Vascular Response to Stress in Health and Disease

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The body's vasculature plays a critical role in the development of functional and structural alterations responsible for tissue and organ damage in laboratory animals and human subjects during illness and senescence, and in response to stress. Components of the vasculature, namely, major arteries such as the aorta, smaller arteries, arterioles, capillaries, post-capillary venules, and collecting central veins, all serve as conduits through which vital substrates are delivered to cellular masses and/or waste products are removed. A number of physical and neurohumoral agents known to be responsive to stress stimuli exert functional control over the vasculature. Both physical and emotional stress have been found to cause significant hemodynamic alterations. Large artery rigidity, for instance, develops rapidly following stress-induced activation of the autonomic nervous system. Associated with this process is increased release into the circulation of catecholamines and angiotensin-II. At the same time, insulin resistance develops, accompanied by nitric oxide release and changes in the immune system. The response of large arterial conduits to stress is characterized by increased pulse pressure, which in turn affects the endothelium of the arterial vessels responsible for determining total peripheral resistance. Microcirculation networks, where a large fraction of the blood volume is contained, are affected as well, and the blood in them is subject to redistribution into adjacent interstitial fluid compartments. Changes in endothelial permeability, secondary to variations in pulse pressure, can lead to interstitial edema and changes in the physicochemical properties of interstitial compartments. These changes give rise to alterations in the traffic of substrates and waste products between blood and cells. This sequence of events also takes place in the vasa vasorum microcirculation that nourishes large arteries, and likely contributes to remodeling of the vascular wall and to atherogenesis. The contribution of large artery rigidity to the morbidity and mortality associated with arterial hypertension, diabetes mellitus, heart failure, and terminal uremia, is relatively well established in human populations. In addition, it appears that aortic rigidity precedes the development of arterial hypertension in the spontaneously hypertensive rat (SHR) model, as well as in individuals with borderline hypertension. The fact that some of the functional and structural vascular alterations produced by stress are reversible reinforces the importance of developing behavioral techniques and pharmacologic agents that can successfully interrupt this pathological sequence of events.

THE IMPACT OF environmental stress on the adaptive responses of laboratory animals and human subjects has been examined in increasingly greater depth during the half century since Hans Selye[1] first observed that nonspecific stress stimuli can produce lesions such as peptic ulcers in laboratory animals, and that the pathways involved in mediating such adverse effects arise in the central nervous system and involve the pituitary-adrenal axis. The sequence of biological events that lie between an externally imposed stress and its ultimate effect (whether beneficial or deleterious) on various components of the vasculature is complex, involving large blood vessels, microcirculation networks, and a growing number of mediators. The nature of this sequence is currently under investigation in many laboratories.[2]

Initially, scientists engaged in studying the effects of stress were principally concerned with experimental models or clinical situations in which the stressors were abrupt and severe. In animals subjected to severely stressful experiences, there occurs an intense activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathoadrenal system (SAS). The overall effect is reminiscent of the post-traumatic stress disorder (PTSD), which can occur in vulnerable individuals who are exposed to a traumatic experience of overwhelming proportions.[3] Regrettably, much less attention has been paid to day-to-day stressful situations such as jobs that demand hard physical or mental work, familial or psychosocial tension, and commonplace environmental stresses such as atmospheric pollution, noise pollution, or excessive ambient heat or cold (in 1734, Montesquieu[4] elegantly described the remarkable differences in behavior and outlook that distinguished people living in the cold and dark winters of Northern Europe from those residing in the warm and sunny climate of the Mediterranean basin).

Although the vascular adaptations of individuals who are exposed to continuous or intermittent mild stress stimuli are ultimately more important biologically than the intense responses to much more dramatic and severe, but far less frequent, stressful experiences, the subtle effects on the body's vasculature of the milder forms of stress are difficult to reproduce experimentally. Shown diagrammatically on the left side of Fig 1 is the drastic and potentially irreversible disruption of an organism's equilibrium following exposure to an acute, massive stress ("hard stress"). On the figure's right side is shown (in contrast) the gradual progressive adaptation, mediated by vasoactive autacoids, that follows each of a succession of relatively mild stress stimuli ("soft stress"). When the two sides are compared, it will be noted that, although the extent of the disruption in homeostasis (indicated by the distance from point A to point B) is far greater in response to a hard stress, the cumulative extent of a succession of adaptations to soft stress stimuli covers about the same distance.

