antibodies, autoantibodies that include anti-dsDNA and anti-histone antibodies, may instigate ischemic/reperfusion injury, as seen in patients with systemic lupus erythematosus.

Dynamic flux in neuronal ischemia: An important point of distinction appears to exist between a purely neuronal form of ischemia and a regional field of involvement in brain ischemia. VEGF appears to operate both in the induction of angiogenesis and also in neuronal protection[14].

Individual red shrunken neurons are widely recognized as a morphologic manifestation of individual neuronal ischemia[15].

This contrasts sharply with the liquefactive necrosis that develops in the brain affected by cerebral thrombosis or embolism.

One main point of difference may lie in a considerably increased degree of severity of the ischemic hypoxia that develops with vascular occlusion. The red shrunken neuron may appear to be essentially a manifestation of hypoxic hypoxia rather than a result of ischemia or ischemic hypoxia. Elevated extracellular levels of amino acids have also been implicated in stroke, inducing neuro-excitotoxicity[16].

Such a possible distinction may help delineate better the essential difference in the effects of ischemia from pure hypoxia. Prolonged episodes of severe hypoglycemia also tend to produce red shrunken neurons rather than a liquefactive area of necrosis.

One distinguishes an essential difference between a true infarct from hypoxic neuronal injury in the absence of a significant degree of ischemia. The red shrunken neuron phenomenon attests to the exquisite sensitivity of the neuron to hypoxia. An important point would be the occurrence of red shrunken neurons as a universal phenomenon in the early stages of development of a cerebral infarct.

Whether in fact all the neurons or most of them in a region of the brain affected by clinically significant ischemia first pass through an initial stage of red shrunken neurons or not, only subsequently being completely involved in a focus of liquefactive necrosis, appears important to determine. Neurons in ischemic and nonischemic regions may die from different mechanisms, including a possible mixed or hybrid form of both necrotic and apoptotic changes affecting primarily individual cells[17].

Red shrunken neurons appear mainly present in zones bordering a region of complete or near complete ischemia in the brain, rather than a feature of the actual area of early ischemic necrosis. Red shrunken neurons are primarily not necrotic nor, perhaps, dead neurons. It may be reasonable to suggest that at least some red shrunken neurons are in fact potentially recoverable. An essential feature of hypoxic neuronal injury and perhaps also of ischemic neurons, is the injury that encompasses a whole spectrum of severity of neuronal injury, including both pre- and post-mitochondrial cell death pathways[18]. This would better illustrate the nature of the pathologic insult to any group of neurons affected by ischemia or even pure hypoxia.

One may appreciate the very dynamic flux of pathophysiologic effects of ischemia in an involved area of the brain. The actual dimensions of an infarct are to an important extent potentially highly variable parameters in an individual patient depending on therapeutic measures that potentially reduce the size of any infarct that develops subsequent to occlusion of an occluded artery.

The very nature of development of a cerebral infarct is one of flux whereby numerous dynamic parameters probably interplay in determining the size of the eventual focus of liquefactive infarction. Protease-activated receptor-1 and serine proteases in general and their receptors, are implicated in neuronal injury after hypoxia/ischemia[19]. Both tissue plasminogen activator and plasmin, which are broad spectrum protease enzymes, are potentially neurotoxic[20] if they reach the extracellular space.

Acute management in the early stages of cerebral ischemia or hypoxia may potentially improve significantly outcome for a patient affected by cerebrovascular accidents in general. A period of dynamic flux of parametric influence may actually provide an important opportunity to help prevent a severe regional lesion from developing. Lack of recovery from protein synthesis inhibition closely correlates with neuronal death following ischemia and reperfusion[21].

The early stage of a cellular lesion is one that is primarily controllable and not necessarily progressive in itself. Later secondary events may be largely responsible in determining whether a cellular injury such as from ischemia would result in neuronal death or recovery. The c-Jun N-terminal protein kinase signaling pathway is implicated in ischemia-induced neuronal apoptosis linked strongly to mitochondrial apoptogenic proteins[22].

Potential recovery may to an important extent depend on dynamic flux in pathophysiologic events in the early stages of the inflicted cellular injury.

