Insulin resistance and hyperinsulinemia in hypertension

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Genetic predisposition: Insulin resistance and reactive hyperinsulinemia occur not only with obesity, impaired glucose tolerance or non-insulin-dependent (type 2) diabetes mellitus, but also in many non-obese, non-diabetic patients with essential hypertension and their currently normotensive, lean, young offspring, as well as in some other conditions known to promote hypertension. Insulin resistance impairs glucose tolerance, while insulin resistance and/or hyperinsulinemia promote dyslipidemia, body fat deposition and probably atherogenesis. Therefore, the common coexistence of a genetic predisposition for hypertension with insulin resistance helps to explain the frequent, although temporally often dissociated, occurrence of hypertension together with dyslipidemia, obesity and type 2 diabetes in a given patient.

Insulin resistance and hyperinsulinemia as slow pressor mechanisms: In the pathogenesis of hypertension, inappropriate vasoconstriction (due to an imbalance of vasoactive substances and/or raised cytosolic calcium) and/or structural vasculopathy is particularly important. Among the mosaic of assumed pressor mechanisms, distinct Na^+ retention is almost invariably involved in diabetes mellitus, while sympathetic activation tends to occur in essential hypertension, particularly in association with obesity.

Insulin resistance may develop as a consequence of an intracellular excess of Ca^{2+} or a decrease in Mg^{2+}, an impaired insulin-mediated rise in skeletal muscle blood flow, increased sympathetic activity or excess body weight. Acute hyperinsulinemia causes arterial vasodilation on one hand and increases sympathetic activity and renal Na^+ reabsorption on the other. Chronically, hyperinsulinemia may promote cardiovascular muscle cell proliferation and atherogenesis, while insulin resistance may be associated with certain transmembraneous cation transporters, leading to an increase in cytosolic Ca^{2+}. Hyperinsulinemia and/or insulin resistance may also be associated with an increased blood pressure sensitivity to high salt intake. In the mosaic of many different blood pressure-raising mechanisms, insulin resistance and/or hyperinsulinemia is likely to represent an amplifying slow or very slow pressor factor.

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Introduction

Insulin resistance, defined as impaired insulin-mediated glucose disposal, is a common consequence of excess body weight and a cause of impaired glucose tolerance or type 2 diabetes. Moreover, insulin resistance and reactive hyperinsulinemia occur in association with several other hypertension-prone or hypertensive conditions [1–3], such as aging, pregnancy, uremia, acromegaly, Cushing's syndrome, alcohol abuse and, most notably, essential hypertension [4,5].

In offspring of essential hypertensive, non-diabetic parents, insulin resistance, hyperinsulinemia and related increases in serum low-density lipoprotein cholesterol and triglycerides have been shown to occur before the development of hypertension, any excess body weight [6–9] or a central redistribution of body fat [8]. In contrast, offspring of type 2 diabetic families not only have a presumably hereditary tendency towards insulin resistance [10], but are also more likely to become hypertensive [11]. These reports are complemented by findings of an exaggerated insulin response to a glucose load and higher

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blood pressure in offspring of parents with impaired glucose tolerance and hyperinsulinemia than in offspring of normoinsulinemic parents [12]. Therefore, a genetic background of either hypertension or diabetes seems to carry a predisposition to both disturbances.

Prehypertensive subjects whose parental blood pressure or glucose status was not specified, but who subsequently developed hypertension, were characterized by a tendency towards high plasma insulin levels, subtle impairment of glucose tolerance, dyslipidemia and a higher body mass index, and high insulin levels at baseline emerged as a body weight-independent, significant predictor of future hypertension [13–15]. In a mixed group of 127 initially normotensive non-diabetic or type 2 diabetic subjects, those with higher baseline plasma insulin values after a glucose load showed a greater tendency to develop hypertension during 5 years of follow-up [16]. Thus, the cluster of atherogenic changes associated with hypertension actually precede the established hypertensive state.

