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REVIEW

Vascular Changes in Hypertension: Is There Cell Death Involved? – A Narrative Review

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Abstract: *Background: Cardiovascular disease can be triggered and accelerated by hypertension and the underlying changes in the structure and function of arteries. The purpose of this review is to explore some vascular changes that occur in hypertension as a consequence of the imbalance between cell proliferation and cell death, processes that play an important role in stabilizing the thickness of the arterial wall during vascular remodeling. Methods: The authors conducted research through PubMed and Google Scholar databases using the following search formula: (hypertensive*) AND ((vascular modifications)) OR (vascular changes)) AND (cell death). Results: From 40 articles, only 17 publications were included in this study, taking into account four processes that can be preceded or followed by inflammation and depend on the interaction between local growth factors, vasoactive substances, and hemodynamic stimuli: Cell proliferation and growth; Cell migration; Cell death; Degradation or reorganization of extracellular matrix. Conclusions: To summarize, maladaptive vascular changes in hypertension can represent a major argument for prompt and maximal therapeutic intervention in patients with high cardiovascular risk. Moreover, they can represent an important step in discovering new markers of cardiovascular risk and in the development of new targeted therapies for different pathways of cellular signaling through which the reversibility of abnormal vascular changes could be obtained.*

Keywords: *cell death; inflammation; cellular metabolism alteration; vascular remodeling; hypertension; pathophysiology*

INTRODUCTION

Cardiovascular disease, one of the leading causes of death worldwide, can be triggered and accelerated by hypertension and the underlying changes in the structure and function of arteries. Knowing the pathophysiological mechanisms that are responsible for the maladaptive changes occurring at the vascular level in the context of hypertension, can represent a first step in the development of new targeted therapies for different pathways through which the reversibility of the abnormal vascular changes can be obtained.

Some studies have shown that hypertension linked to the imbalance between cell death and cell proliferation could explain vascular remodeling: accelerates endothelial apoptosis, promotes cell migration, and accelerates the proliferation of vascular smooth muscle cells [1] resulting in the thickening of the middle tunic of the arteries [1,2]. The role of cell death in blood pressure charge is still unknown [3]. The prevalence of hypertension increases with age and the proposed pathophysiological mechanisms are represented by hemodynamic changes, arterial stiffness (due to elastic lamina disruption and intimal hyperplasia), and neurohormonal and renal dysfunction [4]. In the elderly, vascular injuries can heal through the formation of vascular scars due to the increase in the proliferation of smooth muscle cells and the reduction of their apoptosis and decrease in sensitivity to apoptotic stimuli in fibroblasts and myofibroblasts, with secondary fibrosis [5,6].

In terms of the cell death process, some major pathways have been described (apoptosis, necrosis, and autophagy), depending on the injury and the type of cell [7]. Programmed cell death and necrotic cell death sometimes have mechanisms that can be overlapped [5]. The initiation of apoptosis is the result of death signaling pathways, intrinsic (mechanisms triggered by cellular stress through hypoxia, oxidative stress, and ADN damage) or extrinsic (mediated by transmembrane receptors of the TNF receptors family). In apoptosis, an

essential process in maintaining tissue homeostasis, as a result of caspase cascade activation and imbalance between pro and antiapoptotic factors, the cell is broken for-ming membrane-bound vesicles and apoptotic bodies (after the shrinkage of the cell, fragmentation of nucleus and chromatin and plasma membrane blebbing [7]) responsible for clearance of dead cells and also for intercellular communication [8]. Necrosis is an accidental form of cell death but in certain instances is initiated or modulated under programmed control mechanisms. Unlike apoptosis, which requires energy consumption, necrosis is a process in which cells die without energy consumption; in the necrotic cell death process, as a result of the breaking of the cell membrane and the elimination of the cell content in the extra-cellular space, inflammation occurs. It has been described as a form of programmed necrosis (necroptosis), caspase-independent, with mitochondrial changes involvement [5]. Another type of cell death, autophagy, is the process through a staving or deprivation of growth factors cell generate energy and metabolites by digesting its organelles or macromolecules. There were also described multiple sub-types of cell death, depending on caspase involvement or the presence of some of the necrosis criteria: aponecrosis, paraptosis, anoikis, cornification, etc [5].

Recent studies examine how certain factors affect endothelial apoptosis in patients with hypertension and other comorbidities [1,4,9]. Endothelial cell apoptosis was found in patients with hypertension and peripheral arterial disease by studying endothelial cell cultures [9]. Vascular cell re-modeling, an active process, involves changes in at least 4 cellular processes: cell growth and cell migration, inflammation, cell death, and degradation or reorganization of the extracellular matrix. It is dependent on the interaction between local growth factors, vasoactive substances, and hemodynamic stimuli [10].

Although the in vitro studies [11] demonstrated a relationship between the level of some plasma membrane receptors involved in apoptosis induction (named death receptors) [12] and the phenomenon of apoptosis, the causal link between cell death and vascular changes was not proved yet [11].

