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Perivascular Tissue Ischemia Promotes Hypertensive Hemodynamics

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Abstract: Arterial hypertension might primarily relate to disturbances of oxygen delivery and of blood flow that arise and progress further as ischemic phenomena of vascular myofibers and of focal regions in tissues of supply. Indeed, one might speak of a centrally operative mechanistic pathway of ischemic phenomena that act as predeterminants in inducing instability of hemodynamic blood flow and of perfusion pressure characterizing the arterial hypertensive state. A concept of strictly multigenic determinants primarily inducing various different organ pathologies ranging from kidneys to myocardium to brain would essentially constitute a paradoxical congenic aggregate clustering of effects that progresses specifically as a single pathway of ischemic effect. Beyond considerations even of thrombogenicity or of embolism in a context of progressive atherosclerosis or of diabetic disease, arterial hypertension might be recognized as progressing in terms of endresult involvement of multiple different organs. The essential Hypertensive state might incorporate a tendency for interactivity of pathologies primarily affecting kidneys, myocardium and brain. Within any simple context of Na^+ imbalance or of dysregulation of various hemodynamic parameters, the association of kidney disease with progressive hemodynamic stress would progress towards pathways of vascular wall damage and rupture. The intracranial hemorrhages of hypertensive type, as constituted by intracerebral bleeds and subarachnoid berry aneurysms, would involve progressive tissue Ischemia. Indeed, Binswanger's disease would constitute one example of how perivascular tissue Ischemia is a prime pathogenesis towards hemodynamic instability of hypertensive type.

Key words: Hypertensive, hemodynamic, perivascular, Ischemia

INTRODUCTION

Hypertension as hemodynamic dysequilibrium: Gene therapy appears to involve an essential modulation of gene expression by a cellular genome that allows a significant degree of suppression or of enhancement of transcription of its component genes. In fact, gene expression operates as an expression of such a manipulation of the genetic controlling mechanisms that dictate and further determine duration of protein synthesis and of regulation of metabolic pathways of the cell. The Hypertensive state may result in different types of stroke ranging from lacunar infarcts to hemorrhage, embolism or large vessel Ischemia[1]. Stroke in young adults appears a particularly heterogeneous group of etiologic and pathologic factors[2].

Hypertension constitutes an abnormality in regulation arising directly from quantitative attributes of raised blood pressure. A dysregulation affecting a set threshold value or a progressive increment beyond fixed controlling influence would implicate juxtaposition of manometric dysregulation affecting raised systolic and diastolic blood pressure. Microvascular alterations may include medial thickening, decreased capillary density, perivascular fibrosis and an impaired endothelium-dependent coronary vasodilation in patients with hypertension[3].

Patterns of post-stroke hypertension therapy are important as standardization of treatment thresholds[4]. A multi-gene dysequilibrium in hypertension would incorporate persistently recurrent attempts at hemodynamic stabilization involving increased systolic and diastolic blood pressure. Overall, multi-genic dysequilibrium would tend to progress as increasingly dynamic over-compensation of cardiovascular hemodynamics. Small vessel disease is a main underlying mechanism in the development of heart failure in hypertensive patients particularly involving vascular medial hypertrophy together with myocardial and perivascular fibrosis[5]. Predictive factors for stroke in hypertensive patients would include age, pulse pressure, baseline presence of a transient ischemic attack, arrhythmias and a sedentary life style[6]. Also, an excessive reduction in blood pressure would promote the development of cerebral infarction in patients with hypertension or a previous stroke[7].

Operatively dynamic and transforming regulation of arterial hypertensive states: The intracellular compartment would show some main attributes of a modified extracellular compartment. Such a concept would implicate similar homeostatic mechanisms inside and

outside cells, in the added context of possible hypertensive hemorrhage. As such, antiactin-targeted immunoliposomes might ameliorate vascular membrane damage and even reduce risk of hemorrhage after thrombolytic therapy in cases of cerebral embolic Ischemia[8].

The establishment of intracellular receptor sites involving binding ligands and hormones would implicate centrally operative cell membrane receptivity responsible for intracellular responsiveness. Intracrine loops of intracellular organelle turnover would progress as receptor systems of dysregulatory homeostatic control.