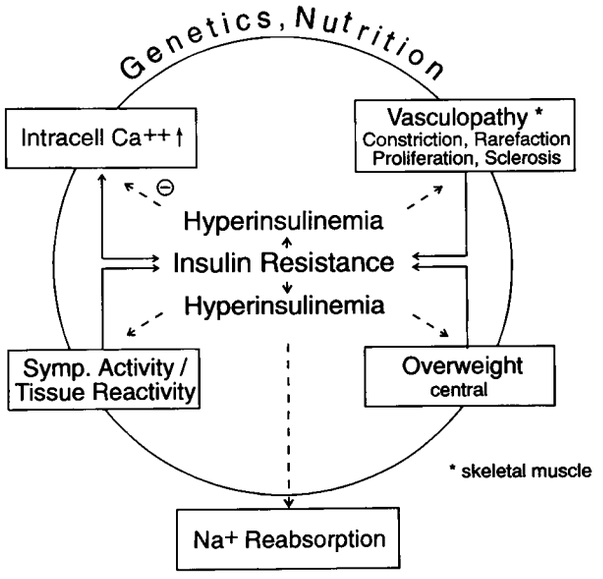

Fig. 1. Interrelationships among (predisposition to) hypertension, excess body weight and metabolic disturbances [19]. Symp., sympathetic.

Mechanisms of insulin resistance in essential hypertension

In non-obese essential hypertensives, the non-oxidative pathway of insulin-mediated glucose disposal is impaired, and the site of this disturbance is predominantly the skeletal muscle [17,18]. Potential causes under consideration (Fig. 1) include: a reduced skeletal blood flow due to an increased proportion of fast (type II) versus slow (type I) muscle fibers, structural vascular changes, vasoconstriction [20,21] and/or an attenuated insulin-mediated rise in muscle blood flow [22]; increased sympathetic activity [20,23,24], although so far, there is no evidence of this in the normotensive offspring of essential hypertensive parents [25,26]; an insulin receptor disturbance; or, more likely, a post-receptor defect, resulting in an excess in cytosolic calcium [9,27–29] and decreased intracellular magnesium [29], which could promote insulin resistance both directly [28] and through vasoconstriction. A high salt intake might also facilitate postprandial hyperglycemia and hyperinsulinemia [30].

Once excess body weight, particularly central obesity, is present, insulin resistance also involves the liver and adipocytes and is thus less tissue-selective than in lean essential hypertensives. Moreover, insulin resistance is more marked in obese hypertensive than in obese normotensive subjects [31] and increasingly more pronounced in both lean and obese essential hypertensives and those with associated diabetes type 2 [32]. This implies that the adverse effects of a genetic predisposition to essential hypertension and fat accumulation on insulin sensitivity are additive [33] (Fig. 2). Both insulin resistance and hyperinsulinemia also appear to be more pronounced in hypertensive than in normotensive patients with non-insulin-dependent diabetes [34,35]. In

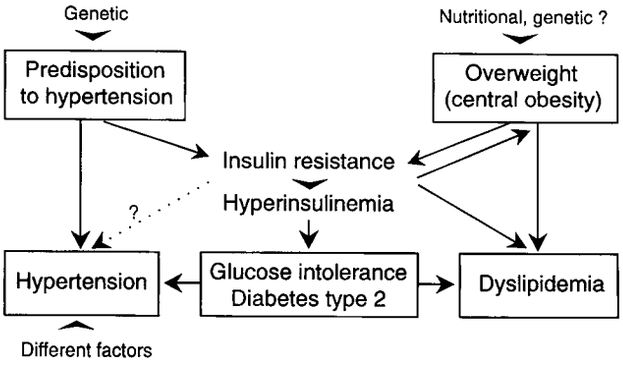

Fig. 2. Potential causes of insulin resistance and possible effects of insulin resistance and/or hyperinsulinemia on blood pressure-regulating factors. Acutely, hyperinsulinemia lowers the transmembraneous Ca^{2+} influx and thus decreases vascular contractility [19].

contrast, a high blood pressure alone apparently does not produce insulin resistance; insulin sensitivity has been reported to be normal in human renovascular hypertension [36,37] and in rats with renovascular or deoxycorticosterone acetate-salt as opposed to spontaneous hypertension [38]. Furthermore, it is interesting that fasting and postglucose-load plasma insulin levels also were significantly higher in sustained essential hypertensive compared with white-coat hypertensive patients [39].