The mechanisms involved in day-to-day vascular adaptation

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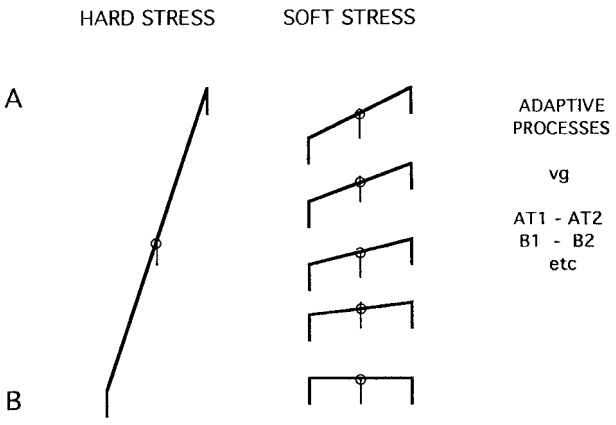

Fig 1. Balance disruption following hard stress (left) and soft stress (right). Disruption goes from A to B, in an abrupt manner or in a gradual way, where progressive adaptation is mediated by vasoactive autacoids capable of opposing their vascular impact: AT_1 and AT_2, B_1 and B_2 for angiotensin and bradykinin vascular actions, respectively.

to soft stress have not been extensively studied; yet, recent research in the field of vascular physiopathology suggests that depending on the circumstances, different receptors for a particular vascular agonist are capable of responding in opposite ways to a similar, or even the same, pharmacologic stimulation. This is what occurs in the case of angiotensin II, via AT_1 and AT_2 receptors,[5] and bradykinin, via B_1 and B_2 receptors.[6] It is interesting that stimulation of these receptors can result in opposing vascular responses—responses which could be interpreted as being counterregulatory adaptations, at least in terms of the vascular control of the systemic and microcirculatory domains. We recently documented such counterregulatory mechanisms in the renal handling of phosphate transport in experimental models of uremia,[7] an observation suggesting that the same mediators could induce opposite vascular responses which, in effect, act to re-establish physiopathological balance in disease states. Relationships between phosphate secretory and reabsorptive mechanisms could be regulated in opposite directions by the balance of B_1 and B_2 receptors in the proximal tubule of the rat nephron.

STRESS, HEALTH, AND SENESCENCE

Interest in the concept of adaptation to "soft" stress has been stimulated by the possibility that early intervention in the stress-response process might prevent development of irreversible damage to vital organs. It seems reasonable to suggest that some of the biological cascades resulting from exposure to soft stress could be prevented or counteracted by any of a number of suitable measures such as the employment of a relaxation technique, a basic change in mental/philosophic outlook, or use of appropriate medications.

In the past, the term "senescence" (which implies a progressive, generalized deterioration) was thought to be more or less equivalent to aging. This concept has since changed and we now distinguish between chronological age and physiological age—a person can be physiologically much younger (or older) than his or her chronological age. This revised perspective carries with it the implication that senescence is a pathological, not a natural, process and that its course and outcome are modifiable by suitable therapeutic interventions.[8] It is likely, therefore, that some of the ailments that arise during senescence could be prevented, mitigated, or even reversed. Graded adaptation to soft stress could well be included in the list of preventive measures. Examples of treatable conditions associated with senescence include atherogenesis, osteoporosis, obesity, and alterations in fluid, sodium, and divalent ion homeostasis.[9]

FOCUS ON THE VASCULAR SYSTEM

Why should the vasculature play such an important role in the development of senescence? Among the major fluid compartments, the vascular volume is the smallest—5% of total body weight. Once growth is complete, this fluid compartment remains relatively constant until old age.[10] It is also the most dynamic compartment, turning over completely every minute. Some organs served by the vasculature receive up to 20% of the cardiac output.[11]

The endothelial layer, which paves the internal surface of the vascular system, is the cell population most exposed to physical injury, shear stress, and other potentially damaging processes—even under conditions of normal blood pressure.[12] Apart from their vulnerability to injury, vascular endothelial cells are uniquely equipped to deal with the stresses of ongoing fluid movement, as well as wide pressure variations. These cells are capable of making many vasoactive agents and a variety of growth factors involved in production of basement membranes and interstitial macromolecules. Endothelial cells further exhibit a remarkable ability to communicate with each others via gap junctions and are, therefore, able to react in a coordinated fashion to potentially injurious challenges.