Blood maldistributon pattern causing angina pectoris at rest: Angina pectoris at rest is probably an expression of a disturbed redistribution of blood rather than an absolute insufficiency of blood to the myocardium in view of its characteristic transient symptomatology. Reduction of nitrite to nitric oxide during ischemia may protect cardiomyocytes after ischemia-reperfusion injury[23].

Angina at rest may imply an essentially adequate blood supply reaching the heart, but one that involves relative insufficiency at the myofiber levels at some point in time. This would probably implicate a significant degree of disturbance in the pattern of blood delivery once that blood enters the coronary circulation.

The presence of chest pain is related to the extension of ischemia toward long-axis of the left ventricle. Disappearance of pain does not necessarily signify recovery from ischemia[24].

Such disturbed patterns of distribution would potentially result not so much from atherosclerosis of the major epicardial vessels, but may possibly implicate pathophysiologic disturbance further down the coronary arterial network. Ischemia-reperfusion injury is associated with microvascular leakage modulated by inflammatory cascades and matrix metalloproteinases, as seen in the kidney[25]. Intramural vessels of the heart are essentially unaffected by atherosclerotic narrowing and hence one might be justified in suggesting some other mechanism leading to angina at rest.

Such mechanisms may be dynamic rather than structural impedance to coronary blood flow. The mitochondrial electron transport chain contributes to ischemic mitochondrial damage that in turn augments myocyte injury during subsequent reperfusion[26]. As such, they are likely to be related closely to the very nature of the myocardial contractile physioanatomy.

The fact that the attacks, by definition, are transient would be suggestive of spasmodic narrowing of intramural coronary vessels. This may result from vasospasm of the smooth muscle wall of the vessels or perhaps as a direct consequence of the fascicular pattern of setup and distribution of cardiac myofibers around such intramural vessels, leading to vascular narrowing when the cardiac myofibers contract.

Angina pectoris at rest would be primarily precipitated by an abnormal pattern of myofiber contraction of the left ventricle as a whole in causing external spasmodic narrowing of intramural coronary vessels, superimposed on a background of significant atherosclerosis of parent coronary vessels.

Crescendo angina as an ischemia-induced cascade of myofiber hypercontraction: Crescendo angina is characterized by a progressive series of attacks of central

chest pain, often of progressively increasing severity, together with a particular tendency for myocardial infarction.

No doubt, crescendo angina represents a cascade series of events, one promoting the development and augmentation in severity of subsequent events leading to infarction. Delta protein kinase C activation has a critical pro-apoptotic role in cardiac responses following ischemia and reperfusion[27].

Crescendo angina may be due to a programmed series of events, one step leading to the next. As a pathophysiologic process, it would require the presence a substratum of progressive ischemia. It would seem that crescendo angina represents a strong tendency for myocardial field ischemia to spread and involve more of the myocardium. During ischemia there is altered gap junction coupling of cardiomyocytes with a tendency to develop arrhythmias. There is dephosphorylation of Connexin 43 that is sensitive to fluctuations in cellular ATP[28].

Such a process would reflect the profound disturbance affecting the coronary circulation in ischemic heart disease, one that appears greatly enhanced in promoting further myocardial ischemia by other factors related to the heart. Inadequate angiogenic response to ischemia in diabetic myocardium could result in poor collateral circulation[29]. During systole, the myocardium suffers a significant period of ischemia and it is conceivable that such systole-induced ischemia would be promoted further by primary episodes of myocardial ischemia. Mitochondrial injury develops and also exclusive urocortin expression in viable cells[30].

In crescendo angina, a progressive deterioration in blood supply to the myocardium would precipitate critical levels of myofiber ischemia associated with persistent contraction of cardiac muscle as induced by previous ischemic episodes. The sodium-calcium exchanger in particular controls the concentration of Ca(2+) in cardiomyocytes. It underlies an arrhythmogenic transient inward current responsible for delayed after-depolarization and nonreentrant initiation of ventricular tachycardia[31].

As such, it would appear that crescendo angina owes much of its character to ischemia-induced prolongation of contraction of cardiac myofibers.

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