The Cardiology 1 (2): 137-141, 2005

Systems of Progression in Transformation of Endothelial Proinflammatory Ischemia in Atherogenesis

M. Lawrence Agius
Department of Pathology, St Luke's Hospital Gwardamangia
Medical School, University of Malta, Msida Malta Europe

Abstract: Proinflammation attributes ischemic episodes with a series of progressive cellular transformations linking endothelial ischemic injury to a full range of events encompassing cellular degeneration and cell death. Ischemia induces endothelial activation in a process that promotes a subsequent phase of reperfusion injury that accompanies vasodilatation. Endothelial injury appears to activate initial changes in development of the atheromatous plaque and also is involved in subsequent progression towards evolving complicated plaques, including plaque rupture. One might envision endothelial injury as a series of initial activation steps inducing both inflammation and possibly also Ischemia to the tunica intima. Endothelial activation might be significant as a proinflammatory state in atherogenesis.

Key words: Proinflammatory, endothelial, transformation, atherogenesis, Ischemia

INTRODUCTION

Endothelium-dependent vascular dilatation: ndothelium-dependent relaxation of the vascular wall primarily evolves in terms of a three-source-derivation of nitric oxide from neurons, microglia and endothelial cells.

A clear delineation of mechanisms of action of nitric oxide that interacts with reactive oxygen species would allow for the initiation and progression of cerebral vasodilatation. Hypertension and diabetes mellitus on the one hand, and lesions ranging from bacterial meningitis to multiple sclerosis on the other, would primarily determine endothelial response to acetylcholine, nitric oxide, reactive oxygen species, endothelium and adrenomedullin that mainly influence vascular smooth muscle and especially the potassium channels.

Nitric oxide in particular would enhance a series of reactivity patterns that precondition response to various stimuli acting on vascular endothelium. Inhibition of intercellular adhesion molecule-1 expression may ameliorate inflammation related to ischemic vascular endothelium[1]. Microglial Nitric Oxide production and endothelial nitric oxide would permit the evolution of a response pattern primarily involving a neuronal reactivity to injury.

Neuronal recovery is enhanced in rodent models of spinal cord injury on suppressing neuroinflammation, especially by blocking inducible nitric oxide synthase[2]. Minocycline acts by means of an antiinflammatory mode of protection of neurons[3].

Endothelial cell injury: Vascular blood supply predetermines nitric oxide responsiveness of neurons, microglial and endothelial cells in hypertension and diabetes mellitus. One would consider how Ischemia of tissues culminates in vascular wall Ischemia as a vicious cycle of progressive injury to endothelial cells. Indeed, various acute phase reactants mark the pathogenic role of inflammation in atherosclerotic progression of cerebral Ischemia [4,5]. It is in terms of such endothelial cell injury that atherosclerosis promotes a high degree of susceptibility to development of ischemic lesions and also a heightened sensitivity to oxidative stress[6].

The cerebral circulation might prove highly dependent on an intact endothelial cell bed promoting response or nonresponse to nitric oxide. It is in the clear evolutionary derivation of nitric oxide that predominantly interacts with oxygen free radicals that one would better redefine an axial relative progression of Ischemia to the brain.

Interleukin 18 in particular contributes to white matter ischemic injury in the neonatal brain[7], as does interferon gamma in inducing toxicity to premyelinating oligodendrocytes in Ischemia[8].

Vasodilatation and vasoconstriction effects of cerebral blood vessels appear to evoke secondary effects in tissues that are self-progressive even in terms of subsequent evolution of the vascular injury. Statins may modulate proinflammatory Ischemia, and improve endothelial function and coagulation[9]. The endotheliumis particularly susceptible to oxygen free radicals that increase dramatically with reperfusion of ischemic tissues [10]. Allowing for patterns of reactivity on the one hand and for variable response on the other would account for constitutive and inducible forms of nitric oxide production in endothelium, neurons or microglia. Hypoxia stimulates

microglially induced neurotoxicity[11,12].