Arterial hypertension of any type is associated with increased physical stress on blood vessel walls in all segments of the vasculature. Elevated pulse pressure (an increased difference between systolic and diastolic blood pressure values), which results mainly from increased rigidity of large arteries, has been shown to represent an important risk factor for cardiovascular morbidity and mortality, independent of absolute blood pressure, as shown in Fig 2.[13]

It is also of interest that heart rate, a major component of cardiac output, together with vascular volume, is best correlated with the average longevity of animal species—from turtles and whales to birds. The more rapid the heart rate, the shorter the life span.

Segments of the body's vasculature differ in structure and function, from the large arteries that function as major conduits of the blood circulation to the smaller arteries, arterioles, capillaries, post-capillary venules, and collecting and central veins. Each segment has been shown to respond in a different manner to stress—most notably the large vessels. Since the large arteries play a key role in establishing pulse pressure, stress-induced alterations in the structure and function of these vessels have a critical impact on the remaining segments of the vasculature, particularly the smaller arteries and veins and the microcirculation.[14]

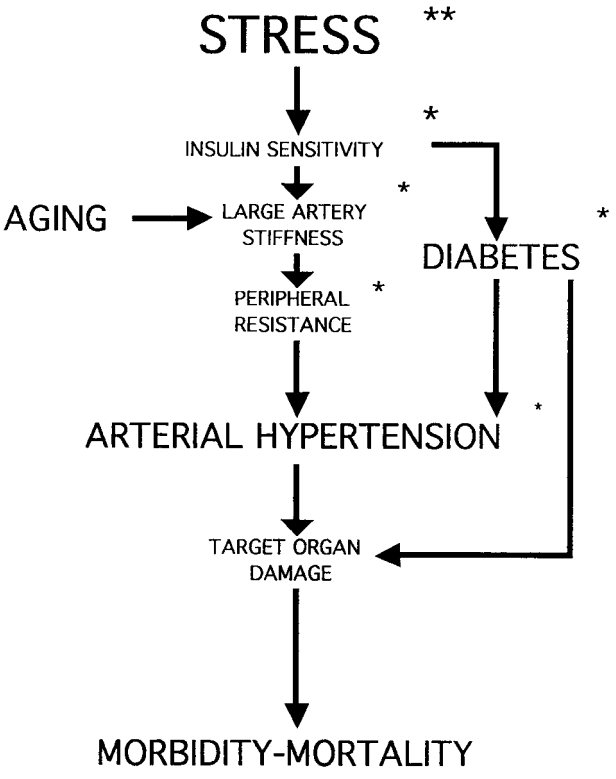

Fig 2. Stress is associated with insulin resistance which increases large artery rigidity and peripheral resistance, responsible for the development of established arterial hypertension, and target organ damage. Aging and diabetes mellitus accentuate this abnormal cascade, upon which therapeutic interventions remain possible. The size of asterisks indicates the theoretical importance of these interventions, from early (large size) to late (small size) in the disease process.

Elevated pulse pressure induced by large artery rigidity affects the smaller distal arteries, inducing smooth muscle cell hypertrophy, which contributes to peripheral resistance and leads to established hypertension. Recent studies from our laboratory[15] indicate that increased rigidity of large arteries precedes development of hypertension in the young, spontaneously hypertensive rat (SHR). Transmission of increased pulse pressure to capillary endothelium triggers these responsive cells and alters their permeability characteristics.[16] Enhanced permeability to macromolecules, such as albumin, leads to movements of fluids and solutes into adjacent interstitial compartments. Increase in size and changes in the physicochemical properties of the interstitium are reponsible for alteration in the traffic of vital substrates and removal of waste products to and from cellular masses, potentially leading to target organ damage.[17]

A summary of these potentially impaired physiological pathways is presented in Fig 3. Increased rigidity in large arterial conduits seems to develop relatively early, owing to structural reorganization of the interstitial matrix and/or dysfunction of vascular smooth muscle. Structural changes include increased collagen deposition, decreased elastin and, as recently reported, marked reduction in the glycosaminoglycan (GAG) content of the vascular matrix.[15] The latter abnormality appears to be the most important, since aortic compliance was found to be best correlated with the interstitial GAGs.

