Renal Process of Blood Pressure Control and Essential Hypertension

RESUMO

OBJETIVO: O estudo investigou os mecanismos renais fisiológicos do controle da pressão arterial e correlacionou com os distúrbios produtores de hipertensão arterial sistêmica. MÉTODO: Trata-se de uma pesquisa qualitativa, fundamental e exploratória. O estudo foi desenvolvido através de uma revisão integrativa, em que foram analisados 16 artigos científicos de 2020 a 2024 do Google Scholar, Scielo e PubMed. A delimitação de pesquisa será feita por meio de descritores como "Fisiologia"; "Pressão arterial"; "Hipertensão essencial", e seus termos equivalentes em português e espanhol.RESULTADO:Os distúrbios dos mecanismos renais que controlam em longo prazo a pressão arterial estão muito relacionados com as anormalidades hipertensivas. CONCLUSÃO: O sistema apresenta relações que vão além do controle da pressão arterial, tendo em vista sua influência na COVID-19 e na retração da capacidade de contração cardíaca advinda da elevação de angiotensina-2, assim como no potencial efeito benéfico advindo da indução de síntese de angiotensina 1-7.

DESCRITORES: Natriurese. Angiotensina. Fisiologia renal.

ABSTRACT

OBJECTIVE: The study investigated the physiological renal mechanisms of blood pressure control and correlated them with disorders that produce systemic arterial hypertension. METHOD: This is a qualitative, fundamental and exploratory research. The study was developed through an integrative review, in which 16 scientific articles from 2020 to 2024 were analyzed from Google Scholar, Scielo and PubMed. The research will be delimitated using descriptors such as "Physiology"; "Blood pressure"; "Essential hypertension", and their equivalent terms in Portuguese and Spanish. RESULT: Disorders of the renal mechanisms that control blood pressure in the long term are closely related to hypertensive abnormalities. CONCLUSION: The system presents relationships that go beyond blood pressure control, considering its influence on COVID-19 and the reduction in cardiac contraction capacity resulting from the elevation of angiotensin-2, as well as the potential beneficial effect resulting from the induction of angiotensin 1-7 synthesis.

DESCRIPTORS: Natriuresis. Angiotensin. Renal physiology.

RESUMEN

OBJETIVO: El estudio investigó los mecanismos renales fisiológicos del control de la presión arterial y los correlacionó con los trastornos que producen hipertensión arterial sistémica. MÉTODO: Se trata de una investigación cualitativa, fundamental y exploratoria. El estudio se desarrolló a través de una revisión integradora, en la que se analizaron 16 artículos científicos del año 2020 al 2024 de Google Scholar, Scielo y PubMed. La delimitación de la investigación se realizará a través de descriptores como "Fisiología"; "Presión arterial"; "Hipertensión esencial" y sus términos equivalentes en portugués y español. RESULTADO: Los trastornos de los mecanismos renales que controlan la presión arterial a largo plazo están estrechamente relacionados con las anomalías hipertensivas. CONCLUSIÓN: El sistema presenta relaciones que van más allá del control de la presión arterial, considerando su influencia en la COVID-19 y la reducción de la capacidad de contracción cardíaca resultante de la elevación de la angiotensina-2, así como el potencial efecto beneficioso resultante de la inducción de la síntesis de angiotensina 1-7.

DESCRIPTORES: Natriuresis. Angiotensina. Fisiología renal.

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INTRODUCTION

Systemic and localized blood pressure (BP) is controlled by various physiological body factors, intrinsic to circulatory physiology. Intrinsic control of BP is represented rapidly by the nervous system and in the long term by renal systems and mechanisms. As well as internal factors, external factors such as an increase in the amount of salt ingested can influence the average value of blood pressure. Not only in a harmful way, external factors such as adequate water and salt intake can help control blood pressure. The renal mechanism for controlling blood pressure can also be altered by drugs that act on the angiotensin 2 synthesis cascade, acting indirectly on renal control. [1]

The renal system for controlling blood pressure is predominantly long-term and is mainly represented by the plasma kidney-volume system and the effective Renin-Angiotensin-Aldosterone System (RAAS). The kidney-volume system works by varying the excretion of sodium and water through the renal system. A low plasma volume signals a decrease in the excretion of water and salt, while an increase in plasma volume signals an increase in the excretion of water and salt, for effective volume control, which directly influences the force exerted on the arterial walls [2].