Metabolic consequences of insulin resistance and hyperinsulinemia

Insulin resistance elicits compensatory hyperinsulinemia and, once the latter is no longer sufficient, impaired glucose tolerance. In the presence of normal or increased glucose levels, insulin resistance and/or hyperinsuline-

mia also promote hypertriglyceridemia, a decrease in high-density lipoprotein cholesterol and conversion of the excess very-low-density lipoprotein into low-density lipoprotein particles [19,40]. Concomitantly, deposition of body fat is increased. Moreover, hyperinsulinemia promotes cholesterol accumulation in, and proliferation of, vascular smooth muscle cells [41–43] and, thereby, is likely to accelerate atherogenesis, including coronary heart disease [44–47].

The vicious cycle of metabolic events initiated by insulin resistance helps to explain why a familial predisposition to hypertension poses an increased risk of developing not only high blood pressure, but also dyslipidemia [6,7], obesity [48] and non-insulin-dependent diabetes [49] (Fig. 2). These disturbances are distinctly more common in the hypertensive than in the normotensive population and concomitantly promote atherosclerosis and cardiac complications.

Effects of hyperinsulinemia or insulin resistance on blood pressure regulation

Insulin can modulate various factors with partly opposing effects on blood pressure regulation (Fig. 1).

At the level of vascular smooth muscle cells, hyperinsulinemia acutely lowers the transmembraneous Ca^{2+} influx, shortens Ca^{2+}-dependent action potentials and hyperpolarizes the cell membrane, thereby causing arterial vasodilation [22,50,51] and opposing norepinephrine-mediated vasoconstriction [52]. The vasodilator effect of insulin may involve several mechanisms [50,53] and may be mediated, at least in part, by modulation of the α_2-adrenergic vasoconstrictive pathway [54]. In contrast, sympathetic nervous activity is increased markedly by acute systemic hyperinsulinemia of even a mild degree [51,53,55–57], and plasma insulin levels in subjects ranging from lean to obese were correlated positively with muscle sympathetic nerve activity [56,58]. Moreover, acute hyperinsulinemia increases renal Na^+ reabsorption [59,60] and may also exert positive chronotropic and inotropic effects [61,62].

In obese subjects, the potential of insulin to acutely stimulate sympathetic activity [63] and Na^+ reabsorption [64] seems to be intact. However, its acute vasodilator influence is diminished [50], and a tendency for blood pressure to increase during acute hyperinsulinemia was observed in obese, insulin-resistant, hypertensive subjects [65]. This suggests an obesity-associated defect in insulin-mediated vasoregulation.

In type 2 diabetics, acute hyperinsulinemia was observed to produce an unaltered Na^+-retaining effect, while blood pressure tended to decline and plasma norepinephrine increased slightly [66,67]. In patients with autonomic impairment due to disease and/or old age the potential of hyperinsulinemia to cause sympathetic activation is likely to dissipate [68,69].

A recent study has also suggested that in essential hypertension hyperinsulinemia may, at least acutely, blunt the natriuretic action of atrial natriuretic factor [70].

Whether or not the Na^+ retention and sympathetic stimulation induced by hyperinsulinemia persist in humans under chronic conditions is unknown. Hyperinsulinemia and/or insulin resistance may also promote salt sensitivity (increase in blood pressure upon changing from a low to a high salt intake) [71–73], and in the long term, hyperinsulinemia could stimulate vascular smooth muscle cell proliferation [43] (Fig. 1), and thereby increase vascular resistance and blood pressure. Moreover, lipid alterations induced by hyperinsulinemia and/or insulin resistance may not only promote atherosclerosis with arterial stiffening and narrowing, but also alter cell membrane fluidity and thereby transmembraneous transport mechanisms [74–76].

The state of vascular contraction is determined by cytosolic calcium levels which, in turn, depend strongly on transmembraneous exchange rates. In different tissues hyperinsulinemia may inhibit the voltage- and receptor-operated Ca^{2+} influx and stimulate Ca^{2+}-ATPase, Na^+,K^+-ATPase, Na^+–H^+ coutertransport, Na^+–amino acid co-transport and perhaps also, through the activation of renal 1α-hydroxylase, $1,25(OH)_2$-cholecalciferol-mediated cellular Ca^{2+} uptake [19] (Fig. 3).