Considering that the phenomenon of cell death and cardio-vascular outcomes are linked through metabolic risk factors intervention and exogenous causes of cellular stress that lead to cell destruction via different pathways and demonstrating to what extent the alteration of cellular signaling, the alteration of the extracellular environment and the triggering of cell death mechanisms are responsible for the abnormal remodeling of the arterial wall in the hypertensive patients, the research could be directed to discover new markers of cardiovascular risk and new therapies that can be targeted in patients with cardiovascular risk factors. The benefit could be major, the measurement of death receptors levels related to cell death phenomena that can predict cardiovascular outcomes and death [11], in patients with high cardiovascular risk, became a major argument for prompt and maximal therapeutic intervention in this specific populational group.

The purpose of this review is to explore some vascular changes that occur in hypertension as a consequence of an imbalance between cell proliferation and cell death, processes that play an important role in stabilizing the thickness of the arterial wall during vascular remodeling.

MATERIALS AND METHODS

A comprehensive search through PubMed and Google Scholar using the following search formula: (hypertension*) AND ((vascular modifications)) OR (vascular changes)) AND (cell death) was performed. Only full-text freely available articles published in English between 2000 and 2021 were used. Articles that were most relevant to the subject of this review were included after thorough consideration. Inclusion criteria were published in English, publication within the mentioned period, and inclusion of hypertensive models or animal models, or cell cultures studies. From 40 articles, only 17 publications were included in this study. All the selected papers were reviewed by an independent reviewer to check that the interpretations were correct.

Hypertension has a great impact on the cardiovascular system; the thickness of the arterial wall during the remodeling process could be the result of cell death mechanisms triggered by factors potentially involved in the etiology of arterial hypertension. Considering that the connection between cell proliferation and cell death is responsible by a vascular re-modeling process in hypertension, we take into account for our study four processes that can be preceded or followed by inflammation and depend on the interaction between local growth factors, vasoactive substances, and hemodynamic stimuli:

- Cell proliferation and growth
- Cell migration
- Cell death
- Degradation or reorganization of extracellular matrix

RESULTS

The search strategy identified 40 articles of which 17 were deemed to be eligible for inclusion in this systematic review. Of these, 12 studies addressed markers of cell proliferation/growth, 7 studies addressed cell migration, 12 studies addressed cell death processes/markers, 7 studies focused on

the degradation of extracellular matrix, and 13 studies addressed inflammation markers (shown in Table 1).

Table 1: Type of processes involved in vascular remodeling

Reference	First author, year of publishing	Study type	Pathophysiological mechanisms, Type of process					
			Arterial remodelling	Inflammation	Cell proliferation/ cell growth	Cell migration	Cell death	Reorganization/ degradation of extracellular matrix
1	Brown, I.A.M *et al,* 2018	Review	X	X	VSMC hypertrophy and hyperplasia	X	X	
2	Xu, C. *et al,* 2001	Experimental study	X		X		X	
16	Martinez-Quinones, P. *et al,* 2018	Review	X	X	VSMC hypertrophy and hyperplasia	X		X
10	Renna, N.F. *et al,* 2013	Review	X	X	X	X	X	X
21	Schiffrin, E.L. 2012	Review	X	X	VSMC hypertrophy and hyperplasia		X (apoptosis; anoikis – in endotelial cells)	X
19	Virdis, A. *et al*, 2014	Review	X	X	X	X		
15	Sun, H.J *et al,* 2020	Review	X			X		X
18	Munoz-Durango, N. *et al,* 2016	Review	X	X	X	X	X	X
17	Bruno, R.M. *et al*, 2017	Research article	X	X	X		X (apoptosis)	
3	Abdelbary, M. *et al*, 2019	Comparative study		X	X		X (necrosis, apoptosis)	
22	Intengan, H.D.; Schiffrin, E.L. , 2001	Review	X	X	X		X (apoptosis)	X
9	Gardner, A.W. *et al*, 2019	Randomized Controlled Trial		X			X (apoptosis)	
26	Krishna, S. M. *et al*, 2021	Randomized Controlled Trial	X	X			X (apoptosis)	X
27	Fekete, A. A. *et al*, 2016	Randomized Controlled Trial	X	X				
28	Li, X. *et al*, 2022	Review	X	X	X	X	X (apoptosis)	X
32	Xu, W.;Erzurum, S.C., 2011	Review	X		X		X (apoptosis)	
33	Levy, M. *et al*, 2007	Clinical research	X	X	X		X (apoptosis)	

In hypertension, the connection between cell proliferation and cell death could be critical in determining the thickness of the arterial wall during the remodeling process. There are 2 types of criteria for classifying cell remodeling:

- according to the size of the middle tunic: hypertrophic, eutrophic, and hypotrophic
- according to the size of the lumen: internal and external remodeling.

