Sympathetic Hyperactivity and Coronary Risk in Hypertension

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One of the most interesting questions in the field of human hypertension is the apparent paradox of coronary heart disease. Coronary risk is related in a linear fashion to the prevailing blood pressure, and the incidence of coronary heart disease in the hypertensive population is higher than in the normotensive population. Nevertheless, modern antihypertensive treatment, which is very successful in reducing mortality from stroke and congestive heart failure, has much less of a robust effect on the reduction of coronary morbidity and mortality. Many explanations for this discrepancy have been offered. Maybe the treatment was started too late and the blood pressure reduction was not sufficiently aggressive to protect the coronaries. The majority of controlled trials used antihypertensive drugs that increase coronary risk by their effect on electrolytes, blood lipids, and glucose, and this could have offset the positive effect of blood pressure reduction. Finally, too drastic a blood pressure lowering in a subset of patients in clinical trials may have been deleterious: the so-called J-curve effect.

In this review, I will marshal evidence for yet another interpretation of the coronary heart disease paradox in hypertension. Some of the coronary morbidity in hypertension may not be a direct consequence of blood pressure elevation. Hypertension is a complex syndrome in which blood pressure elevation is only one sign of multiple underlying pathophysiological abnormalities. In their own right, and somewhat independently of blood pressure level, many of these abnormalities contribute to the development of coronary heart disease as well as to poorer coronary outcomes in hypertension.

It will also be suggested that increased sympathetic activity, which is present in a large proportion of patients with hypertension, is the common link among many of the "non-pressure-related" coronary risk factors in hypertension.

Of necessity, I will focus only on one point of view. Alternative explanations of the same evidence, for example, that hyperinsulinemia may be the primary abnormality causing all other aberrations, are equally feasible.

**Sympathetic Abnormality in Hypertension**

**The Evidence**

The evidence for increased sympathetic drive is particularly strong in the early phases of the hypertensive process: borderline and mild hypertension. In these subjects, increased cardiac β-adrenergic and vascular α-adrenergic drive have been documented by selective receptor blockade. The evidence from pharmacological experiments is corroborated by measurements of plasma norepinephrine, which tends to be elevated in younger subjects with mild hypertension. In older patients, the elevation is less prominent, and high catecholamine levels are found only in the arterial and not in the venous blood. Because plasma catecholamines do not directly reflect sympathetic tone, Esler and coworkers studied the true norepinephrine "spillover" with a radioactive tracer and found high spillover rates in young patients with hypertension. A high sympathetic tone in hypertension has also been inferred from spectral analysis of heart rate period variability. Finally, the Iowa group documented with microneurographic recordings a significant increase in peroneal nerve sympathetic traffic in patients with borderline hypertension.

**Hemodynamic Transition**

Typically, patients with increased sympathetic tone have a "hyperkinetic" circulation; i.e., in addition to high plasma norepinephrine values, their cardiac output and heart rate are also elevated. This hemodynamic constellation is different from established hypertension, in which vascular resistance is elevated and cardiac output is normal. Consequently, two questions arise: 1) Do these patients have a form of hypertension that is different from established hypertension or is the hyperkinetic state just a phase in the development of established hypertension? and 2) if the hyperkinetic state is a stage in the evolution of established hypertension, how does cardiac output become normal and how does vascular resistance increase during the course of hypertension?

There is substantial evidence for a transition from the hyperkinetic state to established hypertension. Tachycardia, the hallmark of the hyperkinetic state, predicts the later development of hypertension. Compared with normotensive subjects, subjects with transient tachycardia, and particularly when their tachycardia is combined with transient hypertension, have a fivefold incidence of later hypertension. The actual transition from a hyperkinetic to high-resistance state has been inferred from a relatively short-term clinical studies and has been recently confirmed in a unique longitudinal study by Lund-Johansen. In the first 10 years of follow-up, blood pressure of the initially hyperkinetic group did not increase, but cardiac output decreased and vascular resistance increased. However, after 20 years, almost all of the subjects developed...
Changes in Sympathetic Tone in the Course of Hypertension