Although acute hyperinsulinemia normally lowers the transmembraneous Ca^{2+} influx and thus vascular contractility [27,77], the function of at least some transmembraneous transport processes and the net response by cytosolic Ca^{2+} might be altered in patients with insulin resistance and/or chronic hyperinsulinemia. It has been proposed that insulin resistance accompanying obesity or type 2 diabetes may, in addition to glucose disposal, also involve Ca^{2+}-ATPase, Na^+,K^+-ATPase and the voltage- and receptor-operated Ca^{2+} influx at the vascular level [27,49,78,79] (Fig. 3). Together with the stimulatory effect of insulin on Na^+–H^+ countertransport, this would raise intracellular Ca^{2+} and blood vessel tone. Furthermore, erythrocyte Na^+–Li^+ countertransport, which is thought by some to represent a mode of functioning of Na^+–H^+ countertransport, tends to be elevated in essential hypertensives with insulin resistance and hyperinsulinemia [80]. Activation of Na^+–H^+ countertransport (Fig. 3) at the vascular level would promote a rise in cytosolic Ca^{2+} [81] together with smooth muscle cell proliferation and hypertrophy. A recent report of blunted insulin-mediated inhibition of agonist-stimulated calcium, pH and aggregatory responses in platelets from essential hypertensive patients provides support for the theory of an altered cellular response in this condition [82].

Nevertheless, different sequences of events seem possible. (1) Insulin resistance and hyperinsulinemia of endogenous origin or due to exogenous insulin administration may promote cellular Ca^{2+} overload, vasoconstriction

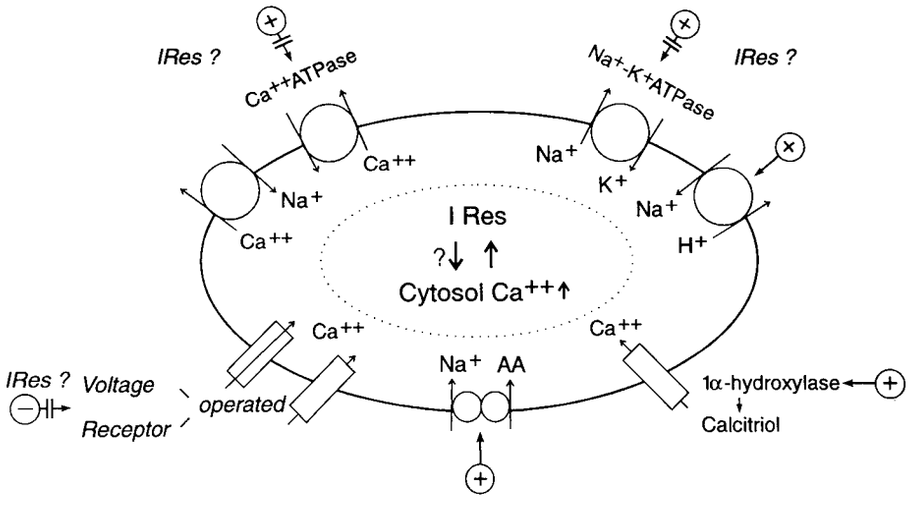

Fig. 3. Effects of insulin or insulin resistance (IRes) on transmembraneous electrolyte pumps [19]. ⊕, Stimulation; ⊖, inhibition by hyperinsulinemia; -II→, suspected resistance to insulin action; AA, amino acid.

and/or hypertrophic and atherosclerotic vascular alterations; (2) cellular Ca^{2+} overload or vasculopathy, of whatever origin, is the primary disturbance, which produces insulin resistance on one hand and hypertension on the other hand; or (3) both sequences can occur so that the process escalates in a vicious cycle.

Vasculopathy, the proximal pathogenetic event in hypertension

Vasculopathy, defined as dysfunction in the form of inappropriate vasoconstriction and/or structural alteration expressed as arterial narrowing and stiffening due to muscle cell proliferation and atherosclerosis, is the proximal pathogenic event in both essential or diabetes-associated hypertension (Fig. 4). The intracellular electrolyte alterations triggering inappropriate vasoconstriction may be induced by a variety of mechanisms, including sympathetic activation, some other imbalance in the different vasoconstrictor/vasodilator hormones, intrinsic defects of vascular smooth muscle cells, endothelial dysfunction [83–85] and peripheral tissue blood flow autoregulation secondary to a hypervolemic–high cardiac output state [86]. In diabetes, at least, overall Na^+ retention might contribute [87,88].