The consequences of cell remodeling are:

- high pulse pressure,
- stiffening of the arterial wall
- changes in the extracellular matrix.

All consequences of cell remodeling are determined by the

release of growth factors and cytokines. The immune system, namely T lymphocytes, plays a key role in remodeling, more precisely based on a T-reg/T-effector imbalance.

Because of its ability to modify the vascular tone, vascular endothelium plays a significant role in hypertension. Endothelial dysfunction is caused by a reduction in nitric oxide (NO) availability, which causes endothelial dysfunction. The main cause of the decline in NO is the excessive production of reactive oxygen species (ROS)[13].

Blood pressure is affected by the phenomenon of cell death that can occur at different levels of the arterial wall, however, in hypertension the role of different types of vascular cell death is unclear. Researchers discovered that vascular smooth muscle cell growth is increased by cell death [1]. The cell death process is thought to play a key part in remodeling, but it is unclear whether it is the main process or a growth-related compensatory mechanism, being influenced by reactive oxygen species, NO, angiotensin type 2 (AT-II), and endothelins.

Due to vascular damage, elevated blood pressure values may alter the integrity of the endothelium and may also represent a risk factor for the onset and progression of vascular atherosclerosis changes leading to the destabilization of atheroma plaques [14]. Atherosclerosis favors the processes of inflammation and necrosis of the blood vessel and plaque can become unstable without proper treatment and cause even more complications.

DISCUSSION

In our study, we collected a lot of information about vascular modifications in hypertension. From the 17 selected articles, in 15 we found information about vascular remodeling (88.23%), in 14 articles we found arguments for the presence of the inflammatory phenomenon (82.35%), 13 articles (77.47%) argued for the presence of cell death and also 13 described cell proliferation, 7 articles (41.17%) described the phenomenon of cell migration, and 8 articles (47.05%) described reorganization of the extracellular matrix.

Starting from the information provided by the articles included in our study, our hypothesis related to the involvement of cell death at the vascular level in arterial hypertension seems to be valid. Maintaining a balance between the processes of cell proliferation, cell migration, cell death, and degradation of the extracellular matrix could ensure adequate vascular elasticity and delay the installation of specific hypertensive vascular changes. It seems that cells from all layers of the vascular wall are involved and can be affected by different types of death, the damage to each cell type leading to cellular metabolic changes and changes in the extracellular environment.

Vascular tone and vascular remodeling

The endothelial cells which form the tunica interna of the arterial wall, are essential for regulating hemostasis, vascular tone, and host defense [15]. Secretion, protection as a barrier, and local metabolism are the endothelium's three primary activities, each of which is altered by hypertension. The endothelial cells produce vasoactive substances such as nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H2S)[15], prostacyclin (PGI2), endothelin 1 (ET-1), AT-II, prostaglandins. Normally, there is an equilibrium between these substances to maintain proper blood flow. In hypertension, at the vascular level is an increased production of vasoconstrictor factors (ET-1, AT-II, prostaglandins) which determine endothelium dysfunction (increased permeability, induce inflammation, and edema). It was discovered that the substances and structures that are released from a cell when it dies can affect the endothelial function in an autocrine, paracrine or endocrine model [16].

The endothelium is important for both short-term vascular tone modulation and long-term vascular remodeling. Nitric oxide is the most significant endothelium-derived vasodilator molecule which, under healthy conditions, is capable of inhibiting the primary fundamental pathways driving the formation of atherosclerosis and thereby improving vascular health. Reduced NO availability and endothelial dysfunction are caused by NO breakdown by reactive oxygen species (ROS) in physiological aging and many pathological diseases, including arterial hypertension.

Essential hypertension patients (HT) had a lower endothelial response to acetylcholine (Ach) than normotensive people (NT) in each age group, but it was proved that the vascular response to Ach in both HT and NT patients decreases as they become older [17]. In the pathogenesis of endothelial dysfunction and the cardiovascular consequences related to endothelial inflammation [18], apart from the effects of nitric oxide and carbon monoxide, the role of hydrogen sulfide has been also described. H2S formation was detected in smooth muscle cells, vascular endothelial cells, and cardiomyocytes and it was shown that H2S could protect endothelial cells against apoptosis by attenuating the overproduction of ROS and inhibiting mitochondrial apoptosis [15].

The vascular smooth muscle cells (VSMCs) that form tunica media are responsible for vasoconstriction, vasodilatation, and the process of remodeling [19]. The hyperplasia and hypertrophy of VSMCs are the processes that underlie vascular remodeling. The most frequent type of remodeling in hypertension is the inward type causing the narrowing of the arterial lumen. The outward type of remodeling occurs during anti-hypertensive treatment and is also caused by increased

blood flow[16]. Some studies have revealed that a marked cell death influences and accelerates the proliferation of vascular smooth muscle cells, resulting in the thickening of the middle tunic of the arteries [2]. As a result of cell death through necrosis and the breakdown of plasma membrane integrity, the contents of necrotic cells are released, triggering a proinflammatory response [3].