ATP and noradrenaline release from perivascular sympathetic nerves act on P2X-purinoceptors on smooth muscle cells to induce vasoconstriction. ATP from endothelial cells during hypoxia and ADP from platelets result in eventual vasodilatation due to the production of endothelium-derived relaxing factor[9].

Biologic memory systems would progress as essential intracrine loops of recurring and enhancing/mitigating effect; ligands not only enter cells and bind to specific organelle receptors but .tend to promote variably operative pathways of hemodynamic disturbance. Disorders of coronary microcirculation in hypertensive patients may include increased tunica media thickness and reduction of coronary capillaries, within a context of evolving interstitial and perivascular fibrosis. The renin angiotensin system also is implicated in cardiac remodeling[10].

Biologic regulatory pathways, in arterial hypertension, would implicate both basal thresholds of operability and also a fluctuating flow of stimulatory and inhibitory influence as represented by classic cell membrane receptor/ligand binding dynamics. Serum total cholesterol would appear an independent risk factor in ischemic stroke in diabetic patients[11].

A biologic system of single loop regulatory factors would involve intrinsically dynamic and also qualitatively transforming hemodynamics. During infarction-induced remodeling in the heart, reduced blood perfusion results from disproportional cardiac hypertrophy relative to vascular growth rather than to vascular remodeling[12]. The same microangiopathic lesions would underlie hypertensive hemorrhages and ischemic strokes[13].

Vascular myofiber contractility as active propagation of increased peripheral arteriolar resistance: The pathophysiologic role of small arteries induces hypertension and also determines dysregulation of microcirculatory blood flow as seen in unstable hypertensive states characterizing especially postrenal transplantation patients[14].

A determining role in regulatory arteriolar resistance that influences quantitative hemodynamics would also tend to redefine susceptibility as variably effective pathobiologic modulation of homeostatic systems. It is perhaps in terms of modulation of arteriolar tone that small arteries and arterioles would promote progression of the hypertensive state. Angiotensin II is implicated in cardiac remodeling following chronic hypertension and after myocardial infarction. Interstitial and perivascular fibrosis possibly evolves due to prevention of fibroblast proliferation[15].

This would relate especially to variable responsiveness to nitric oxide, bradykinin and histamine, as targeted pathways of dynamic interaction involving arteriolar tone and luminal patency.

Borderline isolated systolic hypertension, like isolated systolic hypertension and diastolic hypertension, also carries an increased risk for ischemic stroke and intracerebral hemorrhage[16].

Indeed, Ischemia is in large part characterized by variable myofiber tone or contractility directly influencing blood ingress and egress in and out of the microcirculation. In patients with stable heart failure, cardiac collagen deposition is decreased by spironolactone given together with diuretics and angiotensin converting enzyme inhibitors[17].

The capillary bed would appear to characterize interactive tone and contractility of the vascular smooth myofibers incorporating whole regional networks of arterioles and capillaries leading to venular beds of perfusion/drainage.

Vascular perfusion arrangements tend primarily to protect susceptible capillary beds from a head pressure of arterial blood flow. There would exist a series of operative systems involving patterned induction and reversal of effects as exerted on a micro-circulation whereby neural to chemokine, neuropepetide, and myofilament mechanisms determine stability of blood flow /blood perfusion pressure relationships. Aldosterone is involved in inducing cardiac vascular inflammation as mediated by Angiotensin II implicating cyclooxygenase 2 and osteopontin[18].

It is significant that falls in blood pressure during sleep would be associated with cerebral Ischemia in elderly hypertensives[19].

Essential tone of small arteries and arterioles would relate to contractility of the vascular smooth myofibers. Synaptic connections between sympathetic supplying nerves on vascular smooth myofibers would tend to sustain a modulated vascular myofiber tone.

Active contraction waves involving small arteries and arterioles might participate in hemodynamic patterns of variability and of adjustability based primarily on modulated vascular smooth myofiber tone.

Generation and propagation of active contraction waves affecting vascular myofibers would culminate in patterns of hemodynamic blood flow and of perfusion pressure that modulate and are in turn modulated by intraluminal hemodynamics and by transmural transfer mechanics. Elevated plasma angiotensin II is related to vascular hyperpermeability with efflux of plasma macromolecules into the perivascular and interstitial space. This is followed by perivascular fibrogenesis[20]. In a rat embolic stroke model, hemorrhage develops in regions of low perfusion and of early blood-brain damage as a complication of the spontaneous hypertensive state[21].