It has been shown recently that functional alterations in the muscle tone of the specific aortic circular subpopulation of smooth muscle cells are also present in the SHR before hypertension begins.[18] As a consequence of increased rigidity in this important arterial conduit, pulse pressure increases and enhances physical stress in the distal arteries that determine peripheral resistance. In those arteries, medial smooth muscle cells become hypertrophic, and blood pressure increases.

Even if peripheral microcirculation networks remain relatively well autoregulated, pulse pressure is transmitted across pre-capillary resistances and is capable of influencing capillary endothelial structures. Several groups of investigators have examined the potential consequences of increased pulse pressure in isolated endothelial cell layers in culture.[16] Marked structural changes develop in response to absolute or relative pressure changes; in particular, endothelial cells become disjuncted, owing, probably, to cytoskeleton activation. These structural changes represent the morphological basis for enhanced endothelial permeability to macromolecules and, as a result, changes in the physicochemical properties and size of the interstitium.

The damaging effects on target organs of such changes is illustrated in Fig 4. Once plasma extravasation develops in a given interstitial fluid compartment (compartments may differ markedly from one organ to another), the distance between microvessels and any cellular mass is increased. Also affected are the physicochemical properties of the particular interstitial compartment. For instance, hydraulic conductivity is reduced when collagen contents become increased, or when GAGs accumulate. As a consequence, movements of fluid and solutes

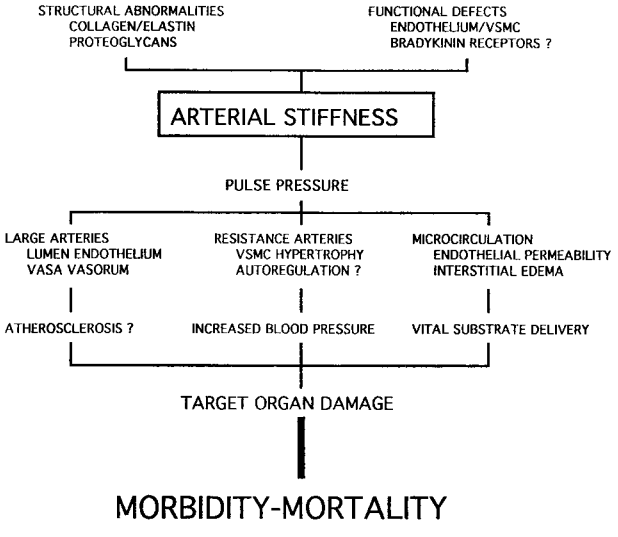

Fig 3. According to present knowledge, arterial stiffness (or rigidity) develops from structural (collagen, elastin, glycosaminoglycans) and/or functional alterations (bradykinin B_2 receptor hyper-reactivity). Arterial stiffness is associated with increased pulse pressure which affects vasa vasorum, resistance arteries and microcirculation networks. These effects result in altered vital substrate delivery, increased peripheral resistance, and likely atherosclerosis.

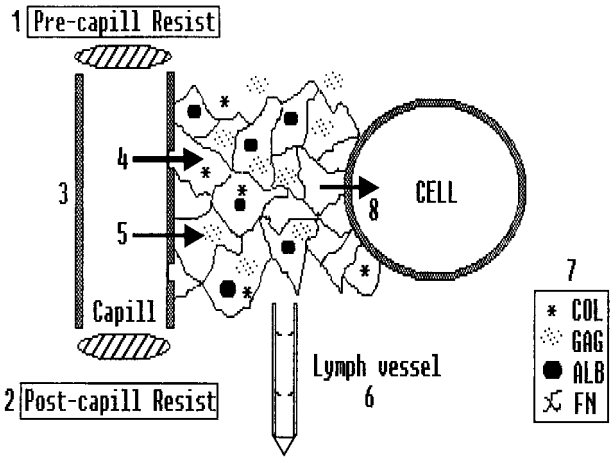

Fig 4. Summary of vascular (3) including pre- and post-capillary resistances (1, 2) and interstitial events (7) responsible for target organ damage (8) in a variety of diseases associated with microcirculation disturbances. On the left side of the figure, alteration in endothelial (3) permeability to albumin (4, 5) is associated with extravasation of plasma into the interstitial compartment. Changes in collagen (COL), albumin (ALB), fibronectin (FN), and glycosaminoglycans (GAG) develop, and affect the size and physicochemical properties of this strategic fluid compartment, depending on the limited capacity of lymphatic flow to adapt (6) in tissues provided with this specialized circulation. As a result, the vital traffic of substrates and waste products from blood (left) to cellular masses (right) is disrupted, resulting in target organ damage.