Fibroblasts that form the tunica externa secrete chemokines, cytokines, and growth factors that contribute to normal vascular function and participate in the degradation of the extracellular matrix components. They play an important role in remodeling as a response to injury. However, fibroblasts suffer structural changes that are accompanied by proliferation and migration into the tunica media during hypertension [16].

Cell remodeling

Cell remodeling involves cell growth and cell migration, cell death, and degradation of the extracellular matrix and is dependent on multiple factors [10]. The media-to-lumen ratio (M/L), modifying the vessel wall width for increasing muscle mass, the reorganization of cellular and noncellular elements and the lumen dimensions are the most prominent manifestations of these adaptations [20]. As a result, remodeling can be classified based on the degree of change of the medium arterial tunic in hypertrophic, which is the most common, hypotrophic, or eutrophic remodeling, as well as the size of the lumen in internal or exterior remodeling [21]. With age, large arteries undergo outward hypertrophic remodeling and stiffening [4], and in hypertension, this process may be accelerated, resulting in higher pulse pressure [22-24]. The elastic laminae, on the other hand, develop multiplication and fragmentation in severe hypertension, with increased deposition of collagen and fetal fibronectin, leading to greater stiffness [23]. Small artery remodeling has typically been associated with increased media thickness in hypertension, but new studies have shown that there are two forms of remodeling, inward eutrophic and inward hypertrophic, depending on whether the media cross-sectional area is enlarged [23]. The discovery that inward eutrophic remodeling may be prominent in some kinds of hypertension has raised the prospect that countervailing mechanisms in hypertension, including apoptosis, may compensate for or modify growth [23,25]. The outer and lumen diameters are decreased, the media cross-sectional area is unchanged and the M/L is increased without stiffening in inward eutrophic remodeling [25]. Inward eutrophic remodeling reduces the outer diameter of the vessel through a mix of growth and apoptosis, with apoptosis concentrated to the periphery, whilst inward growth decreases lumen diameter, which may explain the preservation of media volume. It is uncertain whether apoptosis is a growth-related compensatory mechanism or a primary process[25]. Mechanical forces exerted on the arterial wall also play a significant role in remodeling. Changes in the extracellular matrix, the cellular release of growth factors and cytokines, and vascular sensitivity to circulating humoral factors are all caused by them. Force duration, load, and force properties all have an impact on all of these factors [1].

Low-grade inflammation

In hypertension and cardiovascular disease, low-grade inflammation plays a critical pathogenic function [26-28]. Innate and adaptive immune systems, specifically T cells, are implicated, according to a significant body of research. T-lymphocytes play a key role in the development of hypertension-related vascular remodeling. The balance between T-effector and Treg lymphocytes is a critical regulatory system that, when disrupted, favors blood pressure increase and the development of organ damage [21]. Treg lymphocytes have potent anti-inflammatory characteristics, ensuring vascular homeostasis and protecting the arterial wall against the onset of atherosclerosis [21,29]. In humans, the majority of data establishing essential hypertension as a chronic low-grade inflammatory state found a clear and independent link between c-reactive protein (CRP), tumor necrosis factor (TNF), Interleukin 1 beta (IL-1 beta)[30], Interleukin-6 (IL-6), and adhesion molecules and vascular alterations in essential hypertensive patients [21].

An important role in the process of vascular remodeling is played by the renin-angiotensin-aldosterone system (RAAS)[29,31] because of its role in VSMC migration and inflammation [24,32]. This system acts through 2 types of angiotensin II receptors AT1-R and AT2-R, but the AT1-R is thought to be the primary receptor that causes Ang II's proliferative and profibrotic actions [20,33]. The AT2-Rs are thought to cause opposite effects, preventing vascular deterioration. But there are times when AT2-R acts similarly to AT1-R (for example, in renovascular hypertension it causes tonic renal medullary vasoconstriction) [32,34]. Recent studies showed that there exists an AT1-R autoantibody (AT1-AA) which is an agonist of AT1-R. AT1-AA raises AT2-R expression and encourages cell migration through cytoskeletal remodeling [34]. The RAAS is implicated in physiological and pathological actions when it comes to vascular changes. It reduces ROS generation and modifies vascular tone via vasoconstriction and vasodilatation. During hypertension, this RAA system induces fibroblast proliferation, collagen deposition, and vascular hypertrophy [20].

Cell death

Apoptosis is a type of gene-controlled cell death that was first discovered in development as a mechanism for fine-tuning

growth. The vascular system has a large number of apoptosis modulators. Reactive oxygen species, NO, angiotensin type 2 receptors, and the endothelin system are all possible candidates. Reactive oxygen species play a key role in the pathogenesis of hypertension and vascular cell apoptosis [35], with O_2^- inducing proliferation and H_2O_2 inducing apoptosis through a protein kinase C–dependent pathway, respectively. Angiotensin II is also a potential apoptotic trigger [25,31,36].