The sequence described above does not explain the apparent normalization of sympathetic tone during the course of hypertension. Increased plasma norepinephrine levels and an elevated norepinephrine turnover are found in young but not in older patients with hypertension. Why would plasma catecholamine levels and “spillover” be elevated in the early phases of hypertension but not in the later established hypertension? We believe that the answer lies in understanding the mechanism by which the central nervous system regulates the circulation. To control the circulation, the central nervous system must receive some information about the state of the peripheral circulation. Our analysis suggests that the central nervous system permits large oscillations of the underlying hemodynamics but closely regulates the pressure response. For example, during mental arithmetic and isometric exercise, the characteristic response is an elevation of blood pressure predominantly through a higher cardiac output. If the increase in cardiac output is prevented by β-adrenergic blockade or by defective cardiac function, the low stroke volume in borderline hypertension will be preserved, and the underlying hemodynamic pattern will be shifted to an increase in vascular resistance. Such changes of underlying hemodynamics with a preserved blood pressure response have been observed in a wide range of circumstances. Admittedly, most of the hemodynamic plasticity has been observed with acute reflexes, but the brain shows a similar capacity to redirect the autonomic tone to different parts of the circulation also during longer-lasting responses. For example, hemodynamic plasticity has been shown with hindquarter compression of dogs: a neurogenic elevation of the blood pressure occurred that lasted without change during 9 hours of observation and could be elicited for 6 hours each day over a period of 9 weeks.

The responsiveness to a variety of stimuli and to the “blood pressure seeking property” of the central nervous system is a major determinant of the direction of the hemodynamic pattern. In other words, the central nervous system does “what it takes” to achieve a certain blood pressure level by directing the drive to responsive organs. We call this the “blood pressure seeking property” of the central nervous system. If one accepts this property of the central nervous system as a fundamental way by which the brain regulates blood pressure, the decrease of sympathetic tone during the course of hypertension is a fully expected development. If in some patients the brain causes a neurogenic hypertension, this will initially require a relatively large sympathetic discharge to the periphery. Later, as the responses of hypertrophic vessels become amplified, less sympathetic discharge is needed to maintain the same vasoconstriction. If the brain is poised to maintain elevated blood pressures in hypertension, as the vascular overresponsiveness evolves, the sympathetic discharge from the central nervous system will decrease. Nevertheless, in spite of a nominally normal sympathetic tone, the central nervous system continues to be a major factor in the genesis of high resistance and elevated blood pressure in these individuals.

Sympathetics and Atherogenesis in Hypertension

Subjects with borderline hypertension characteristically are overweight; have higher cholesterol, insulin, and triglyceride levels; and have decreased high density lipoprotein cholesterol. Interestingly, these abnormalities have also been found in “white coat” hypertensive subjects in Tecumseh who have only a temporary and presumably stress-related blood pressure elevation in the physician's office. In both of these groups, resting heart rate is significantly faster. It has been
previously shown that the tachycardia in these subjects is neurogenic; a blockade of the heart with propranolol and atropine normalizes heart rate. Consequently, in epidemiological studies in Tecumseh, we take the increased heart rate to symbolize the increased autonomic drive to the heart. The relation between tachycardia, higher blood pressure, and various metabolic abnormalities in Tecumseh is seen not only in subjects with borderline hypertension but also across the whole range of blood pressures in the entire population of participants in the Tecumseh Blood Pressure Study (Figure 1). Note in Figure 1 the association of faster heart rates with higher plasma norepinephrine levels.

Inasmuch as the relation is seen also in the normotensive range, the data from Figure 1 suggest that there may be a basic physiological relation between sympathetic tone, blood pressure, and metabolic risk factors for atherosclerosis. Of particular interest is the strong relation of insulin, a known risk factor for coronary heart disease, and blood pressure levels in Tecumseh. We believe that increased sympathetic tone may well be a primary mechanism for the increase of both blood pressure and plasma insulin values.

It need not be argued that sympathetic overactivity may affect glucose delivery. If the microvasculature in skeletal muscle is acutely constricted or chronically rarefied, the diffusion distance between the nutritional blood vessel and the metabolizing cell becomes longer. This will impede the delivery of the poorly diffusible glucose to the muscle cell, thereby creating a state of relative insulin resistance. The arguments in favor of this concept are 1) that rarefaction of blood vessels in the skeletal muscle of patients with hypertension has been demonstrated both functionally and anatomically, 2) that vasodilators improve insulin sensitivity in hypertension, 3) that β-blockers decrease cardiac output and are associated with a worsening of insulin resistance in hypertension, 4) that exercise training improves microcapillarization and positively affects insulin resistance, and 5) that insulin resistance is associated with inadequate postprandial skeletal muscle vasodilation.

