Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105186

Understanding high blood pressure: pathophysiological advances

Entender la hipertensión arterial: avances fisiopatológicos

David Cardona-Müller, MD* Ernesto G Cardona-Muñoz, MD*

Keywords:
High blood pressure, pathophysiology, arterial function, cardiovascular disease.

Palabras clave:
Hipertensión arterial, fisiopatología, función arterial, enfermedad cardiovascular.

ABSTRACT

High blood pressure (HBP) has been identified as a major risk factor for cardiovascular events such as stroke and myocardial infarction. To understand the pathophysiology of high blood pressure and other diseases which affect the cardiovascular system, it is necessary to understand how they occur. Here, we discuss pathophysiological elements which lead to HBP including a discussion on arterial stiffness, as well as the biophysical and hemodynamic components which lead to the sustenance and increase in systemic blood pressure levels in adults. We also discuss humoral components which regulate blood pressure and which, when dysregulated, play a pivotal role in the pathophysiology of HBP.

RESUMEN

La hipertensión arterial (HTA) se ha identificado como uno de los principales factores de riesgo de eventos cardiovasculares como el ictus y el infarto de miocardio. Para entender la fisiopatología de la hipertensión arterial y otras enfermedades que afectan al sistema cardiovascular, es necesario comprender cómo se producen. En este artículo se analizan los elementos fisiopatológicos que conducen a la HTA, incluida una discusión sobre la rigidez arterial, así como los componentes biofísicos y hemodinámicos que conducen al mantenimiento y al aumento de los niveles de presión arterial sistémica en los adultos. También se analizan los componentes humorales que regulan la presión arterial y que, cuando están desregulados, desempeñan un papel fundamental en la fisiopatología de la HTA.

INTRODUCTION

For the last 70 years, high blood pressure (HBP) has been extensively studied and identified as major risk factor for cardiovascular events such as stroke and myocardial infarction. However, oftentimes we make the mistake of setting our goals only on lowering blood pressure levels and because of this, our knowledge regarding this pathology and its consequences is limited. To understand the pathophysiology of high blood pressure and other diseases which affect the cardiovascular system, it is necessary to understand how they occur. Thus, it is of vital importance to understand the neurohumoral systems involved in its regulation, as well as the physical and mechanical characteristics of its different components.

ARTERIAL STIFFNESS

Arterial stiffness is the discipline that arises to help understand the relationship between the mechanics of continuous media in the arterial wall and that of the fluids contained by them. For this it is necessary to know the composition of the arterial wall, which in turn has:

1. **Solid components:** extracellular matrix, collagen fibers and elastin.
2. **Liquids:** water, mucopolysaccharides and glycoproteins.
3. **Interaction** with external, internal and neurohumoral stimuli, mainly mediated by blood flow, which is a viscous fluid and conditions that vary cyclically according to the cardiac cycle. In addition to the

* Investigador Asociado, Universidad de Guadalajara, Jalisco, México. Asociación Nacional de Cardiólogos de México, Ciudad de México, México, Miembro GREHTA.

How to cite: Cardona-Müller D, Cardona-Muñoz EG. Understanding high blood pressure: pathophysiological advances. Cardiovasc Metab Sci. 2022; 33 (s3): s211-s215. https://dx.doi.org/10.35366/105186

cyclical variation that arteries face, they also present changes in their structure over time, both due to associated physiological and pathological conditions.

Arterial behavior also presents variations according to the caliber and arterial wall composition. In physiological conditions we can divide the arterial tree into arteries of large, medium, and small caliber, according to their caliber.

1. **Large-caliber arteries** have as a characteristic the ability to distend and comply to the challenges that arise due to cardiac activity.
2. **Small caliber arteries** act dissipating the energy and those of medium caliber with an intermediate function between both.[1,2]

Each of these types of arteries is responsible for carrying out a different function to guarantee blood flow to the organism.

1. **Conduction:** to channel blood from the heart to the capillaries. This function is carried out mainly by the large and medium caliber arteries.
2. **Pressure reservoir:** the ventricular systole and the pulsatile wave that it produces, generates a significant distension of the walls of the large-caliber arteries. During diastole, the elasticity that characterizes these arteries causes their diameter to return to normal, driving blood content in the distended artery in an antegrade direction. Thus, large-caliber arteries function as a reservoir for the volume and kinetic energy generated by the left ventricle during systole.
3. **Regulation of volume and blood flow:** this function corresponds to medium caliber arteries and arterioles. The high content of muscle fibers in these arteries allows the regulation of the arterial diameter according to the muscle tone that is present, either vasodilation or vasoconstriction. This function is tightly regulated by different neurohumoral factors.
4. **Dampening of pulsatility:** the cardiac cycle generates pulsatility with a significant variation between systolic and diastolic pressure. Arterioles are responsible for dampening this variation, functioning as sphincters which regulate blood flow to the capillary bed, thus favoring continuous capillary flow and pressure during systole and diastole.[2]