are impaired within this strategic compartment. This phenomenon can reduce the traffic of vital substrates and toxic metabolites across interstitial space—a common denominator in terms of target organ damage.[17]

Atherogenesis also represents a major consequence of vascular injury secondary to stress-induced metabolic disturbances such as carbohydrate and lipid abnormalities.[19] The development of atherosclerotic plaques in large and middle-sized arteries is responsible for acute (and often fatal) heart attacks and strokes. Less immediately fatal but extremely damaging to health is the chronic reduction by atherosclerotic lesions of blood flow in the renal arteries. Atherosclerotic disease of the peripheral arteries gives rise to the troublesome ischemic disease so commonly observed in diabetic patients.

The development of atherosclerotic plaques remains a challenging investigative problem for scientists involved in the study of vascular physiopathology. Morbid sequences responsible for death caused by atherosclerosis include cellular processes and a variety of vasoactive autacoids and hormones activated by such risk factors as arterial hypertension, dyslipidemia, obesity, diabetes mellitus, smoking habits, and shear stress phenomena. Aging and classical stress are usually not included in the traditional list of risk factors.

As shown in Fig 5, new links need to be established between aging, large artery rigidity, pulse pressure, microcirculatory disturbances, and atherogenesis on the one hand, and stress, insulin resistance, diabetes mellitus, and atherogenesis on the other hand.[20] It has been reported recently that leptin, produced and released by adipocytes, stimulates angiogenesis and is responsible for the activation of vascular calcifying cells, a process that leads to hardening of blood vessels—probably via local production of GAGs.[21] This effect of leptin is one example of endothelial dysfunctions potentially involved in the development of atherosclerosis.

Finally, recent studies indicate that the adventitial microcirculation network that serves large arteries, the *vasa vasorum* system, could play an important role in removing from the interstitial matrix, macromolecules, including lipoproteins, that penetrate the blood vessel wall from the intimal endothelial layer.[22] Since the *vasa vasorum* contain angiotensin AT_1 and