Recent studies examine how certain factors affect endothelial apoptosis in patients with hypertension and other comorbidities. Endothelial cell apoptosis was found in patients with hypertension and peripheral arterial disease (PAD) by studying endothelial cell cultures. They demonstrated that physical activity can lower this type of cell death[9]. PAD patients present increased cardiovascular stress, inflammation, and oxidative stress. Inflammation and oxidative stress speed up the progression of myopathy and increase the risk of apoptosis and sarcopenia. In older persons, exercise decreases oxidative stress and improves reactivity to oxidative processes [9].

Inflammation, VSMC apoptosis, and oxidative stress in patients with hypertension [1,18,19] can also play an important role in the pathology of abdominal aortic aneurysm AAA [37,38]. According to some studies [39] a member of the seric proteinase inhibitor superfamily, Human Kallistatin, acts as a protective factor by blocking the pathway that stimulates AAA generation [39], and even whey-protein supplementation has a beneficial effect, improving vascular function by inhibiting the serum angiotensin-converting enzyme [40].

Lesions that appear on the arterial wall and the dysfunction of endothelial cells determined by high blood pressure values are factors that contribute to atherosclerosis. In the injured artery intima, extra low-density lipoprotein (LDL) accumulated suffer processes of oxidation and can attract monocytes and macrophages, forming the foam cells. The local inflammatory reaction is severe [41] and it triggers a cascade of events [38,42]. Foam cell secretion, deposition, and apoptosis [43] are crucial steps in the occurrence of atheroma plaque [44]. In advanced stages, the macrophage function of phagocytosis is destabilized, the atheromatous plaque continues to grow and, in the end, it will become unstable, promoting local inflammation and necrosis without the proper treatment [41]. Studies have revealed that at the cellular level microRNA plays a role in the control of atherosclerosis [41,45], acting on the TGF-β signaling pathway, inducing proliferation, migration, and apoptosis of endothelial cells, VSMCs, and macrophages [37,43,46].

Sometimes, associated with long-term uncontrolled hypertension and left ventricular dysfunction (or other conditions such as left heart disease, thromboembolic pulmonary condition, lung disease, liver disease, hematologic disease, metabolic disease, connective tissue disease, human immunodeficiency virus infection, thyroid diseases, etc.), pulmonary hypertension may occur [47,48]. In this situation, through the lungs arteries that have a reduced lumen and thickened walls, blood will flow slowly. Pulmonary arterial hypertension (PAH) is defined by mean pulmonary arterial pressure (mPAP)>20 mmHg at rest assessed by right heart catheterization [47-49]. Histopathological changes at the pulmonary level are neointima formation in pulmonary arteries, wall thickness, and plexiform lesions formed by the proliferation of endothelial cells. There is an increased level of ROS that contributes to oxidative stress and vascular remodeling [50], similar to the changes found in the arteries of hypertensive patients. It has been discovered that there is a deficient activity of NO-synthase, the level of NO is low and so are the vasodilatory effects. The role of proapoptotic and antiapoptotic proteins has been incriminated in the initiation of the pathogenesis of PAH and the proliferation of apoptosis-resistant vascular cells [51,52]. Both reversible and irreversible PAH express the apoptotic markers (caspase-3 and p-53) [51,53], while irreversible PAH expresses BCL-2 only in severely wounded endothelial cells [51]. Apoptosis plays an important role in pulmonary hypertension among the proliferation of VCMCs and plexiform lesions [51,52].

In our study we highlighted some evidence in favor of the hypothesis that cell death is involved and has consequences on vascular changes in people with arterial hypertension; the vascular changes occurring in the hypertensive patient may be due to the alteration of the cellular metabolism, which may represent a triggering factor of cell death processes by activating abnormal cellular signaling pathways. However, there are insufficient data to show the cell death types involved and the types of cells in the vascular walls involved in the process of vascular remodeling, therefore we consider that further studies are necessary to elucidate these aspects

CONCLUSIONS

Cell death and cardiovascular outcomes seem to be linked through metabolic risk factors intervention and exogenous causes of cellular stress. Demonstrating that alteration of cellular signaling, the alteration of the extracellular environment, and abnormal cell death mechanisms are responsible for the abnormal remodeling of the arterial wall in hypertensive patients could direct future research toward the identification of new molecules as plasma membrane receptors involved in apoptosis and new therapies that can be targeted in patients with cardiovascular risk factors. Once the vascular impact of imbalances between cell proliferation and

cell death will be demonstrated, its early detection could become an argument for maximum therapeutic intervention in this population group.

Conflicts of interest and sources of funding
The authors declare no conflict of interest.

Authors' contribution
EB conceived of the presented idea. AMD, EB contributed to documentation on the topic of interest, work conception and revised the manuscript. EB, ŞSB, OA performed the final revision of the manuscript. All authors discussed the results and contributed to the final manuscript. ŞSB and OA gave final approval. All authors have read and agreed to the published version of the manuscript. EB, ŞSB, OA had equal contributions.