The RAAS is an effective system and involves several body regions to systematically control blood pressure. The morphofunctional unit of the kidneys, the nephrons, perceive variations in sodium concentration, afferent blood supply and glomerular pressure and initiate the system. The perception of an abnormality in blood pressure triggers the release of renin by the renal juxtaglomerular apparatus, which converts the renin substrate made in the liver, angiotensinogen, into angiotensin 1. Due to its low systemic effects, angiotensin 1 is converted into angiotensin 2 by the Angiotensin Converting Enzyme (ACE), which enhances the molecule and potentiates its vasoconstrictive effects. Angiotensin 2, in turn, increases the release of Aldosterone and has systemic and local vasoconstrictive effects, which raises blood pressure [3].

> “Due to its importance, the aim is to integrate anatomophysiological, pathophysiological and epidemiological knowledge in order to understand, summarize and discuss the functioning of the renal system and its contribution to the adequate control of physiological blood pressure, the pathological and epidemiological profile of systemic arterial hypertension, as well as to relate the impacts of renal disorders on the pathophysiology of essential arterial hypertension [1].”

Therefore, an integrative review based on EBM is fundamental to medical knowledge about the multifaceted control of blood pressure. Adding to this knowledge is essential because BP control through renal mechanisms, represented mainly by the kidney-plasma volume system and the renin-angiotensin-aldosterone system, is essential for homeostasis and for physiological and hemodynamically favorable perfusion. In addition to the aforementioned controls, osmolarity regulation, the secondary effects of elevated extracellular sodium and rapid nervous and endocrine control [4].

METHOD

This is a qualitative study with the fundamental nature of exploratory research. The study was developed through an integrative review, in which 16 scientific articles from 2020 to 2024 from Google Scholar, Scielo and PubMed were analyzed. The search was delimited using descriptors such as "Physiology"; "Blood pressure"; "Essential hypertension", and their equivalent terms in Portuguese and Spanish. An operational integrative review tool was used to adapt the research bases to the theme and to evidence-based medicine.

The process of preparing the integrative review was carried out in 6 phases: preparation of the guiding question, literature search or sampling, data collection, critical analysis of the studies included, discussion of the results and presentation of the integrative review. There was no need for ethics committee approval and it was authorized and carried out through the scientific development project of the Valença Faculty of Medicine. Sixteen articles were selected using the inclusion and exclusion criteria and the integrative review operational tool shown in the flowchart in figure 1.