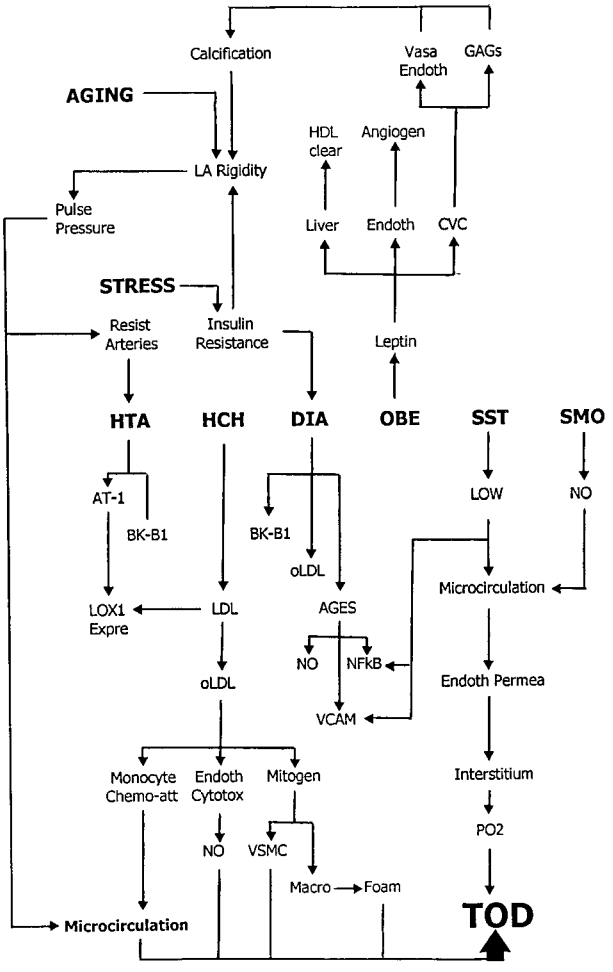

Fig 5. Physiopathology of atherosclerosis, the terminal consequence of the vascular impact (target organ damage [TOD]), is associated with the well-established risk factors (hypertension [HTA]; hypercholesterolemia [HCH]; diabetes mellitus [DIA]; obesity [OBE]; shear stress [SST]; smoking habits [SMO]), as well as additional risk factors (AGING, STRESS). The cellular and vascular mediators responsible for the development of atherosclerosis are illustrated, and include from top to bottom of the figure, the following events: vasa vasorum endothelium (vasa endoth), glycosaminoglycans (GAGs), hepatic high-density lipoprotein clearance (HDL clear), angiogenesis (angiogen), calcifying vascular cells (CVC), angiotensin receptor (AT_1), bradykinin receptor ($BK\text{-}B_1$), advanced glycation end products (AGES), nitric oxide (NO), adhesion molecules (VCAM), oxidized low-density lipoprotein (oLDL) and its receptor (LOX1) expression.

AT_2 receptors, as well as B_1 and B_2 bradykinin receptors, it is likely that some of these receptors could play a role in the development of atherosclerotic plaques.[23]

POTENTIAL INTERVENTIONS FOR PREVENTION OF STRESS-INDUCED VASCULAR DAMAGE

Nonpharmacologic Measures

Several nonpharmacologic measures, introduced in recent years, are thought to be effective in opposing development of stress-induced vascular disease. These include increased physical exercise, achievement and maintenance of desirable body weight and composition, and sustained adherence to a healthy diet. Increased exercise tends to reduce the insulin resistance associated with a sedentary lifestyle and stress-induced overeating. In addition, physical exercise may enhance endorphin release by the brain, a response known to ameliorate the effects of stress. Unfortunately, the effects of "mental exercise" on the physiological response to stress has not yet been thoroughly examined. There is preliminary evidence that certain kinds of mental exercise may be beneficial; for example, that associated with meditation. On the other hand, "mental stress" has been reported to have adverse effects on the cardiovascular system.[24]

Like exercise, dietary adjustment, and also weight control, can improve insulin resistance, which leads to hyperinsulinemia, a potent activator of the sympathetic nervous system, as well as a facilitator of left ventricular and vascular hypertrophy.[25]

Above all other nonpharmacologic measures, it is critically important to develop and maintain mental attitudes that can buffer the activating effects of everyday soft stress on the sympathetic nervous system, with all the biological consequences of such activation, as shown in Fig 1.

Pharmacologic Measures

A large number of drugs are now available to counteract the well-established consequences of stress on the vasculature. Some of these are even capable of reversing target organ damage induced by the morbid physiopathological axis described in Fig 5. Use of receptor antagonists to block angiotensin AT_1 and AT_2 receptors, and also bradykinin B_1 and B_2 receptors[26-29] has been shown to reverse damage produced in microcirculation networks by stress-associated disease processes such as arterial hypertension and diabetes mellitus. Similar success is expected from drugs that affect leptin production and release.[21]

Among older drugs used in treatment of cardiovascular disorders, diuretics—which exhibit vascular as well as renal pharmacological actions—have been shown to have positive effects on vascular matrix composition, particularly glycosaminoglycans.[30] As an example, indapamide increases polysaccharide chain sulfation of glycosaminoglycans, thereby boosting the polyanionic characteristics of these macromolecules. Specific dietary interventions, including food items possessing sulfate radicals, such as garlic, have been shown to produce similar effects on large artery matrix composition, thereby improving the elasticity of large blood vessels. Finally, mention should be made of the widely used adrenergic-receptor (alpha- and beta-) blocking agents, which act to antagonize the effects of catecholamines at the level of the peripheral tissue and thereby eliminate or attenuate the effects in the periphery of sympathetic nervous system activation.