References:

1. Brown, I.A.M.; Diederich, L.; Good, M.E.; DeLalio, L.J.; Murphy, S.A.; Cortese-Krott, M.M.; Hall, J.L.; Le, T.H.; Isakson, B.E. Vascular smooth muscle remodeling in conductive and resistance arteries in hypertension. Arterioscler Thromb Vasc Biol 2018, 38, 1969-1985.

2. Xu, C.; Lee, S.; Singh, T.M.; Sho, E.; Li, X.; Sho, M.; Masuda, H.; Zarins, C.K. Molecular mechanisms of aortic wall remodeling in response to hypertension. J Vasc Surg 2001, 33, 570-578.

3. Abdelbary, M.; Rafikova, O.; Gillis, E.E.; Musall, J.B.; Baban, B.; O'Connor, P.M.; Brands, M.W.; Sullivan, J.C. Necrosis con-tributes to the development of hypertension in male, but not female, spontaneously hypertensive rats. Hypertension 2019, 74, 1524-1531.

4. Oliveros, E.; Patel, H.; Kyung, S.; Fugar, S.; Goldberg, A.; Madan, N.; Williams, K.A. Hypertension in older adults: Assessment, management, and challenges. Clin Cardiol 2020, 43, 99-107.

5. Tower, J. Programmed cell death in aging. Ageing Res Rev 2015, 23, 90-100.

6. Kapetanaki, M.G.; Mora, A.L.; Rojas, M. Influence of age on wound healing and fibrosis. J Pathol 2013, 229, 310-322.

7. Hotchkiss, R.S.; Strasser, A.; McDunn, J.E.; Swanson, P.E. Cell death. N Engl J Med 2009, 361, 1570-1583.

8. Santavanond, J.P.; Rutter, S.F.; Atkin-Smith, G.K.; Poon, I.K.H. Apoptotic bodies: Mechanism of formation, isolation and functional relevance. Subcell Biochem 2021, 97, 61-88.

9. Gardner, A.W.; Parker, D.E.; Montgomery, P.S. Changes in vascular and inflammatory biomarkers after exercise rehabilitation in patients with symptomatic peripheral artery dis-ease. J Vasc Surg 2019, 70, 1280-1290.

10. Renna, N.F.; de Las Heras, N.; Miatello, R.M. Pathophysiology of vascular remodeling in hypertension. Int J Hy-pertens 2013, 2013, 808353.

11. Hartley, A.; Haskard, D.; Khamis, R. Markers of apoptosis predict cardiovascular outcomes and point to 'response to injury' as a common pathway leading to diabetes and cardiovascular events. EBioMedicine 2018, 28, 19-20.

12. Guicciardi, M.E.; Gores, G.J. Life and death by death receptors. FASEB J 2009, 23, 1625-1637.

13. Akhigbe, R.; Ajayi, A. The impact of reactive oxygen species in the development of cardiometabolic disorders: A review. Lipids Health Dis 2021, 20, 23.

14. Ning, B.; Chen, Y.; Waqar, A.B.; Yan, H.; Shiomi, M.; Zhang, J.; Chen, Y.E.; Wang, Y.; Itabe, H.; Liang, J., et al. Hypertension enhances advanced atherosclerosis and induces cardiac death in Watanabe heritable hyperlipidemic rabbits. Am J Pathol 2018, 188, 2936-2947.

15. Sun, H.J.; Wu, Z.Y.; Nie, X.W.; Bian, J.S. Role of endothelial dysfunction in cardiovascular diseases: The link between inflammation and hydrogen sulfide. Front Pharmacol 2019, 10, 1568.

16. Martinez-Quinones, P.; McCarthy, C.G.; Watts, S.W.; Klee, N.S.; Komic, A.; Calmasini, F.B.; Priviero, F.; Warn-er, A.; Chenghao, Y.; Wenceslau, C.F. Hypertension induced morphological and physiological changes in cells of the arterial wall. Am J Hypertens 2018, 31, 1067-1078.

17. Bruno, R.M.; Duranti, E.; Ippolito, C.; Segnani, C.; Bernardini, N.; Di Candio, G.; Chiarugi, M.; Taddei, S.; Virdis, A. Different impact of essential hypertension on structural and functional age-related vascular changes. Hypertension 2017, 69, 71-78.

18. Qi, H.M.; Cao, Q.; Liu, Q. Tlr4 regulates vascular smooth muscle cell proliferation in hypertension via modulation of the nlrp3 inflammasome. Am J Transl Res 2021, 13, 314-325.

19. Sorokin, V.; Vickneson, K.; Kofidis, T.; Woo, C.C.; Lin, X.Y.; Foo, R.; Shanahan, C.M. Role of vascular smooth muscle cell plasticity and interactions in vessel wall inflammation. Front Immunol 2020, 11, 599415.