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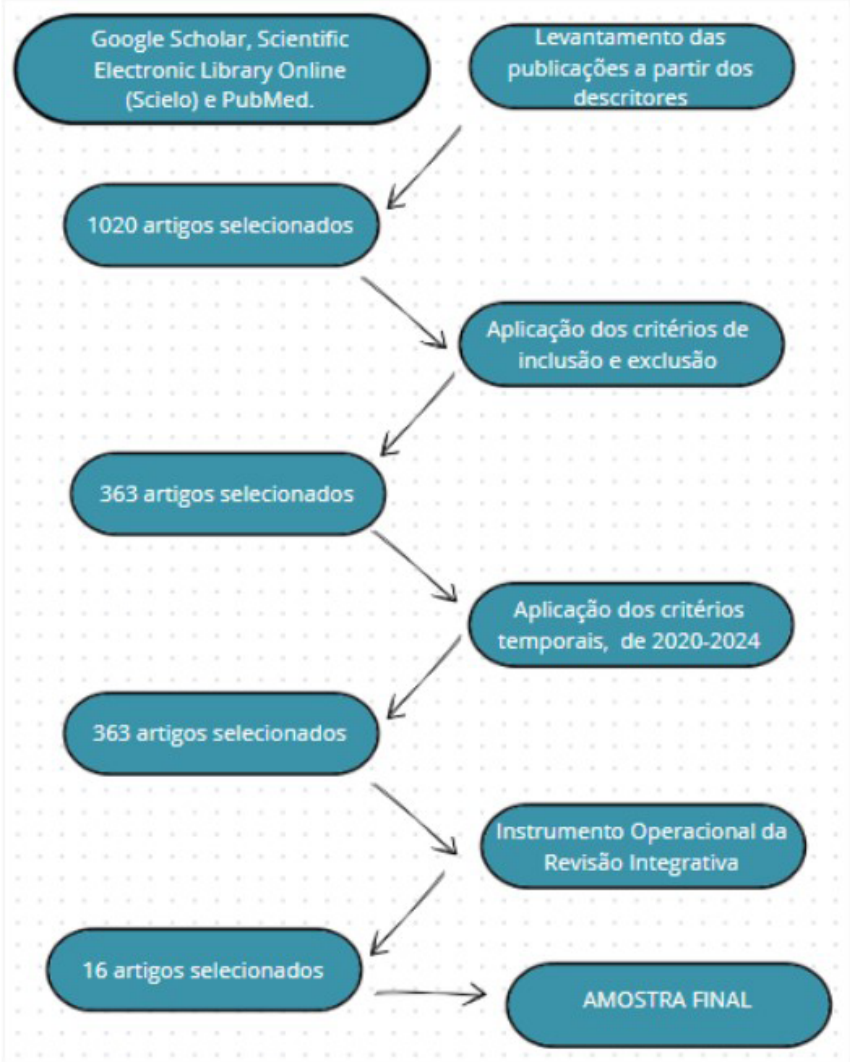
Figure 1: Flowchart of study selection with detailed steps.



Source: Produced by the authors.

RESULTS AND DISCUSSIONS

Renin Angiotensin Aldosterone System (RAAS)

RAAS is divided into systemic or circulating and tissue or local. The systemic action has the essential participation of the kidney, liver and pulmonary vascular endothelium, with hormonal functioning. Local action, the main example of which is intrarenal RAAS, acts in a paracrine and autocrine manner. The main constituents of RAAS are: angiotensinogen, angiotensins I, II, III, IV and I-VII, Tonin, Cathepsin, Renin, angiotensin-converting enzymes 1 and 2 (ACE 1 and 2) and angiotensin receptors 1, 2, 4 and 1-7 [5].

All the components of the RAAS have been found in heart, brain, kidney, adrenal and reproductive tissues, which favors the theory of two courses of action, local and systemic-circulatory. Renal hypoperfusion could activate the different courses of action. Visceral adiposity increases the activation of RAAS through the overexpression of angiotensinogen (ANT) in inflamed white adipocytes and of ANT and ANG-2 in adipose tissue in general. The same adiposity produces a fat-soluble factor and protein 1, which increases the synthesis of Aldosterone (ALD) in the adrenal glomerular zone via the tumor necrosis factor C1q. Activation of the RAAS involves sympathetic stimulation at the renal corpuscular level. Renal sympathetic denervation contributes to fine control of the RAAS and, consequently, of systemic arterial hypertension (SAH), since sympathetic activation ceases [6,7].

Angiotensinogen (ANT), Renin and Angiotensin-1 (ANG-1)

Hepatic angiotensinogen is released into the bloodstream in an inactive form. The aforementioned glycoprotein is only activated by cleavage mediated mainly by renin. Cleavage can form both ANG-1 and ANG-2. The indiscriminate use of glucocorticoids and estrogen can increase the synthesis of angiotensinogen. It is known that sympathetic activation via beta-1 (B1) is one of the ways of triggering RAAS.[5]