Resistance arterioles would progress as a series of modulated propagation pathways of hemodynamic blood flow disturbances related to impedance of blood flow or as disturbed vascular smooth muscle tone in hypertensive individuals. In this regard, also, vasospasm- associated proliferative vasculopathy, as seen particularly with systemic hypertension, would induce vascular wall rigidity and reduced autoregulatory capability of cerebral vessels[22].

Plasminogen activator inhibitor-1 deficiency protects against hypertension and perivascular fibrosis in cases of short-term inhibition of nitric oxide synthase[23].

Thrombogenicity and embolism stroke in patients suffering from hypertension and atherosclerosis: The acute therapeutic lowering of blood pressure in a hypertensive patient appears to involve hemodynamic transformation in terms of variable regional blood flow. An acutely evolving stroke in a hypertensive patient would constitute a multi-variant set of circumstances primarily involving cardiac parameters and atherosclerotic narrowing. This latter is both a regional and a focal phenomenon affecting vessels, determining occlusive and hemorrhagic complications evolving as a modulated Ischemia and hemorrhage of tissues. Platelet hypofunction and a raised serum lipid profile are significant in predisposing to the development of hypertensive hemorrhage and cerebral atherogenesis respectively[24] of potential significance is the thrombogenicity arising in a setting of arterial hypertension. Indeed, low frequency use of aspirin reduces risk for ischemic stroke in hypertensive women[25].

Endothelial dysfunction may relate particularly to endothelin, growth factors, cytokines and adhesion molecules, with a risk of thrombosis[26].

A significantly increased tendency for thrombosis might predominantly determine progression of hypertensive pathology arising from causative and associative factors of modulated responsiveness and interaction. For example, matrix metalloproteinase inhibitors would help reduce the risk for post-embolic hemorrhage after hypertensive stroke[27].

Thrombosis and embolus appear to promote stroke in hypertensive patients in terms largely of factors associated with the development and progression of atherosclerosis. Hemorrhagic strokes would result from an atherosclerotic progression that predisposes to hemodynamic instability. The stroke in a hypertensive patient might constitute an evolving process of atherosclerosis and of enhanced thrombosis and embolism. In such a context, for example, the penetrating atherosclerotic ulcer as distinct from the intramural hematoma would particularly predispose to significant vascular injury as represented also by thoracic aortic dissections[28].

The endothelial cell as a convergence/ transformation point of mediated effects on vascular myofibers inducing hypertensive instability: The Hypertensive State would involve a range of raised blood pressure levels as hemodynamic variability of response rather than simply as dysregulatory pathways of instability. Such a central point of distinction, characterizing the Hypertensive state as not simply a quantitative increase in blood pressure but as an actual qualitative transformation of circulatory hemodynamics and circulatory volume inter-relationships might arise directly from interactions of nitric oxide with free oxygen radicals. Indeed, for example, low vitamin C levels in plasma increase the risk for stroke in hypertensives[29].

It would appear that rapid generation of free oxygen radicals by endothelial cells in some way would influence and damage contractility of smooth myofibers of the vessel wall. Inflammatory-immune mechanisms can precipitate hypertensive complications such as hemorrhage and thrombosis involving the cerebral circulation[30]. Such a risk evolves in a context of decreased luminal area, increased wall thickness and perivascular fibrosis[31].

Also, rebleeding in hypertensive patients may relate to an amyloid angiopathy as typically found at the grey-white matter junction[32].

Endothelially derived factors and circulating hormonal influences would tend to predispose to hemodynamic stress through the immediate participation of the endothelial cell. The endothelial cell would relate to ultimate end-pathway interactions of nitric oxide and nitric oxide derivatives with free oxygen radicals. Indeed, the endothelial cell would constitute a convergence point whereby hemodynamic stress and instability subsequently translate as a persistent state of vasoconstriction.

Silent subcortical ischemic lesions depend on small

vessel vasculopathy in cases of hypertension associated with lacunar infarction[33].