Aging produces functional and structural changes in the arterial system characterized primarily by the substitution of elastin for fibrin and collagen, causing originally elastic arteries to become rigid and non-compliant. This leads to changes in the interaction between the heart, blood and several organs which are more susceptible to these variations. This pulse wave represents the transmission of energy through a fluid (plasma) without necessarily implying a massive movement of this fluid. Energy is transmitted through an elastic tube (blood vessel), and the resulting pulse wave represents the interaction between the energy applied to the fluid, the characteristics of the blood, and of the blood vessel.[3]

Structural changes produced by aging also modify the pulse wave. Recently, the value of pulse wave velocity (PWV) has been associated to changes produced by aging, where an increase in PWV has a direct relationship with aging. Measurement of PWV is accepted as the simplest, non-invasive, robust, and reproducible method to determine arterial stiffness. Carotid-femoral PWV (cfPWV) is a direct measure and corresponds to the widely accepted propagative model of the arterial system and as the gold standard for PWV measurement. Of the different methods that assess arterial stiffness, cfPWV is considered the gold standard, due to its easy determination, reproducibility and high reliability, in addition to having evidence of its association with cardiovascular disease and mortality independent of traditional cardiovascular risk factors.[4-6]

Studies such as these have supported the inclusion of cfPWV as one of the markers considered to be equivalent to subclinical organ damage since the 2013 European guidelines for HBP. Elevated cfPWV (≥ 10 m/s) is a marker of arterial stiffness that due to its correlation with mortality and major cardiovascular events independent of traditional risk factors. cfPWV is

currently considered the gold standard to assess arterial stiffness and the equivalent of HBP-mediated organ damage, which is especially relevant in patients with low and intermediate cardiovascular risk.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) AND HIGH BLOOD PRESSURE

The RAAS is responsible for the regulation of BP, electrolyte balance and extracellular fluid. RAAS activation is a body defense system, which is preferentially activated in the presence of hypoperfusion, hyponatremia, sympathetic system activation and tissue damage. Dysregulation of the RAAS can lead to HBP, electrolyte disbalance, proliferation, fibrosis, apoptosis, thrombosis, fibrinolysis, and systemic inflammatory activity.[7,8] The traditional concept of RAAS changed radically in recent years, with the expression of tissue components becoming increasingly important in the genesis of tissue damage. Pro-renin, previously considered an inactive component of the system, seems to regulate the expression of the renin gene itself and of other components of the RAAS, highlighting the link between the RAAS and the natriuretic peptide system.[9] The harmful effect of the over-expression of RAAS components in the genesis and progression of organ damage in HBP and diabetes mellitus is incontrovertible.[10]

Another factor strongly linked to neurohumoral alterations is endothelial dysfunction. Vascular aging/damage reduces its vasodilator and antithrombotic capacity and increases oxidative stress and the presence of inflammatory cytokines which favor hypertrophy, atherogenesis and thrombosis. Clinical and experimental studies show that nitric oxide (NO) depletion is a key factor in endothelial dysfunction and the genesis of cardiovascular disease. Endothelial nitric oxide synthase (eNOS) is the enzyme responsible for producing NO from L-arginine in the presence of its co-factor tetrahydrobiopterin (BH4). The uncoupling between it and its co-factor BH4, decreases NO production and increases the production of pro-oxidant factors, which leads to chronic inflammation and increases NO degradation.[11]

SARS-CoV-2 AND HIGH BLOOD PRESSURE

The SARS-CoV-2 virus appears to employ receptor recognition mechanisms like those used by other coronaviruses. The spike protein of the coronavirus facilitates the entry of the virus into cells and increases expression for the angiotensin-converting enzyme 2 (ACE-2) as an entry receptor. The efficiency with which the virus binds to ACE2 is decisive for its transmissibility. Key mechanisms which may play a role in the pathophysiology of multiorgan injury secondary to SARS-CoV-2 infection include:

1. Direct viral toxicity.
2. Endothelial cell damage and thrombo/inflammation.
3. Dysregulation of the immune response.
4. Dysregulation of the renin-angiotensin-aldosterone system. (RAAS).