In an inflammatory condition, the sympathetic autonomic nervous system (SNAS) is activated, which stimulates the B1 receptors in the cells of the renal juxtaglomerular apparatus, increasing renin synthesis. Thus, inflammation has been shown to be a potent activator of the RAAS. In obesity, a generalized inflammation, the activation of the RAAS is great, in addition to the synthesis of ANG-2 through renin-independent Cathepsins-G and Tonin and the increase in Angiotensinogen.[5]

Angiotensin Converting Enzyme (ACE) and Angiotensin 2 (ANG-2)

Physiologically, the amount of plasma ANG-2 is estimated at 10-20pM. The actions of ANG-2 are mediated by G protein on its four basic receptors - AT1, AT2, AT4, and AT1-7. The main known mechanism is the favoring of BP elevation by the AT1 recep-

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tor present in vascular smooth muscle, the adrenal glands, cardiac tissue and the brain, while AT2 counterbalances its effects. ANG-2 is known to generate fibrosis, cell proliferation and an increase in collagen synthesis, which contributes to arterial hypertrophy. ANG-2 also increases the expression of tissue plasminogen activator inhibitor type 1 and 2, the expression of ALD and even nitric oxide [8,9].

ANG-2 influences renal glomerular filtration, as it initially causes vasoconstriction of the afferent and efferent arterioles, as well as decreasing the glomerular filtration rate (GFR) by reducing glomerular perfusion. However, it is believed that the synthesis of TGF-B1, nitric oxide and prostaglandins reduces the ability of ANG-2 to regulate afferent arterioles, promoting afferent vasodilation which increases GFR [8].

With ANG-2 synthesis, stress, fibrosis and cardiac remodeling may be favored, since RAAS is activated in an attempt to maintain tissue perfusion in cases of heart failure. ACE favors a decrease in adipogenesis and ectopic deposition in cardiomyocytes, which impairs myocardial contraction - contrary to the compensatory effects of RAAS in heart failure (HF), Continued elevation of ANG-2 for six weeks leads to increased blood pressure, renovascular remodeling, increased urinary flow, GFR and renal blood flow, as well as proteinuria, glomerulosclerosis and loss of podocytes in the urine. This condition simulates chronic kidney disease (CKD) associated with continuous elevation of ANG-2 [8,10].

It is known that SARS-COV-2 is essentially recognized and invaded by alveolar ACE receptors, which makes it the main viral gateway. While ACE-1 seems to favor the progression of the disease, ACE-2 favors the synthesis of ANG1-7, which counterbalances ANG-2. This counterbalance has an impact on the infectivity and affinity of the virus's S-glycoprotein with the receptors, which highlights its crucial role in the disease. The clinical diversity of COVID-19 can be explained by the wide expression of the ACE receptor in the lungs, gastrointestinal tract, kidneys, liver and heart muscle, which may be the main mechanism linking cardiovascular events to SARS-CoV-2 infection [11,12].

SYSTEMIC ARTERIAL HYPERTENSION

Systemic Arterial Hypertension (SAH) is defined as a Chronic Non-Communicable Disease (CNCD) in a persistent condition of systolic blood pressure (BP) greater than or equal to 140mmHg and/or diastolic BP greater than or equal to 90mmHg, measured in the doctor's office, with home BP monitoring (HBPM) or ambulatory BP monitoring (ABPM), respecting the appropriate forms of measurement. The official classification in Brazil divides patients into optimal BP, normal BP, pre-hypertension and three stages of hypertension (Table 1).

Figure 2- Classification of SAH.

Classificação	PA Sistólica (mmHg)	PA diastólica (mmHg)
PA Ótima	<120	<80
PA Normal	120-129	80-84
Pré -Hipertenso	130-139	85-89
HAS 1	140-159	90-99
HAS 2	160-179	100-109
HAS 3	≥ 180	≥110

Source: Brazilian Hypertension Guidelines, 2020.

Another important condition is Resistant Arterial Hypertension (RAH), which is characterized by hypertension even with the appropriate use of 3 or more classes of synergistic antihypertensive drugs at maximum recommended or tolerated doses, one of which is a thiazide. SAH can also be controlled with 4 or more drugs and is defined as controlled ARH [13].