Inflammatory states affecting the central nervous system would constitute a radically altered responsiveness of endothelial cells to Ischemia or otherwise injured CNS tissues. Neuronal DNA injury results particularly from an inability to utilize glucose as occurs after activation of poly(ADP-ribose) polymerase-1 (PARP) [13]. Inducible nitric oxide interacts with PARP and aggravates cerebral Ischemia[14]. PARP affects DNA repair, genomic stability, transcription and cell death[15]. Only in such terms can one allow for the emergence of multiple sclerosis plaques that predominantly evolve as endothelially induced and mediated responsiveness to injured white matter. Oligodendrocytes would not simply evolve as an endtarget of inflammation but primarily induce an aberrant responsiveness on the part of endothelial cells within demyelinating plaques in multiple sclerosis.

The strict role played by an essential state of vasodilatation in inflammation of the CNS would perhaps have to involve an especially increased vulnerability to the inflammation[16] that induces oxidative stress, leukocytic infiltration, macrophage activation and even ischemic endtarget responses on the part of neurons, glia and microglia. Ischemia triggers acute inflammation and exacerbates primary brain injury, via also activation of the innate immune system [17].

An essential endpoint coupling between vasodilatation of cerebral vessels and of eventual forms of tissue ischemic effect would paradoxically evolve in terms primarily of impaired endothelial-dependent vasodiatation of the vessels. Oxidative stress in Ischemia/reperfusion culminates in excessive cytokine and chemokine response, upregulation of adhesion molecules and over production of nitric oxide[18].

Tissue Ischemia: Ischemia of tissues would primarily entail vascular wall reactivity that progresses particularly in terms of aberrant endothelial cell response.

A cyclical reproduction of events once vasodilatation sets in would perhaps promote subsequent sequences of events prone particularly to exacerbation of injury to the vascular wall. Realization of the vascular wall as the primary target in ischemic lesions would account for a varied series of events promoting further progression of Ischemia in the face, paradoxically of vasodilatation. Reperfusion injury is itself a prime mechanism that would promote cyclical evolutionary pathways to affect the vascular wall as part of operatively induced Ischemia to CNS tissues. Peroxisome proliferator-activated receptor agonists exert potent anti-inflammatory effect in protecting against atherosclerosis and Ischemia[19]. This action is mediated also by improvement of insulin resistance of vascular endothelium [20].

In this sense, even hypervascular tissues that evolve in terms of a rich blood supply are especially prone to Ischemia that induces extensive necrosis of tissues even beyond defined tumor margins. Vascular endothelial growth factor induces angiogenesis, vascular permeability and inflammation with breakdown of the blood-brain barrier[21].

Circulatory steal phenomenae only partly take into account a series of endothelially induced pathways that disturb blood supply patterns primarily affecting vascular walls. A resynthesis of vascular wall Ischemia based on endothelially derived progressiveness that promotes further reaction to persistent injury to supplied tissues would permit a clearer delineation of events culminating in an Ischemia based on a predominant but aberrant vasodilatation of vessels.

Persistent vascular dilatation might in fact constitute a possibly effective mechanism in vascular wall injury first induced by endothelial injury and later by Ischemia to the vessel wall smooth muscle. Vascular smooth muscle appears a primary target for endothelial cell reactivity primarily evolving as response to nitric oxide, reactive oxygen species and peroxynitrite.

A strict concept of blood supply regionally distributed via blood vessels would not fully account for patterns of Ischemia in the brain. Genes that are downregulated in cerebral Ischemia include ion channel genes and neurotransmitter receptor genes and synaptic proteins genes that may affect postinjury recovery[22].

In particular, the inflammatory lesions in cases of multiple sclerosis and of meningitis would reconstitute differential aspects of a response to injury based at least partly on aberrant endothelial cell reactivity.

An appreciation of a variety of lesions ranging from reperfusion-associated injury [23] to no-flow phenomena to vasoconstriction and vasodilatation that persist indefinitely in the face of vascular wall injury might especially emphasize how injury to vessels constitutes a primary form of progressive injury in inflammatory states. The brain Angiotensin II system induces brain artery remodeling and inflammation in spontaneously hypertensive rats[24].

Leukocytic infiltration of the vessel wall and of tissues would constitute variable responsiveness as induced nitric oxide production by microglia and endothelial cells.