Hypertension might implicate multigenic inheritance of cardiac Ischemia, chronic renal failure, and stroke: Polygenic inheritance of hypertension might correlate with patterns of susceptibility for stroke, ischemic heart disease, chronic renal failure and insulin insufficiency and obesity within schemes of variably interactive pathways of group risk factors. Also, cumulative risk factors for stroke tend to develop particularly in association with increasing age even though age alone is not a critical factor in pathogenesis[34].

A congenic strategy for elucidation of the inheritance patterns in hypertensive patients might concern not only a clustering in the causation of hypertension but especially a combination of pathologic disorders. In this regard, hyperhomocysteinaemia is associated with an increased combined risk for both ischemic heart disease and cerebrovascular disease[35].

Hypertension would be identifiable largely as one component of a full set of aggregate congenic clusters. Hypertension appears to play an important role in pathogenesis of severe diabetic heart disease[36]. The TT genotype of the α1- antichymotrypsin gene polymorphism appears associated with hemorrhagic stroke even in normotensive subjects[37] .

Hence, the association, for example, of stroke and ischemic heart disease and of chronic renal failure with the Hypertensive state might form a congenic clustering involving multiple traits predisposing to the development of ischemic heart disease, stroke and/or chronic renal failure. Impaired endothelial function may contribute to coronary artery risk due to vasoconstriction, thrombosis and proliferative factors in hypertensive individuals. Perivascular fibrosis would contribute to impaired myocardial blood supply[38]. Mutations of the phospholipase C-delta 1 gene appear implicated in causing spontaneous hypertension in rats[39]. In addition, development of the Hypertensive state might paradoxically depend on inherited susceptibility traits that evolve specifically as polygenic pathways of a mediated phenotype involving blood flow dynamics and microcirculatory transfer.

Combined primary renal and cardiovascular approach in essential hypertension: The dramatic response of the hypertensive state in Liddle's syndrome to amiloride therapy would relate to both the Na^+ epithelial channel of the vascular myofiber and the renal epithelial tubular cell in combined cardiovascular and renal treatment of arterial hypertension.

An intrinsic pathway of combined renal and cardiovascular systems would account for progression as an increased risk for various complications. Any effective control of the Hypertensive state would necessitate a combined Na^+ restriction management influencing renal epithelial channels and vascular smooth myofibers.

Arterial hypertension implicates Ischemia and hemorrhage as an integrally operative system: Antigen-presenting cells in the nervous system would function in terms of permeability of the blood-brain barrier, a phenomenon involving also participating microglial and blood cellular elements.

Blood-brain barrier disturbances as shown by magnetic resonance imaging parameters reliably indicate a risk for hypertensive hemorrhage following thrombolysis of a cerebral embolus[40].

The highly characteristic biologic and morphologic characteristics of microglia appear conditioned by the brain microenvironment as a highly migratory cell population. Microglia reflect integral brain pathophysiology. The ability of microglia to migrate would help account for an integral central nervous system that is reflected also in terms of inflammatory/infective, neoplastic and degenerative concepts of disease.

Chemical factors, adenosine and H^+ are important in regulation of the cerebral vascular bed together with neurogenic control of blood flow. Release of adenosine and H^+ from tissue and changes in their concentration in perivascular tissues determine the diameter of both medium and small pial arteries as well as of intracerebral arterioles[41].

Involvement of the organ as a whole rather than in terms of subregional foci would emphasize central relationships of the brain with its blood supply. Intrinsic attributes of the cerebral blood supply would help account for a potential functionality for physiologic or pathophysiologic progression.

A conventional concept of the blood-brain barrier would appear an oversimplification referable mainly to natural attributes of the cerebral blood supply. The term barrier would implicate attributes of adjustable selectivity affecting both blood flow and blood vessel permeability, particularly in view of the susceptibility of neurons to hypoxia, Ischemia and hypoglycemia.

Hypertensive endothelial dehiscence (gaps) tends to develop together with focal intimal damage and possible subsequent endothelial cell necrosis and defects. Leukocyte migration and endothelial loading with lipid deposits are possible additional features[42].