Direct viral toxicity. Histopathological studies show organotropism of SARS-CoV-2 beyond the respiratory tract, including the renal, myocardial, neurological, pharyngeal, and gastrointestinal systems. Furthermore, single-cell RNA sequencing studies have confirmed the expression of ACE-2 and TMPRSS2 in the pulmonary alveolar epithelium.[12]

Endothelial cell damage and thrombo/inflammation. Endothelial damage produced by the entry of SARS-CoV-2 into the cell mediated by ACE2 and the subsequent inflammation generate a prothrombotic environment, which is a significant pathophysiological mechanism in severe forms of COVID-19. ACE2 expression has been demonstrated in arteries and venous endothelium of various organs with increased thrombin production, inhibiting fibrinolysis and activating complement pathways, triggering a process of thrombosis and inflammation with microthrombi deposition and microvascular dysfunction.[13]

Dysregulation of the immune response.

Dysregulation of the RAAS. Recently, Carlos Ferrario, MD described the enzyme ACE2, a membrane-bound aminopeptidase, as a potent counter-regulator of the RAAS pathway. ACE2 converts angiotensin I to inactive angiotensin 1-9 and angiotensin II to angiotensin 1-7 (decreasing the adverse ACE/AngII/AT1 axis),

which has vasodilatory, antiproliferative, and antifibrotic properties. Although the mechanism of infection and damage of SARS-CoV-2 may not be limited exclusively to pathways related to ACE2, this enzyme plays a very significant role in both the mechanism of infection and damage, as well as many of the clinical manifestations of COVID-19. Chen et al found a decrease in the degradation of angiotensin II especially when the balance between the ACE and ACE2 was disrupted in COVID-19 patients. Increases in angiotensin II could lead to myocardial inflammation, oxidative stress, and myocyte apoptosis. This hypothesis explains why elevated blood pressure could occur in parallel with mild cardiac injury in COVID-19 patients.[14-16]

LIPID DISORDERS, OBESITY, AND HIGH BLOOD PRESSURE

Whilst obesity is commonly seen as an increase in weight, it can be better conceptualized as a state of excess adipose tissue. Although it is not a direct measure of adiposity, the most used method to define obesity is the body-mass index (BMI), which is equal to the individual's weight divided by height squared (kg/m^2). A BMI > 30 kg/m^2 is commonly used as the definition of obesity. Obesity is considered to play a part in the etiology of HBP, where multiple pathophysiological mechanisms participate in its development. Mechanisms which link both obesity and HBP include insulin resistance, inflammation, oxidative stress, modified adipokine secretion (such as adiponectin and leptin), increased activity of the sympathetic nervous system, and the renin-angiotensin aldosterone system. In obesity, when excess triglycerides exceed the storage capacity of peripheral adipocytes, these are stored in liver, skeletal muscle, and visceral adipocytes. This abnormal accumulation of triglycerides is associated with insulin resistance in the liver and muscles, leading to ectopic fat deposition.

The adipocyte was considered for a long time only as a fat depot, but recent evidence highlights it also as an endocrine cell, which secretes several hormones which together are known as adipokines. Notably, some of these adipokines are related to endothelial dysfunction and cardiovascular risk *(Table 1)*.

Table 1: Adipokines related to the pathophysiology of high blood pressure.

Increase with obesity	Decrease with obesity
Free fatty acids	Adiponectin
TNF-α	
Resistin	
Leptin	
PAI-I	
Angiotensinogen	

Excess free fatty acids which are present in obesity directly cause endothelial dysfunction, in addition to inhibiting glucose-stimulated insulin release, which can lead to progressive β-cell dysfunction in susceptible individuals and even sometimes to apoptosis. TNF-α is a cytokine produced by adipose tissue, most commonly by infiltrating macrophages, which directly suppresses insulin signaling by increasing serine phosphorylation on insulin receptor substrate 1 (IRS-1), thereby decreasing insulin receptor kinase activity leading to insulin resistance, in addition to being a proinflammatory factor related to atherosclerosis.[17]

Increased plasminogen activator inhibitor-1 (PAI-1) values are associated with antifibrinolysis while increased angiotensinogen concentration together with an increased activity of the RAAS is related to the appearance of HBP.[18] Obstructive sleep apnea, which is extremely common in obesity, also causes sympathetic stimulation, further contributing to elevated blood pressure in this patient population.[17] The combination of enhanced sympathetic nervous system activity and RAAS activity in obesity also causes impaired natiuresis, increased renal sodium reabsorption, and extracellular volume expansion, further propagating the development of HBP in obesity.

REFERENCES

1. Jordan J, Kurschat C, Reuter H. Arterial hypertension. Dtsch Arztebl Int. 2018; 115: 557-568. Available in: https://doi.org/10.3238/arztebl.2018.0557.