Reperfusion: It is in terms that resolve as part of a full spectrum of types of injury ranging from reperfusion injury to Ischemia that there would be set in motion a

variety of other injuries that specifically affect either white matter or neurons as primary targets. Neuroregulin-1 is induced in the penumbral ischemic region of an infarct and blocks apoptosis of cortical neurons[25].

The operative influences of endothelium-dependent vasodilatation would perhaps presuppose blood stream-mediated effects in progression of inflammatory lesions of the CNS. CSF Interleukin-6 may constitute a biologic marker of dementia in cerebrovascular disease[26]. Besides leukocyte pavementation of endothelial cells based on adhesion molecular biology there might also evolve a series of activated cells transforming endothelial and vascular smooth muscle interactions. Platelet proinflammatory adhesion to leukocytes occurs and predisposes to Ischemia[27] .

Ischemic tissue as an induced endtarget effect of vascular pathology would entail characterization of events initiated by progressive pathology affecting primarily the endothelium. Endothelium is a major target of inflammatory cytokines[28]. One might recognize Ischemia as induced nonresponsiveness or over responsiveness on the part of endothelium or the vascular wall that is influenced by hemodynamic attributes of blood flow.

Interactivity of endothelial cells with both flowing blood stream and vascular smooth muscle may very well act as a driving force in aberrant hyperperfusion type in inflammatory states. Hyperperfusion might be reflected in various forms of vascular wall injury that characterize even focally progressive and reperfused ischemic tissues.

Reperfusion of blood flow dynamics would allow for evolution of a state of hyperperfusion relative to the state of Ischemia suffered by tissues in the field of supply. It is in resolving such dramatic changes or transformed events that one would consider associated reactive oxidative injury a form of reperfusion of permanently damaged tissues.

Oxidative stress might evolve in terms of an endothelial ischemic injury to tissues that one initially propagates to involve also the vascular wall. Initial inflammatory involvement would transform susceptibility patterns to injury that largely are not resolved simply by cessation of the inflammatory activity. In this sense, post-inflammatory states would correlate with reperfusion states of injury affecting tissues suffering from established forms of ischemic injury. In fact, chronic inflammation plays a pivotal role in progression of atherosclerosis[28].

Categorization of essential states of Ischemia would incorporate an inflammatory component and hence a reperfusion and hyperperfusion of damaged tissues that specifically predetermine outcome both as regenerative and as reparative phenomena. A combined scheme of reparation and regenerative replacement might involve a hyperperfusion that on the one hand reperfuses tissues and on the other critically alters deficiencies induced by tissue injury in response to various agonists such as growth factors and cytokines.

Prehypertension appears linked to inflammatory markers and atherosclerosis independently of other coexisting risk factors [29].

It is in terms of transformed attributes of tissue response to injury that reperfusion allows the ingrowth of vascularized granulation tissue that has replaced ischemically injured tissues.

Biochemical transformation in ischemic injury might form part of reperfusion-induced injury that progresses in association with cytoskeletal injury. Cytoskeletal effects are only a representation morphologically of how Ischemia and inflammatory states constitute often aspects of one central process of biochemical injury that combines cellular homeostatic control with progressive transformation. Growth factors and inflammatory cytokines affect endothelial cell permeability and contractility, and secondarily modify vascular leak as a contributor of Ischemia and inflammation[30] .

Events that both promote and further participate in injury would perhaps allow for the development of vascularity patterns that are primarily endothelial responses to either Ischemia or inflammatory states. Significant relationships may link insulin resistance and cardiovascular disease as a consequence of low-grade inflammation[31] . Induced responses to cell injury are primarily proinflammatory.

It is in resolving such injury that one would perhaps better characterize Ischemia as inherently proinflammatory in its own right.

Patterns of response allow the evolution of ischemic lesions that incorporate also reperfusion states of injury. Such a dual set of superimposed events would also interactively promote conversion of blood flow hemodynamics as hyperperfusion and hypoperfusion states of vascular supply.