In addition to the acute effect of vasoconstriction on insulin resistance, sympathetic stimulation can also induce acute insulin resistance through β-adrenergic receptors. Diebert and DeFronzo elicited an acute insulin resistance by infusions of epinephrine to normal volunteers. The impeded glucose utilization was mediated by β-adrenergic effects of epinephrine; blockade with propranolol reinstated a normal glucose uptake. In hemodynamic terms, the response to epinephrine infusion is similar to the adjustment to mental stress. Both responses are predominantly β-adrenergic; cardiac output and heart rate increase, and pulse pressure widens. Present techniques do not permit the assessment of quick changes in insulin sensitivity, but it is reasonable to think that the β-adrenerg-
gic response during mental stress encompasses also a component of insulin resistance.

Because acute sympathetic vasoconstriction, epinephrine infusion, and mental stresses are short-lived, the question arises whether these mechanisms have any relevance to the chronic state of insulin resistance.

There are two mechanisms by which repeated sympathetic stimulation could lead to a permanent insulin resistance. First is the effect of sympathetics on the composition of muscle fibers. Normally, muscle fibers consist of a larger proportion of type 1 slow-twitch, insulin-sensitive fibers and a smaller proportion of type 2b fast-twitch, insulin-resistant fibers. Patients with hypertension show a decreased number of slow-twitch fibers,57,58 and this might contribute to their insulin resistance. The ratio between fast- and slow-twitch fibers is not fixed; it can, for example, be affected by exercise.51-52 Of great interest to our hypothesis is the observation that prolonged infusion of a β-adrenergic agonist causes conversion from slow- to fast-twitch fibers.59 Repeated sympathetic activation in hypertension may favor the conversion from slow- to fast-twitch insulin-resistant fibers. A decrease of slow-twitch fibers in hypertension has been described.57

The second mechanism by which increased sympathetic tone in hypertension could lead to chronic insulin resistance relates to hemodynamics in skeletal muscle.38-41 Chronic hypertension is associated with a decrease of small blood vessels in the skeletal muscles,45 which increases the diffusion distance for glucose and leads to a relative insulin resistance. A negative relation between human capillary density and sensitivity to insulin has been described.60

The most plausible explanation for the loss of small capillaries in the course of hypertension is through hypertrophy of the muscular layer of the vascular wall. This process eventually can lead to the closure of some of the smaller vessels, the so-called vascular rarefaction.61 Whereas blood pressure elevation per se plays a role in the development of vascular hypertrophy, this is more likely to happen in an environment of increased sympathetic tone. Sympathetically denervated blood vessels in the brain fail to develop hypertrophy.62-63 In patients with borderline hypertension, minimal forearm vascular resistance, a measure of vascular hypertrophy, significantly correlates with plasma norepinephrine values,65 suggesting that sympathetic tone may be an important determinant of vascular hypertrophy.

The proposed mechanisms by which sympathetic overactivity and insulin resistance may be related are illustrated in the top quadrant of Figure 2. The figure suggests that insulin resistance may cause atherosclerosis through elevation of plasma insulin values. Elevated plasma insulin is an independent predictor of future atherosclerosis.56,67 It is not clear whether insulin is atherogenic through a direct vascular “trophic” action, through its effect on lipid metabolism,66 or through a combination of these and other not yet explained factors.

Increased sympathetic tone could be atherogenic independently of insulin resistance. Sympathetic overactivity may increase plasma triglycerides through its effect on lipoprotein lipase. Sympathetics may affect insulin release and thereby alter the hepatic production of very low density lipoproteins. Finally, through α-adrenergic receptors, sympathetic activation may affect the catabolism of low density lipoproteins.69

**Sympathetics and the Tendency for Thrombosis in Hypertension**

Male subjects with higher blood pressures also have higher hematocrit values (Figure 1). Elevation of hematocrit is frequently seen in hypertension,70-72 and in population studies there is a positive correlation between blood pressure and hematocrit.72,73 Higher hematocrit predicts future blood pressure increase64 and a poorer coronary risk.75-77 Hematocrit is an important determinant of human blood viscosity,78 and the increased viscosity is likely to be conducive to coronary thrombosis in hypertension.