As an expression of vasculopathy, vascular hyperactivity to norepinephrine, and sometimes angiotensin II, occurs commonly in young currently normotensive offspring of essential hypertensives [89], patients with borderline or established essential hypertension [90], particularly those with blood pressure salt-sensitivity [91], and already in the early uncomplicated stage of diabetes [87,92].

Insulin appears to be one of a mosaic of factors contributing to vasculopathy (Fig. 4). Thus, hyperinsulinemia can cause both structural and, through sympathetic activation and perhaps mildly increased renal Na^+ reabsorption, functional vasculopathy. The net effect of chronic hyperinsulinemia and/or insulin resistance on cytosolic Ca^{2+} in cardiovascular muscle cells remains to be clarified. However, hyperinsulinemia might also facilitate the development of left ventricular hypertrophy [93].

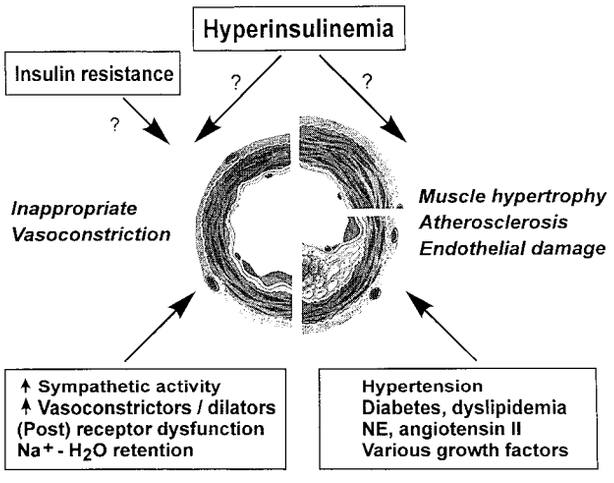

Fig. 4. Some factors that might contribute to functional or structural vasculopathy in hypertension. NE, norepinephrine.

Interactions between insulin or insulin resistance and blood pressure obviously differ from those of the classical, acutely and chronically potent substances norepinephrine and angiotensin II. Nevertheless, in view of the often reciprocal relationships with multiple potential blood pressure-raising factors (Fig. 5), hyperinsulinemia and/or insulin resistance appears to represent an amplifying slow or very slow pressor mechanism [19,33].

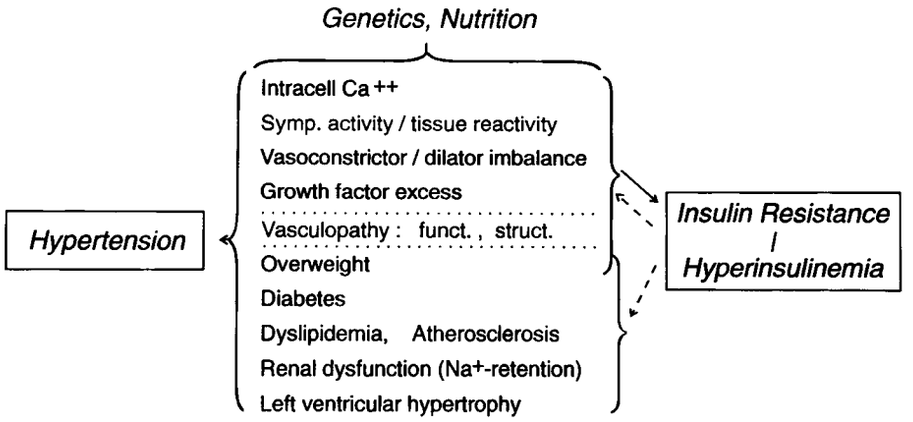

Fig. 5. Mediating disturbances in the interaction between insulin resistance/hyperinsulinemia and hypertension [19]. Intracell, intracellular; Symp., sympathetic; funct., functional; struct., structural.

Blood pressure effects of an improvement in hyperinsulinemia or insulin resistance

The proof of a pathogenetic effect of hyperinsulinemia and/or insulin resistance in hypertension requires the demonstration that an amelioration of the insulin dysregulation produces an antihypertensive effect. This has been reported in several clinical or experimental settings (Table 1) [94–103]. Nevertheless, these observations are based on small samples, often on uncontrolled studies and, except for reduced administration of exogenous insulin [96], a non-insulin-related blood pressure-lowering mechanism of the drugs used in these studies cannot be excluded. However, short-term pharmacological interventions are unlikely to reverse insulin-mediated structural alterations and therefore tend to underestimate the contribution of insulin dysregulation to hypertension.