2. Koenigsberger M, Sauser R, Bény JL, Meister JJ. Effects of arterial wall stress on vasomotion. Biophys J 2006; 91: 1663-1674. Available in: https://doi.org/10.1529/biophysj.106.083311.
3. Attinger EO, Attinger FM. Frequency dynamics of peripheral vascular blood flow. Annu Rev Biophys Bioeng. 1973; 2: 7-36. Available in: https://doi.org/10.1146/annurev.bb.02.060173.000255.
4. Mitchell GF. Arterial stiffness and wave reflection in hypertension: pathophysiologic and therapeutic implications. Curr Hypertens Rep 2004; 6: 436-441. Available in: https://doi.org/10.1007/s11906-004-0037-1.
5. Maldonado J, Pereira T, Polónia J, Silva JA, Morais J, Marques M et al. Arterial stiffness predicts cardiovascular outcome in a low-to-moderate cardiovascular risk population: the EDIVA (Estudo de DIstensibilidade VAscular) project. J Hypertens. 2011; 29: 669-675. Available in: https://doi.org/10.1097/HJH.0b013e3283432063.
6. Sehestedt T, Jeppesen J, Hansen TW, Wachtell K, Ibsen H, Torp-Pedersen C et al. Risk prediction is improved by adding markers of subclinical organ damage to SCORE. Eur Heart J. 2010; 31: 883-891. Available in: https://doi.org/10.1093/eurheartj/ehp546.
7. Azushima K, Morisawa N, Tamura K, Nishiyama A. Recent research advances in renin-angiotensin-aldosterone system receptors. Curr Hypertens Rep. 2020; 22: 22. Available in: https://doi.org/10.1007/s11906-020-1028-6.
8. Alcocer L, Álvarez-López H, Borrayo-Sánchez G, Cardona-Muñoz EG, Chávez-Mendoza A, Díaz ED et al. Hypertension as a persistent public health problem. A position paper from Alliance for a Healthy Heart, Mexico. Ann Clin Hypertens. 2019; 3: 9-30. Available in: https://doi.org/10.29328/journal.ach.1001015.
9. Patel S, Rauf A, Khan H, Abu-Izneid T. Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. Biomed Pharmacother Biomedecine Pharmacother. 2017; 94: 317-325. Available in: https://doi.org/10.1016/j.biopha.2017.07.091.
10. Santos RAS, Oudit GY, Verano-Braga T, Canta G, Steckelings UM, Bader M. The renin-angiotensin system: going beyond the classical paradigms. Am J Physiol Heart Circ Physiol. 2019; 316: H958-H970. Available in: https://doi.org/10.1152/ajpheart.00723.2018.
11. Dikalov SI, Nazarewicz RR. Angiotensin II-induced production of mitochondrial reactive oxygen species: potential mechanisms and relevance for cardiovascular disease. Antioxid Redox Signal. 2013; 19: 1085-1094. Available in: https://doi.org/10.1089/ars.2012.4604.
12. Cao W, Li T. COVID-19: towards understanding of pathogenesis. Cell Res. 2020; 30: 367-369. Available in: https://doi.org/10.1038/s41422-020-0327-4.
13. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020; 116: 1666-1687. Available in: https://doi.org/10.1093/cvr/cvaa106.
14. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020; 63: 364-374. Available in: https://doi.org/10.1007/s11427-020-1643-8.
15. Ravichandran B, Grimm D, Krüger M, Kopp S, Infanger M, Wehland M. SARS-CoV-2 and hypertension. Physiol Rep. 2021; 9: e14800. Available in: https://doi.org/10.14814/phy2.14800.
16. Chen G, Li X, Gong Z, Xia H, Wang Y, Wang X et al. Hypertension as a sequela in patients of SARS-CoV-2 infection. PloS One. 2021; 16: e0250815. Available in: https://doi.org/10.1371/journal.pone.0250815.
17. Cohen JB. Hypertension in obesity and the impact of weight loss. Curr Cardiol Rep. 2017; 19: 98. Available in: https://doi.org/10.1007/s11886-017-0912-4.
18. Miranda PJ, DeFronzo RA, Califf RM, Guyton JR. Metabolic syndrome: definition, pathophysiology, and mechanisms. Am Heart J. 2005; 149: 33-45. Available in: https://doi.org/10.1016/j.ahj.2004.07.013.

Author contributions: Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding: The authors received no specific funding for this work.

Conflict of interest/financial disclosure: The authors declare that they have no conflict of interests.

Correspondence:
David Cardona-Müller, MD
E-mail: david.cardonamuller@gmail.com