REFERENCES

1. Selye H: The Stress of Life. New York, NY, McGraw-Hill, 1956
2. Chrousos GP: The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: Neuroendocrine and target tissue-related causes. Int J Obes Relat Metab Disord 24:S50-S55, 2000 (suppl 2)
3. Seedat S, Stein MB: Post-traumatic stress disorder: A review of recent findings. Curr Psychiatry Rep 3:288-294, 2001
4. Montesquieu C de S: Considérations sur les causes de la grandeur des Romains et de leur décadence. Paris, France, 1734
5. Aguilera G, Kiss A, Luo X, Akbasak BS: The renin angiotensin system and the stress response. Ann NY Acad Sci 771:173-186, 1995
6. Stalcup SA, Davidson D, Mellins RB: Endothelial cell functions in the hemodynamic responses to stress. Ann NY Acad Sci 401:117-131, 1982
7. Servant M, Plante GE: Net tubular secretion of phosphate is bradykinin B_1 receptor-dependent in the 5/6 nephrectomy uremic rat model. Am J Kidney Dis (in press)
8. Udelsman R, Blake MJ, Stagg CA, et al: Vascular heat shock protein expression in response to stress. Endocrine and autonomic regulation of this age-dependent response. J Clin Invest 91:465-473, 1993
9. Fleet JC: Leptin and bone: Does the brain control bone biology? Nutr Rev 58:209-211, 2000
10. Sjostrand T: The total quantity of hemoglobin in man and its relation to age, sex, body weight and height. Acta Physiol Scand 18:324-330, 1949
11. Smith WH: The physiology of renal circulation. Harvey Lectures Series 35:166-175, 1939
12. Sarabi M, Lind L: Mental stress opposes endothelium-dependent vasodilatation in young healthy individuals. Vasc Med 6:3-7, 2001
13. Miura K, Dyer AR, Greenland P, et al: Pulse pressure compared with other blood pressure indexes in the prediction of 25-year cardiovascular and all-cause mortality rates—The Chicago Heart Association Detection Project in Industry Study. Hypertension 38:232-237, 2001
14. Serne HE, Gans ROB, ter Maaten JC, et al: Impaired skin capillary recruitment in essential hypertension is caused by both functional and structural capillary rarefaction. Hypertension 38:238-242, 2001
15. Et-taouil K, Schiavi P, Levy BI, et al: Sodium intake, large artery matrix composition and compliance in the SHR. Hypertension 38:1172-1176, 2001
16. Davies PF: Flow-mediated endothelial mechanotransduction. Physiol Rev 75:519-560, 1995
17. Plante GE, Chakir M, Lehoux S, et al: Disorders of body fluid balance: A new look into the mechanisms of disease. Can J Cardiol 11:788-802, 1995
18. Et-taouil K, Regoli D, Plante GE: Sensibilité du récepteur B_2 de la bradykinine de l'aorte du rat spontanément hypertendu. Med Sci 17:171, 2001 (suppl 1, abstr)
19. Ross R: The pathogenesis of atherosclerosis: A perspective for the 1990s. Nature 362:801-808, 1993
20. Taddei S, Virdis A, Mattei P, et al: Aging and endothelial function in normotensive subjects and patients with essential hypertension. Circulation 91:1981-1987, 1995
21. Parhami F, Tintut Y, Ballard A, et al: Leptin enhances the

calcification of vascular cells. Artery wall as a target of leptin. Circ Res 88:954-962, 2001

22. Caro CG, Lever MJ: Factors affecting arterial wall transport. Biorheology 21:197-205, 1984

23. Shao XP, Chainey A, Plante GE: Pharmacologie des récepteurs de l'angiotensine-II dans la microcirculation de l'aorte thoracique. Med Sci 16:29, 2000 (suppl 1, abstr)

24. Becker LC, Pepine CJ, Bonsall R, et al: Left ventricular, peripheral vascular, and humoral responses to mental stress in normal middle-aged men and women. Circulation 94:2768-2777, 1996

25. Moberg E, Kollind M, Lins P, et al: Acute mental stress impairs insulin sensitivity in IDDM patients. Diabetologia 37:247-254, 1994

26. Plante GE, Chakir M, Regoli D: Microcirculation dysfunctions observed in the diabetic rat are bradykinin-dependent. XIVth International Congress of Nephrology. Sydney, Australia, May 25-29, 1997

27. Plante GE, Alfred J, Chakir M: The blood vessel, linchpin of diabetic lesions. Metabolism 48:406-409, 1999

28. Lortie M, Regoli D, Rhaleb NE, et al: The role of B_1 and B_2 kinin receptors in the renal tubular and hemodynamic response to bradykinin. Am J Physiol 262:R72-R76, 1992

29. Chakir M, D'Orleans-Juste P, Plante GE: Neutral endopeptidase inhibition, a new approach in the exploration of diabetic vasculopathy. Eur J Pharmacol 285:11-18, 1995

30. Plante GE, Brodeur J, Larouche A, et al: Effect of diuretic therapy on thoracic aorta proteoglycan radiosulphate incorporation. I—Studies in the Wistar-Kyoto rat. Can J Physiol Pharmacol (in press)