



Insulin-Resistant Systolic Hypertension

(The critical intersection of metabolic and cardiovascular diseases.)

James LaSalle, D.O. *

***Correspondence to:** James LaSalle, D.O.

Copyright

© 2025 **James LaSalle, D.O.**, This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received: 14 June 2025

Published: 26 June 2025

DOI: <https://doi.org/10.5281/zenodo.15745135>

Introduction

Hypertension affects more than 120 million Americans. Insulin-resistant-systolic hypertension (IRH) 132/70 is often overlooked and underestimated numerically as this phenotype appears benign and often insignificant. However, when detected under the circumstances such as the metabolic syndrome, pre-diabetes, type 2 diabetes it becomes highly significant.

The intent of this review is to synthesize the current understanding of the pathophysiological mechanisms linking insulin resistance to elevations in systolic blood pressure.

Hypertension that is associated with insulin resistance occurs in almost 50% of the cases. The relationship between insulin resistance and elevated systolic blood pressure is not merely associative but mechanistically intertwined. Insulin resistant hypertension (IRH) accelerates vascular injury, increases cardiovascular mortality and often is resistant to standard mono-therapy. Despite its prevalence, the clinical recognition of IRH and its significance is less than optimal in most primary and speciality clinics across America.

Insulin-resistant systolic hypertension (IRH) arises from the convergence of metabolic disturbances and vascular dysregulation. Insulin resistance is defined as a diminished biological response to normal or elevated levels of insulin. Insulin resistance is a central feature of the metabolic syndrome, pre-diabetes, and type 2 diabetes, causing alterations in vascular functions and negatively affecting glucose homeostasis. This process links multiple mechanisms that include significant changes in fat metabolism, kidney function and alterations in vascular structure that contribute to an aggressive posture with a seemingly a benign blood pressure.

In insulin-resistant patients, pancreatic beta-cells compensate by secreting higher levels of the native hormone insulin to maintain euglycemia. This compensatory hyperinsulinemia abnormally stimulates the sympathetic nervous system (SNS) simultaneously through central and peripheral pathways. The result increases in norepinephrine release from sympathetic nerve terminals and enhances adrenal medullary activity, resulting in a sympathetic overdrive leading to increased heart rate, cardiac output, peripheral vasoconstriction and reduced renal blood flow. The cumulative effect of these changes elevates systemic vascular resistance and contribute to sustained increases in systolic blood pressure.

Hyperinsulinemia also has a direct effect on the kidney that favors sodium reabsorption in the proximal tubules leading to expansion of the intravascular volume, increased preload, cardiac output, and elevated arterial

pressure. The long-term cumulative consequences of these actions will cause vascular remodeling and changes in the cardiac structure such as left ventricular hypertrophy.

Insulin normally promotes normal endothelial function through the actions of endothelial nitric oxide synthase (eNOS) activation via the phosphoinositide 3-kinase (P13K)-Akt pathway. This results in nitric oxide (NO) production and vasodilation.

However, in the insulin resistant patient, the normal pathway for NO synthesis is impeded by the simultaneous stimulation of mitogen-activated protein kinase (MAPK) pathway. This pathway (MAPK) overpowers NO synthesis and creates an environment that favors vasoconstriction and vascular smooth muscle proliferation. Consequentially, nitric oxide bioavailability decreases causing increases in oxidative stress, and enhanced production of endothelin1, a potent vasoconstrictor, resulting in arterial stiffness and diminished blood pressure variability.

Additionally, insulin-resistance enhances the activity of the renin-angiotensin-aldosterone system (RAAS) through multiple mechanisms. These mechanisms further enhance sodium retention, cause local and systemic vasoconstriction and promote structural changes in the vasculature and myocardium. The RAAS also promotes inflammation (local and systemic) while stimulating fibrosis that fosters additional vascular damage.

Insulin-resistance also affects adipose tissue, shifting it toward a pro-inflammatory substrate. Adipocytes and infiltrating macrophages secrete pro-inflammatory cytokines that include Tumor Necrosis Factor (TNF-alpha), Interleukin-6 (IL-6), Resistin, and Monocyte Chemoattractant Protein-1 (MCP-1). These molecules trigger endothelial dysfunction, promote vascular smooth muscle proliferation, and impair insulin signaling in vascular tissues. Additionally, adiponectin, a potent anti-inflammatory and vasoprotective adipokine, is significantly reduced in obesity and insulin resistance, further tipping the balance toward vascular damage.

Chronic exposure to all of the above factors, particularly angiotensin-II, aldosterone and inflammatory cytokines lead inevitably to increased collagen deposition, reduced elastin content, and structural changes in the arterial wall. All of these changes reduce arterial compliance and raise pulse wave velocity, increasing systolic blood pressure and negatively affecting pulse pressure. These changes are the hallmarks of hypertensive vascular disease in insulin-resistant patients.

Patients with insulin-resistant systolic hypertension often exhibit blunted nocturnal blood pressure dipping and elevated nighttime pressures. This non-dipping pattern is independently associated with target organ damage, including left ventricular hypertrophy, microalbuminuria, and cerebral vascular accidents.

Insulin-resistant hypertension is primarily systolic in nature and the level of systolic blood pressure elevations may not clinically indicate the severity of the disease. But under the guise of being benign dangerous mechanism increase sympathetic nervous system activity, vasoconstriction, vascular remodeling, increases in heart rate, and mild to moderate peripheral edema. The net result of all of these changes are elevations in the systolic blood pressure and a widening of the pulse pressure. A systolic blood pressure of 140/70 (pulse pressure of 70) is oftener overlooked or ignored seen in most clinics in America. Here is a reminder of the classifications of systolic hypertension:

Stage 1 Systolic pressure 130-139 mmhg with a diastolic pressure less than 80 mmhg.

Stage 2 Systolic blood pressure greater than or equal to 140 mmhg with a diastolic pressure less than 80 mmhg.

Stage 3 Hypertensive crisis-systolic pressure greater than or equal to 180 mmhg with a diastolic pressure that is variable.

A systolic blood pressure elevation of 132/70 may seem benign but in the setting of insulin-resistance, pre-diabetes, or a patient with type 2 diabetes it is not benign but a highly neurohormonal metabolically active condition that if left unattended will inevitably lead to complications.

References

1)Hypertensive patients with type 2 diabetes mellitus:80-90%

(DeFronzo RA et al., Diabetes Care, 2009)

2)Hypertensive patients with obesity (BMI>30):70-80%

(Reaven Gm, Am J Hypertension, 2004)

3)Hypertensive patients with metabolic syndrome: 60-75%

(Grundy SM et al., Hypertension 2005)

4) African Americans adults with hypertension 60-70%

(Howard BV et al., Hypertension 2001)

5) Women with PCOS and hypertension: 65-85%

(Legro RS et al., J Clin Endocrinol Metab, 2007)

6) Adults with NAFLD and hypertension: 70-80%

(Chalansani N et al., Hepatology, 2018).



Medtronic