The high hematocrit values in hypertension mirror a decrease in a patient’s plasma volume. Although Tarazi et al79 thought that the lower plasma volume is characteristic of advanced hypertension, we have found a decrease of plasma volume already in patients with borderline hypertension.80 As indicated above, borderline hypertension is invariably associated with a sign of increased sympathetic drive. Interestingly Geisbock,81 who at the beginning of this century described the extreme cases of low plasma volume hypertension as “polycythemia hypertonica,” saw a connection between mental stress and the high blood pressure in these subjects.

The interconnection between mental stress, excessive sympathetic tone, and low plasma volume/high hematocrit can be best explained by the effect of α-adrenergic vasoconstriction on capillary hemodynamics. Tarazi et al79 have shown that the decrease of plasma volume in hypertension is limited to the intravascular compartment; the size of the extracellular/extravascular fluid space is normal, and there is an abnormal ratio of the intravascular to the extravascular fluid space. The fact that the total extracellular volume is normal speaks against an excessive diuresis as the basis of the decreased plasma volume, and the altered ratio between intravascular and extravascular space suggests that capillary filtration forces might be altered in hypertension. If capillary pressure in hypertension were elevated, some of the plasma volume would be filtered into the extravascular space. Infusion of catecholamines causes an acute decrease in plasma volume.82 Because other pressor agents failed to produce a similar decrease in plasma volume, Cohn82 concluded that sympathetic agonists alter the ratio between precapillary and postcapillary resistance, resulting in increased capillary filtration into the tissues. We have shown that this mechanism is α-adrenergic; 7 minutes after infusion of propranolol, the unopposed α-adrenergic tone leads to a 13% decrease in plasma volume.83 This decrease is of similar magnitude as in borderline hypertension80 and is unrelated to the effect of propranolol on the systemic circulation. An infusion of atropine after propranolol returned cardiac output to the normal range and decreased right atrial pressure, but these changes in systemic circulation had no effect on plasma volume, which continued to remain decreased.83

Increased platelet activity and turnover is another procoagulant mechanism that may favor coronary thrombosis in hypertension. The abundant literature on the effect of mental stress on platelet function has
recently been reviewed by Hjemdahl et al.\textsuperscript{84} Whereas the results vary and to a large degree depend on methodology, the majority of in vitro and in vivo studies of platelet function document a procoagulant platelet activation with mental stresses. Epinephrine is one of the strongest in vitro platelet aggregators,\textsuperscript{85,86} and this effect is mediated through an \( \alpha \)-receptor.\textsuperscript{84} In vivo infusion of epinephrine also causes platelet activation, and that reaction is exaggerated in patients with hypertension.\textsuperscript{87} Plasma \( \beta \)-thromboglobulin level, a measure of platelet turnover, is elevated in patients with hypertension,\textsuperscript{88} and thromboglobulin levels correlate with higher epinephrine levels in these patients.\textsuperscript{89}

It is reasonable to assume that the hematocrit-related increased blood viscosity and enhanced platelet activation in hypertension together with hypertension-induced endothelial damage may be conducive to coronary thrombosis in hypertension. Epidemiological studies support the role of hematocrit as a coronary risk factor, and future studies are needed to determine the relevance of platelet hyperactivity as a predictor of coronary morbidity in hypertension.

**Sympathetics, Cardiac Hypertrophy, and Arrhythmias**

Left ventricular hypertrophy is a strong predictor of cardiovascular mortality, particularly of sudden death.\textsuperscript{90-91} Presumably through the tendency of subjects with left ventricular hypertrophy to develop arrhythmias. The excess deaths are particularly accentuated in subjects with left ventricular hypertrophy who had already suffered a myocardial infarction.