In terms of regional evolution of inflammatory states, a concurrent hyperperfusion and hypoperfusion series of events would involve also ischemic tissues damaged by the superimposed inflammation. A close correlation exists between chronic vascular inflammation and endothelial dysfunction in atherosclerosis that is reflected in C reactive protein levels[32] .

The actual dynamics of inflammatory states affecting ischemic tissues would have to incorporate a wide range in variability of vascular blood flow and of vascular response underlying progression of a multitude of lesion types.

CONCLUSIONS

Atherogenesis may very well constitute a series of injuries to an activated endothelium that progress concurrently with proinflammatory injury to the tunica intima. The complicated atheromatous plaque would evolve as a consequence of such proinflammatory injury that involves a variety of lesions often culminating in plaque rupture and thrombotic narrowing or occlusion of the vascular lumen.

REFERENCES

1. Sonoenday, C.J., D.S. Warren, S.K. Cooke, H.C. Dietz, and R.A. Montgomery, 2004. A novel chimeric ribozyme vector produces potent inhibition of ICAM-1 expression on ischemic vascular endothelium. J. Gene. Med, [Epub ahead of print].
2. Beattie, M.S., 2004. Inflammation and apoptosis: Linked therapeutic targets in spinal cord injury. Trends. Mol. Med., 10: 580-3.
3. Cornet, S., B. Spinnewyn, S. Delaflotte, C. Charnet *et al.,* 2004. Lack of evidence of direct mitochondrial involvement in the neuroprotective effect of minocycline. Eur. J. Pharmacol., 505: 111-9.
4. Cojocaru, I.M., M. Cojocaru, C. Musuronoi, A. Drute, and M. Becanu, 2002. Study of some markers of inflammation in atherothrombotic pathogenesis of acute ischemic stroke. Rom. J. Intl. Med., 40: 103-16.
5. Spagnoli , L.G. , A. Mauriello, G. Sangiorgi and S. Fratoni *et al.,* 2004. Extracranial thrombotically active carotid plaques as a risk factor for ischemic stroke. JAMA, 292: 1845-52.
6. Stocker, R. and J.F. Jr Keeney, 2004. Role of oxidative modifications in atherosclerosis. Physiol. Rev., 84: 1381-478.
7. Hedtjwin, M.,C. Mallerd, P. Arvidsson and H. Hagberg, 2005, white matter injury in the immature brain : Role of interleukin-NB18. Neurosci. Lett., 373: 16-20.
8. Folkerth, R.D., R.J. Keefe, R.L. Haynes, F.L. Trachtenberg, J.J. Volpe and H.C. Kinney, 2004. Interferon-gamma expression in periventricular leukomalacia in the human brain. Brain. Pathol. 14: 265-74.
9. Ray, K.K. and C.P. Cannon, 2004. Intensive statin therapy in acute coronary syndromes: Clinical benefits and vascular biology. Curr. Opin. Lipidol., 15: 637-643.
10. Eltzschig, H.K. and C.D. Collard, 2004. Vascular Ischemia and reperfusion injury. Br. Med. Bull., 70: 71-86.
11. Suk, K., J.H. Park and W.H. Lee, 2004. Neuropeptide PACAP inhibits hypoxic activation of brain microglia: A protective mechanism against microglial neurotoxicity in Ischemia. Brain Res., 1026: 151-6.
12. Zawadzka, M. and B.A. Kaminska, 2005. Novel mechanism of FK506-mediated neuroprotection: Downregulation of cytokine expression in glial cells. Glia ,49: 36-51.
13. Ying, W., C.C. Alano, P. Garnier and R.A. Swanson , 2004. NAD(+) as a metabolic link between DNA damage and cell death. J. Neurosci. Research,
14. Park, E.M., S. Cho, K. Fryo, G. Racchumi, P. Zhou, J. Aurather and C. Iadecola, 2004. Interaction between inducible nitric oxide synthase and poly (ADP-ribose) Polymerase in focal ischemic brain injury. Stroke, 35: 2896-901.
15. Petrilli, V., Z. Hereeg, P.O. Hassa and N.S. Patel *et al.,* 2004. Noncleavable poly(ADP-ribose) polymerase-1 regulates the inflammation response in mice. J. Clin. Invest., 114: 1072-81.
16. Wang, X. and G.Z. Fenerstein, 2004. The Janus face of inflammation in ischemic brain injury. Acta. Neurochir. Suppl., 89: 49-54.
17. Kariko, K., D. Weissman and F.A. Welsh, 2004. Inhibition of toll-like receptor and cytokine signaling: A unifying theme in ischemic tolerance. J. Cereb. Blood. Flow. Metab., 24: 1288-304.
18. Toledo-Pereyra, L.H., F. Lopez-Neblina and A.H. Toledo, 2004. Reactive oxygen species and molecualr biology of Ischemia/reperfusion. Ann. Transplant., 9: 81-3.
19. Sunderarajan, S. and G.E. Landreth, 2004. Antiinflammatory properties Of PPAR gamma agonists following Ischemia. Drugs News Perspect., 17: 229-36.
20. Sidhu, J.S., D. Cowan and J.C. Kashi, 2004. Effects of rosiglitazone on endothelial function in men with coronary artery disease without diabetes mellitus. Am. J. Cardiol., 94: 151-6.
21. Croll, S.D., J.H. Goodman and H.E. Scharfman, 2004. Vascular Endothelial Growth Factor (VEGF) in seizures: A double-edged sword. Adv. Exp. Med. Biol., 548: 57-68.
22. Lee, X.C., A.J. Williams, C. Yeo and R. Berti *et al.,* 2004. Microarray analysis of acute and delayed gene expression profile in rats after focal ischemic brain injury and reperfusion. J. Neurosci. Res., 177: 843-57.
23. Aller, M.A., J.L. Arias and J. Arias, Abnormal inflammatory response to trauma: The paradoxical meaning of the Ischemia-reperfusion. phenomenon. Injury, 35: 835-6.