20. Munoz-Durango, N.; Fuentes, C.A.; Castillo, A.E.; Gonzalez-Gomez, L.M.; Vecchiola, A.; Fardella, C.E.; Kalergis, A.M. Role of the renin-angiotensin-aldosterone system be-yond blood pressure regulation: Molecular and cellular mechanisms involved in end-organ damage during arterial hypertension. Int J Mol Sci 2016, 17.

21. Virdis, A.; Dell'Agnello, U.; Taddei, S. Impact of inflammation on vascular disease in hypertension. Maturitas 2014, 78, 179-183.

22. Balan, R.; Ferdoschi, C.; Balasescu, E.; Ion, D.A. Ag-ing and vascular compliance in hypertensive patients mirrored in routine investigations. Curr Health Sci J 2021, 47, 367-376.

23. Schiffrin, E.L. Vascular remodeling in hypertension: Mechanisms and treatment. Hypertension 2012, 59, 367-374.

24. Chiang, H.Y.; Chu, P.H.; Lee, T.H. Mfg-e8 mediates arterial aging by promoting the proinflammatory phenotype of vascular smooth muscle cells. J Biomed Sci 2019, 26, 61.

25. Intengan, H.D.; Schiffrin, E.L. Vascular remodeling in hypertension: Roles of apoptosis, inflammation, and fibrosis. Hypertension 2001, 38, 581-587.

26. Balan, R.; E, B.A.; Ion, D.A. Inflammation and arterial hypertension-pathophysiological links and clinical aspects. Curr Health Sci J 2020, 46, 383-389.

27. Pietri, P.; Vyssoulis, G.; Vlachopoulos, C.; Zervoudaki, A.; Gialernios, T.; Aznaouridis, K.; Stefanadis, C. Relationship between low-grade inflammation and arterial stiffness in patients with essential hypertension. J Hypertens 2006, 24, 2231-2238.

28. Fukutomi, M.; Hoshide, S.; Eguchi, K.; Watanabe, T.; Kario, K. Low-grade inflammation and ambulatory blood pressure response to antihypertensive treatment: The alpha-bet study. Am J Hypertens 2013, 26, 784-792.

29. Iulita, M.F.; Duchemin, S.; Vallerand, D.; Barhoumi, T.; Alvarez, F.; Istomine, R.; Laurent, C.; Youwakim, J.; Paradis, P.; Arbour, N., et al. Cd4(+) regulatory t lymphocytes prevent impaired cerebral blood flow in angiotensin ii-induced hypertension. J Am Heart Assoc 2019, 8, e009372.

30. Melton, E.; Qiu, H. Interleukin-1beta in multifactorial hypertension: Inflammation, vascular smooth muscle cell and extracellular matrix remodeling, and non-coding RNA regulation. Int J Mol Sci 2021, 22.

31. Ziaja, M.; Urbanek, K.A.; Kowalska, K.; Piastowska-Ciesielska, A.W. Angiotensin ii and angiotensin receptors 1 and 2-multifunctional system in cells biology, what do we know? Cells 2021, 10.

32. Sun, Y.; Li, Y.; Wang, M.; Yue, M.; Bai, L.; Bian, J.; Hao, W.; Sun, J.; Zhang, S.; Liu, H. Increased at2r expression is induced by at1r autoantibody via two axes, KLF-5/IRF-1 and CIRCERBB4/MIR-29a-5p, to promote VSMC migration. Cell Death Dis 2020, 11, 432.

33. Lu, X.; Zhang, J.; Wen, Y.; Ren, J.; Griffiths, R.; Rudemiller, N.P.; Ide, S.; Souma, T.; Crowley, S.D. Type 1 angiotensin receptors on CD11C-expressing cells protect against hypertension by regulating dendritic cell-mediated T-cell activation. Hypertension 2022, 79, 1227-1236.

34. Lin, Q.Y.; Bai, J.; Liu, J.Q.; Li, H.H. Angiotensin ii stimulates the proliferation and migration of lymphatic endothelial cells through angiotensin type 1 receptors. Front Physiol 2020, 11, 560170.

35. Li, Y.; Dang, Q.; Li, Z.; Han, C.; Yang, Y.; Li, M.; Li, P. Restoration of mitochondrial function is essential in the endothelium-dependent vasodilation induced by acacetin in hypertensive rats. Int J Mol Sci 2022, 23.

36. Shi, M.Q.; Su, F.F.; Xu, X.; Liu, X.T.; Wang, H.T.; Zhang, W.; Li, X.; Lian, C.; Zheng, Q.S.; Feng, Z.C. Cilostazol suppresses angiotensin ii-induced apoptosis in endothelial cells. Mol Med Rep 2016, 13, 2597-2605.

37. Lu, H.; Du, W.; Ren, L.; Hamblin, M.H.; Becker, R.C.; Chen, Y.E.; Fan, Y. Vascular smooth muscle cells in aortic aneurysm: From genetics to mechanisms. J Am Heart Assoc 2021, 10, e023601.