It is now recognized that sympathetic stimulation is a pressure-independent "trophic" factor for cardiac hypertrophy. The growth of cultured embryonal heart cells is stimulated by norepinephrine in the culture medium, and this is an \( \alpha \)-adrenergic effect.\textsuperscript{92,93} The relative independence of pressure and sympathetics in left ventricular hypertrophy is underscored by results from trials of regression of left ventricular hypertrophy.\textsuperscript{94-96} Vasodilators that lower blood pressure but elicit a strong sympathetic reflex response do not induce a regression of left ventricular hypertrophy, whereas sympatholytics cause regression in spite of a lesser blood pressure effect.\textsuperscript{96}

Sympathetic activation in the body is frequently associated with an activation of the renin-angiotensin system, and these two pressor agents have many synergistic actions. Both norepinephrine\textsuperscript{92,93} and angiotensin\textsuperscript{97} are known to have "trophic" properties. In patients with borderline hypertension, high norepinephrine values are associated with elevated plasma renin values,\textsuperscript{89} and it is likely that this interaction further reinforces the tendency for cardiac hypertrophy. In an animal model of reflex hypertension, the blood pressure increase is coupled with simultaneous increases of norepinephrine and renin levels.\textsuperscript{96} Repeated pressor episodes in these animals cause development of left ventricular hypertrophy.\textsuperscript{99} In this model, the ventricular hypertrophy can be prevented by a converting enzyme inhibitor but not by a strong vasodilator.\textsuperscript{100}

The described interrelation between sympathetics and the renin-angiotensin system is one example of complex interactions in patients with increased sympathetic tone. Another area is the balance between sympathetic and parasympathetic tone in borderline hypertension. In patients with borderline hypertension, increased sympathetic drive is combined with a decreased parasympathetic inhibition of the heart.\textsuperscript{93} Interestingly, decreased parasympathetic tone in borderline hypertension is not seen only in cardiovascular organs. A decreased saliva production secondary to decreased parasympathetic tone to the parotid glands has also been described in these patients.\textsuperscript{101} Decreased parasympathetic tone to the heart has also been documented in patients with advanced, established hypertension.\textsuperscript{102}

The combination of a decreased parasympathetic and an increased sympathetic tone suggests that the autonomic abnormality in borderline hypertension stems from the central nervous system and localizes the site of dysfunction. Sympathetic and parasympathetic tone are regulated in a reciprocal fashion, and the integration of these two branches occurs in the medulla oblongata. This fact will be useful for understanding the discussion of the relation between the "defense reaction" and multiple pathophysiological abnormalities in hypertension. However, the combination of low parasympathetic tone with a high sympathetic tone that underlies tachycardia in hypertension may also be important in the pathophysiology of arrhythmias in hypertension. Tachycardia is a known independent predictor of cardiovascular mortality.\textsuperscript{103,104}

How hypertension and increased sympathetic tone may combine to favor left ventricular hypertrophy, arrhythmias, and sudden death is graphically illustrated in the lower quadrant of Figure 2.

**Sympathetics and Vascular Reactivity**

Some of the material discussed here reiterates the discussion of the role of sympathetics in insulin resistance. It was stated that sympathetic tone is a trophic factor for development of vascular hypertrophy.\textsuperscript{92,93} As vascular hypertrophy evolves, the medial layer of resistance vessel walls thickens and encroaches more on the vessel lumen. This becomes an amplifying mechanism; the more the vessel is constricted, the larger the interference from the encroaching wall. This fact will be useful for understanding the discussion of the relation between the "defense reaction" and multiple pathophysiological abnormalities in hypertension. However, the combination of low parasympathetic tone with a high sympathetic tone that underlies tachycardia in hypertension may also be important in the pathophysiology of arrhythmias in hypertension. Tachycardia is a known independent predictor of cardiovascular mortality.\textsuperscript{103,104}

How hypertension and increased sympathetic tone may combine to favor left ventricular hypertrophy, arrhythmias, and sudden death is graphically illustrated in the lower quadrant of Figure 2.

**'Defense Reaction': A Common Denominator of Coronary Risk and Sympathetic Hyperactivity in Hypertension?**

Some of the mechanisms presented above and illustrated in Figure 2 are speculative, but the basic ideas are well supported by experimental data. The magnitude and importance of these factors, however, can only be assessed in prospective epidemiological studies.
In closing, I wish to engage in yet another speculation. It is hard to accept the accumulation of the "pressure-unrelated" procoronary factors in hypertension as a chance development. Why would patients with hypertension have excessive sympathetic drive, and why would that excess have such dire consequences?