24. Ando, H., M. Jezova, J. Zhou and J.M. Saavedra, 2004. Angiotensin II AT1 receptor blockade decreases brain artery inflammation in a stress-prone rat strain. Ann. NY. Acad. Sci., 1018: 345-50.
25. Xu, Z., J. Jiang, G. Ford and B.D. Ford, 2004. Neuroregulin-1 is neuroprotective and attenuates inflammatory responses induced by ischemic stroke. Biochem. Biophys. Res. Commun., 322: 440-6.
26. Wada-Isoe, K., Y. Wakutani, K. Urakami and K/ Nakashima, 2004. Elevated interleukin-6 levels in cerebrospinal fluid of vascular dementia patients. Acta. Neurol. Scand., 110: 124-7.
27. Zeller, J.A., K. Frahm, R. Baron, R. Stingele and G. Deuschl, 2004. Platelet-leukocyte interaction and platelet activation in migraine: A link to ischemic stroke? J. Neurosurg. Psychiatry., 75: 984-7.
28. Fichtlscherer, S., S. Breuer, C. Heeschem, S. Dummeler and A.M. Zeiher, 2004. Interleukin-10 serum levels and systemic endothelial vasoreactivity in patients with coronary artery disease. J. Am. Coll. Cardiol., 44: 44-9.
29. Chrysohoou, C., C. Pitsavos, D.B. Panegiotakos, J. Skoumas and C. Stefanadis, 2004. Association between prehypertension status and inflammatory markers related to atherosclerotic disease: The ATTICA, study. Am. J. Hypertens., 17: 568-73.
30. Stockton, R.A., E. Schaefer and M.A. Schwartz, 2004. p21-activated kinase regulates endothelial permeability through modulation of contractility. J. Biol. Chem., 279: 46621-30.
31. Yudkin, J.S., I. Juhan-Vagne, E. Hawe, S.E. Humphries *et al.*, 2004. Low grade inflammation may play a role in the etiology of the metabolic syndrome in patients with coronary heart disease: The hifmeoh study. Metabolism, 53: 852-7.
32. Teragawa, H., Y. Fukuda, K. Matsuda and K. Ueda *et al.*, 2004. Relation between C reactive protein concentrations and coronary microvascular endothelial function. Heart., 90: 750-4.