Ischemia, would relate to hypoxia and hypoglycemia, in terms largely of vascular spasm, embolic occlusion, atherosclerotic stenosis, thrombosis and even, actual rupture of cerebral vessels. In the heart, a diffuse

perivascular and interstitial fibrosis may be associated with an activated renin-angiotensin system, without implicating hemodynamic stress or ventricular loading as causative factors[43].

Within such a scenario, raised blood pressure, particularly the malignant type would constitute an integration mainly of Ischemia-associated hypoxia and Ischemia-associated hypoglycemia.

The fundamental pathobiology associated with the Hypertensive state would implicate impaired blood flow or even an increased risk for vascular rupture and hemorrhage. In fact, arterial hypertension appears a composite endresult of a whole series of interacting pathobiologic events that self-propagate as seen in patients suffering from autosomal dominant polycystic kidney disease[44].

Breakdown of the blood-brain barrier appears critically dependent on an increase in endogenous tissue-type plasminogen activator in perivascular Ischemia[45].

Arterial hypertension would evolve as a fundamental disturbance of hemodynamics, blood fluidity, vascular tone, vascular sclerosis and decreased permeability that promote development of atherosclerosis and arteriosclerosis. Serial MRI studies in a renal rat model of hypertension would involve loss of autoregulation and/or disturbed blood-brain barrier integrity[46].

Arterial hypertension as both the cause and the result of Ischemia/Hypoxia to a region or organ: Multiple diffuse regions of predominantly white matter rarefaction, particularly as noted macroscopically, and also on imaging studies, are characteristic features of Binswanger's Disease and may reflect possible pathogenesis of the lesions caused by arterial hypertension.

How might a persistently raised arterial blood pressure result in multiple gross foci of ischemic/hypoxic injury to the deep cerebral white matter?

In what ways might multiple vessels within an integral vascular bed become progressively occluded in cases of hypertension? Lacunae and white matter lesions may develop in hypertensive patients due to focal Ischemia, perivascular edema and disruption of the blood brain barrier[47].

Binswanger's disease is perhaps the cerebral equivalent of hypertensive nephrosclerosis, and furthermore, would probably relate also to a very similar process of multiple widespread occlusion of smaller vessels affecting the myocardium in patients with arterial hypertension.

Some essential factor appears operative in arterial hypertension that would induce small vessel occlusion. The malignant phase of arterial hypertension might constitute progressive change consequent to small vessel occlusion. Coexistence of hypertensive cardiomegaly and atherosclerosis tends to induce severe Ischemia of the myocardium [48].

Much of the mortality in hypertensive patients, particularly with malignant hypertension, is due to renal ischemic damage. Reperfusion injury appears implicated in kidney allograft survival and vascular lesions may promote renovascular hypertension and also tubulopathy[49]. Patients with malignant hypertension develop ischemic and hemorrhagic lesions in the brain as indicated by progressive papilledema.

The possible development of either hemorrhages or occlusions of smaller vessels in patients with arterial hypertension may hemodynamically be associated with previously developing occlusive lesions in such vessels.

Luminal vasoconstriction may constitute a pathomorphologic spectrum ranging from initial dynamic changes in the vessel wall, including spasm and protein/fluid transudation, to subsequent permanent occlusion. Vasospasm after aneurysmal subarachnoid hemorrhage would implicate numerous mediators ranging from endothelins to free radicals, ferrous hemorrhage and various kinases[50]. Hence, progressive transformation of initially hemodynamic alternation and disturbances would subsequently evolve as progressive occlusive vascular disease and vascular rupture.

What appears particularly relevant with respect to arterial hypertension is its progressively increasing severity as developing ischemic lesions in the various organs affected. In a sense, perhaps, Ischemia and ischemic necrosis in various organs would tend to further augment hypertension, a phenomenon affecting the kidneys in particular. In a more general sense, perhaps, foci of significant Ischemia, as seen also in brain and myocardium, would promote hemodynamic dysregulation and further impaired blood supply to a given region or tissue.

Hypertension might involve disturbed balance between delivery of oxygen and attempts at improving such oxygen delivery. Hemocirculatory parameters of progression or nonprogression in arterial hypertension would originate as pathologic and clinical consequences that operate largely within the integral systems of dynamic oxygen delivery to a region or organ.

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