38. Rombouts, K.B.; van Merrienboer, T.A.R.; Ket, J.C.F.; Bogunovic, N.; van der Velden, J.; Yeung, K.K. The role of vascular smooth muscle cells in the development of aortic aneurysms and dissections. Eur J Clin Invest 2022, 52, e13697.

39. Krishna, S.M.; Li, J.; Wang, Y.; Moran, C.S.; Trollope, A.; Huynh, P.; Jose, R.; Biros, E.; Ma, J.; Golledge, J. Kallistatin limits abdominal aortic aneurysm by attenuating generation of reactive oxygen species and apoptosis. Sci Rep 2021, 11, 17451.

40. Fekete, A.A.; Giromini, C.; Chatzidiakou, Y.; Givens, D.I.; Lovegrove, J.A. Whey protein lowers blood pressure and improves endothelial function and lipid biomarkers in adults with prehypertension and mild hypertension: Results from the chronic whey2go randomized controlled trial. Am J Clin Nutr 2016, 104, 1534-1544.

41. Li, X.; Wang, J.; Wu, C.; Lu, X.; Huang, J. Micro-RNAs involved in the TGF-beta signaling pathway in atherosclerosis. Biomed Pharmacother 2022, 146, 112499.

42. Zhang, P.; Wang, W.; Li, M. Circ_0010283/mir-377-3p/cyclin d1 axis is associated with proliferation, apoptosis, migration, and inflammation of oxidized low-density lipoprotein-stimulated vascular smooth muscle cells. J Cardiovasc Pharmacol 2021, 78, 437-447.

43. Beck-Joseph, J.; Lehoux, S. Molecular interactions between vascular smooth muscle cells and macrophages in atherosclerosis. Front Cardiovasc Med 2021, 8, 737934.

44. Evans, B.R.; Yerly, A.; van der Vorst, E.P.C.; Baumgartner, I.; Bernhard, S.M.; Schindewolf, M.; Doring, Y. Inflammatory mediators in atherosclerotic vascular remodeling. Front Cardiovasc Med 2022, 9, 868934.

45. Feng, M.; Xu, D.; Wang, L. Mir-26a inhibits athero-sclerosis progression by targeting trpc3. Cell Biosci 2018, 8, 4.

46. Liu, J.; Liu, M.; Feng, J.; Zhu, H.; Wu, J.; Zhang, H.; Xiao, S.; Jing, Z.; Zhou, J.; Niu, H., et al. Alpha-ketoglutarate ameliorates abdominal aortic aneurysm via inhibiting PXDN/HOCL/ERK signaling pathways. J Transl Med 2022, 20, 461.

47. Dong, X.; Shi, Y.; Xia, Y.; Zhang, X.; Qian, J.; Zhao, J.; Peng, J.; Wang, Q.; Weng, L.; Li, M., et al. Diversity of hemodynamic types in connective tissue disease-associated pulmonary hypertension: More than a subgroup of pulmonary arterial hypertension. BMC Pulm Med 2022, 22, 295.

48. Simonneau, G.; Montani, D.; Celermajer, D.S.; Denton, C.P.; Gatzoulis, M.A.; Krowka, M.; Williams, P.G.; Souza, R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019, 53.

49. Xu, W.; Erzurum, S.C. Endothelial cell energy metabolism, proliferation, and apoptosis in pulmonary hypertension. Compr Physiol 2011, 1, 357-372.

50. Higashi, Y. Roles of oxidative stress and inflammation in vascular endothelial dysfunction-related disease. Anti-oxidants (Basel) 2022, 11.

51. Levy, M.; Maurey, C.; Celermajer, D.S.; Vouhe, P.R.; Danel, C.; Bonnet, D.; Israel-Biet, D. Impaired apoptosis of pulmonary endothelial cells is associated with intimal proliferation and irreversibility of pulmonary hypertension in congenital heart disease. J Am Coll Cardiol 2007, 49, 803-810.

52. de Mendonca, L.; Felix, N.S.; Blanco, N.G.; Da Silva, J.S.; Ferreira, T.P.; Abreu, S.C.; Cruz, F.F.; Rocha, N.; Silva, P.M.; Martins, V., et al. Mesenchymal stromal cell therapy reduces lung inflammation and vascular remodeling and improves hemodynamics in experimental pulmonary arterial hypertension. Stem Cell Res Ther 2017, 8, 220.

53. Taraseviciene-Stewart, L.; Kasahara, Y.; Alger, L.; Hirth, P.; Mc Mahon, G.; Waltenberger, J.; Voelkel, N.F.; Tuder, R.M. Inhibition of the VEGF receptor 2 combined with chronic hypoxia causes cell death-dependent pulmonary endothelial cell proliferation and severe pulmonary hypertension. FASEB J 2001, 15, 427-438.