SAH can be primary (PAH) or secondary (SCAS). PAH, also known as essential PAH, has no obvious cause and is probably due to an intrinsic abnormality in the mechanisms that regulate BP, while CSAH is caused by complications of underlying abnormalities, such as complications in the renal, endocrine, neural and cardiovascular systems [9].

The pathophysiology of hypertension is known to stem from persistent elevation of BP due to increased intravascular volume, peripheral vascular resistance (PVR), reduced synthesis of vasodilators or disordered activation of vasoconstrictor mechanisms, such as the RAAS. In chronic hypertensive patients, the BP autoregulation curve is shifted, which causes the equilibrium point to rise and contributes to the genesis of PAH and cardiovascular disorders. It is known that the rise in BP and the increase in cardiovascular risk (CVR) have a gradual and continuous relationship since 115x75 mmHg [14].

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> “Heredity is greater than previously believed, given the 25-80% heritability in biological siblings. In kidney transplants, the biological primacy lies with the donor, since the kidney of a genetically hypertensive donor raises the blood pressure of a genetically normotensive recipient [15].”

At a molecular level, the role of vitamin D in the effective control of blood pressure has been shown to be indifferent. Despite the likelihood of aiding control, vitamin D deficit is not a predictor of hypertension, nor does its use help to reduce blood pressure levels. However, it is well known that SAH can bring about variations in body dynamics as a whole, even at the molecular level. SAH can lead to endothelial changes and vascular abnormalities, which favor the synthesis of constructive substances such as reactive oxygen species (ROS), thromboxane A2 (TA2) and ANG-2 [9,16].

Regarding the epidemiology of SAH in Brazil, it is known that self-reported SAH is 21.4%, while adequate measurement or the use of antihypertensive medication showed a prevalence of 32.3% in adult Brazilians. Epidemiology shows that prevalence increases with age, with 71.7% of people over 70 having SAH, and that men have a higher prevalence than women. It is estimated that more than one billion people are hypertensive, despite improvements in detection, prevention, treatment and population awareness [7].

CONCLUSION

The renin-angiotensin-aldosterone system is more complex than expected, with a mechanism of action divided into systemic or circulating and local or tissue. The components of the RAAS are found in various tissues, with an important local action for maintaining local vascular tone and, systemically, controlling blood pressure in the long term. Visceral adiposity can activate the RAAS, increase ANG-2 independently of renin, increase the amount of ANT and activate the sympathetic autonomic nervous system, which again activates the vasopressor system. In addition, the indiscriminate use of glucocorticoids and estrogen can increase the synthesis of RAAS components, especially in the case of hepatic ANT.

The relationship between SARS and SARS-COV-2 is through viral invasion using ACE-2 receptors, hence the direct relationship with symptoms in the respiratory system. Due to its wide distribution throughout the body, the symptoms of COVID-19 are diverse, given that it can enter all the sites that have the ACE-2 receptor. Another important influence of the system is the involvement of ANG-2 in HF. Elevated ANG-2 promotes cardiac remodeling and worsens cardiac contraction, since ANG-2 impairs adipogenesis, making the myocardium susceptible to ectopic fat deposition.

Cardiovascular disorders occur when RAAS is altered. Its decrease can favor vasodilation, low salt reabsorption, hypotension and hydroelectrolytic disorders. An increase in RAAS components can lead to systemic arterial hypertension, due to a disturbance in the intrarenal balance point, specifically in the control of water and salt reabsorption, as well as in the glomerular filtration rate, vasoconstriction of the efferent arterioles and vasodilation of the afferent arterioles.

Thus, the RAAS is essential for the cardiac system, vascular muscle contraction, long-term control of blood pressure, cardiac dynamics and myocardial remodeling, invasion of the COVID-19 virus and the progression of heart failure. Elucidations will come with the progression of scientific research into the action of the system's components and their systemic and local relationships.

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