All the observed hemodynamic and humoral alterations in borderline hypertension fit well into the pattern of the so-called defense reaction, a symptom complex of responses to perceived danger that emanates from discrete pathways in the paleocortex. The purpose of this defense reaction is to prepare the organism for an efficient fight-or-flight response to the environmental threat. Brod was the first to point out that, when subjected to mental stress, patients with hypertension show an exaggerated hemodynamic response compatible with an excessive defense reaction. The pattern of circulation observed in borderline hypertension at rest during invasive studies and noninvasive studies is compatible with the hemodynamics of the defense reaction: elevated blood pressure, high cardiac output, and fast heart rate, as well as vasodilation in the skeletal muscle. Even without the provocation of a mental stress, subjects with borderline hypertension seem to constantly activate the defense response.

The hemodynamics of the defense reaction is geared toward an efficient response to physical threat. The higher pressure head, larger cardiac output, and excessive flow through the skeletal muscles prepare the organism for a good physical performance for either a fight against or flight from danger. The defense response has also been described as "epinephrine-like," as its hemodynamics closely resemble the \( \beta \)-adrenergic responses to an infusion of epinephrine.

Infusion of epinephrine causes an acute \( \beta \)-receptor-mediated insulin resistance. This acute resistance of skeletal muscles to the effects of insulin, together with an actual suppression of insulin secretion, leads to an increase of blood glucose during epinephrine infusion. The metabolic adjustment during the simulated defense response with epinephrine infusion fits well in the teleological scope of the alarm reaction. If one views this adjustment as a preparatory stage toward the anticipated exercise effort, insulin resistance simultaneously with increased perfusion of skeletal muscles is useful. The skeletal muscles, which greatly increase their metabolic demands during exercise, may deplete the available glucose. They are well supplied with blood, but they stop utilizing exogenous glucose. In doing so, the muscles do not compete with the brain for the same fuel. The brain, which critically depends for its function on glucose and is unable to use other fuel, is capable of extracting glucose in the absence of insulin. During the defense reaction, both critical organs are appropriately supplied; muscles are adjusted to the anticipated large increase in the metabolic activity by an increase of flow.

The brain, whose metabolic needs are fairly constant, does not need in the short run a "fast" fuel but is protected against depletion of its most important fuel.

Frequently in the human body, repeated functional demands are later supported by appropriate long-term structural adjustments. This seems to be the case also for insulin resistance in the defense reaction. Long-term \( \beta \)-adrenergic stimulation causes a shift from slow- to fast-twitch fibers. These fibers have fewer capillaries and are insulin resistant. In that context, the trophic properties of angiotensin and norepinephrine may also be useful. How vascular hypertrophy leads to a loss of microvasculature and further "structural reinforcement" of insulin resistance has been described in detail elsewhere.

The sympathetically induced platelet abnormalities and decrease of plasma volume in borderline hypertension also fit into the pattern of the defense reaction. It may be purposeful for procoagulant mechanisms to be activated in the anticipation of combat injuries. Furthermore, the redistribution of plasma from the intravascular to the interstitial compartment may also be useful if, as Page suggested in proposing the mosaic theory, the tissue perfusion is the protected variable in the human body.

In borderline hypertension, sympathetic activation is associated with higher plasma renin levels. Renin, through the effect of angiotensin on aldosterone, is an important regulator of sodium and water in the body. The importance of the preservation of fluid and sodium balance during physical effort or during injuries is self-evident.

If all the adjustments seen during the defense reaction had in fact offered a true survival advantage, it is conceivable that this became a factor in natural selection. It is not difficult to visualize how a substantial proportion of individuals prone to an efficient and vivid defense reaction would be selected to pass on their genes and thereby perpetuate a constellation of increased sympathetic activity, high blood pressure, insulin resistance, and multiple other coronary-prone characteristics. The concept that factors which have offered a survival advantage may become deleterious in modern society has been proposed by Neel, and the tendency to coronary morbidity in hypertension may be a case in point.

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