Table 1. Blood pressure during a short-term improvement in insulin sensitivity and/or hyperinsulinemia in insulin-resistant hypertensive states.

Intervention	State of subjects	n	BP	Ref.
Somatostatin (intravenously)				
10 h	Essential hypertensives			[94]
	Obese, hyperinsulinemic	7	↓	
	Normoinsulinemic	7	=	
7 h	Rats on high-fructose diet	14	↓	[95]
Insulin dose ↓	Type 2 diabetes			[96]
	Hypertensive	6	↓*	
	Normotensive	6	=	
Metformin	Type 2 diabetic hypertensives	27	↓	[97]
	SHR		↓	[98]
	Normotensive rats		=	[98]
Troglitazone†	Obese patients	12		[99]
Ciglitazone†	Obese Zucker rats			[100]
Pioglitazone†	Dahl rats			[101]
	Renal hypertensive		↓	
	Normotensive		=	
CS-045†	Obese Zucker rats		↓	[102]
Vanadyl sulfate†	SHR		↓	[103]
	Normotensive rats		=	[103]

BP, Blood Pressure, SHR, spontaneously hypertensive rats. ↓, decreased; =, unchanged. *With transient natriuresis. †Improvement in insulin sensitivity and hyperinsulinemia.

Synopsis of the relationship between insulin resistance or hyperinsulinemia and hypertension

On the basis of available information, the frequent occurrence of insulin resistance and hyperinsulinemia in essential hypertensives and their young normotensive offspring may reflect the following different hypotheses:

(1) Insulin resistance and hypertension may be causally unrelated but may have a common underlying mechanism, such as altered cellular electrolyte metabolism; increased vascular resistance or decreased vasodilating capacity, particularly in skeletal muscles; increased sympathetic activity; and, once it occurs, excess body weight.

(2) Insulin resistance may occur as a secondary change during the development of hypertension and may have no primary effect on the pathogenesis of hypertension.

(3) Insulin resistance and/or hyperinsulinemia, whatever the underlying mechanism and time of appearance, may cause or aggravate hypertension.

While confirmation of the correct mechanism is still awaited, it seems most likely that insulin resistance and/or hyperinsulinemia may, in the long term, promote increases in blood pressure, thereby acting as a very slow pressor factor which complements the many other and somewhat more important mechanisms in the pathogenetic mosaic of hypertension (Fig. 5).

Synopsis of interactions between hypertension, obesity and diabetes

A number of pathogenetic mechanisms may be involved in the frequent association observed between hypertension, obesity and diabetes mellitus.

A genetic predisposition for essential hypertension not only poses an increased risk of developing high blood pressure. Essential hypertensive patients and their offspring tend to be insulin-resistant and hyperinsulinemic, which makes them prone to develop dyslipidemia, obesity, impaired glucose tolerance and, eventually, type 2 diabetes. However, excess body weight and central obesity in particular, resulting from intrinsic disturbances and/or excess calorie intake, can induce or aggravate insulin resistance, the resulting metabolic changes and hypertension.

The pathogenesis of essential hypertension is undoubtedly multifactorial, involving a variety of neurohumoral, endocrine, metabolic and/or renal mechanisms. Functional and/or structural vasculopathy, which raises peripheral vascular resistance, is an important ultimate event in essential and most other forms of hypertension.

Obesity may promote hypertension through several potential pressor mechanisms [33], including increased sympathetic tone, a tendency towards hyperaldosteronism, increased blood pressure sensitivity to a high salt intake, increased total blood volume leading to increased cardiac output, and perhaps raised cytosolic Ca^{2+} and reduced Mg^{2+}; an inappropriately elevated peripheral vascular resistance in obesity-associated hypertension also leads to vasculopathy.

In hypertension accompanying diabetes mellitus, a genetic predisposition to hypertension, Na^{+} retention, functional and structural vasculopathy, and increased blood pressure salt-sensitivity seem to be particularly important contributory factors [88,104].

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