European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2022 vol. 11, ISSUE N. 2, July-December

ADVANCES IN HYPERTENSION, HEART DISEASE, AND THE CNS

G. Tomassoni[1*] and G. Ronconi[2]

[1] "G. Mazzini" Civil Hospital, Cardiology Department, Teramo, Italy;
[2] Catholic University of Rome, Italy.

Correspondence to:
Gianpaolo Ronconi,
Catholic University of Rome,
Rome, Italy.
e-mail: gianpaolo.ronconi@policlinicogemelli.it

ABSTRACT

It is now known that hypertension is a cardiovascular risk factor, and a better understanding of the pathogenesis of this disease may lead to more specific therapies. Immune cells that cause inflammation may also be involved in hypertension by causing the activation of vasoactive molecules, including the cytokines IL-1, IL-6 and TNF. These inflammatory cytokines are also produced by microglia and can provoke cardiovascular disease, linking the nervous system with hypertension and heart disease. The inhibition of pro-inflammatory cytokines can be a therapeutic strategy in these pathologies.

KEYWORDS: *hypertension, heart disease, CNS, neuroinflammation, microglia, cytokine, immune*

INTRODUCTION

Hypertension has an incidence of about 30% worldwide, is the most frequent cause of mortality, and can cause several other diseases (1). Hypertension occurs when blood pressure is higher than the normal population and it is an important risk factor in cardiovascular disease where it can lead to heart failure, vascular disease, and stroke (2). In addition, blood pressure rises with age and can lead to heart attack, aneurysm, and chronic kidney disease. Hypertension, which has increased in recent years, is the main cardiovascular risk factor, particularly in elderly Western subjects.

In the last twenty years, there has been considerable progress in the research on antihypertensive drugs and today the topic of hypertension is being tackled with greater therapeutic awareness. In hypertension, the smooth muscle cells of the arterial vessels are involved, responsible for regulating blood flow and therefore blood pressure (3). These muscle cells contract in high blood pressure to counteract the blood flow going to the tissues. Hypertension drugs are often rejected by patients because the disease is often asymptomatic, and the drugs can cause unwanted side effects.

In hypertension, the role of inflammation is an important issue linked to cardiovascular risk and other pathological phenomena. In this disease, the activation of immune cells, producing pro-inflammatory cytokines, can cause chronic low-grade inflammation, a topic that is still understudied by clinical research (4). IL-1 inhibition with new inhibitory cytokines such as IL-37, IL-38 or IL-1Ra, may improve clinical status by reducing C-reactive protein (CRP), and counteracting cardiovascular events, although they may not directly improve hypertension (5). The hypertensive phenomenon can activate vasoactive molecules, such as, for example, the NLRP3 inflammasome which could stimulate and lead to the generation of IL-1 by mediating chronic low-grade inflammation (6). IL-1 entering the circulation activates the macrophage cells of innate immunity, but also non-immune cells such as fibroblasts and endothelial cells (7). The

Received: 13 September, 2022
Accepted: 04 November, 2022

2279-5855 (2022)

activation of NLRP3 leads to the generation of IL-1, which causes the formation of fibrosis with renal vascular damage and hypertension (Fig.1).

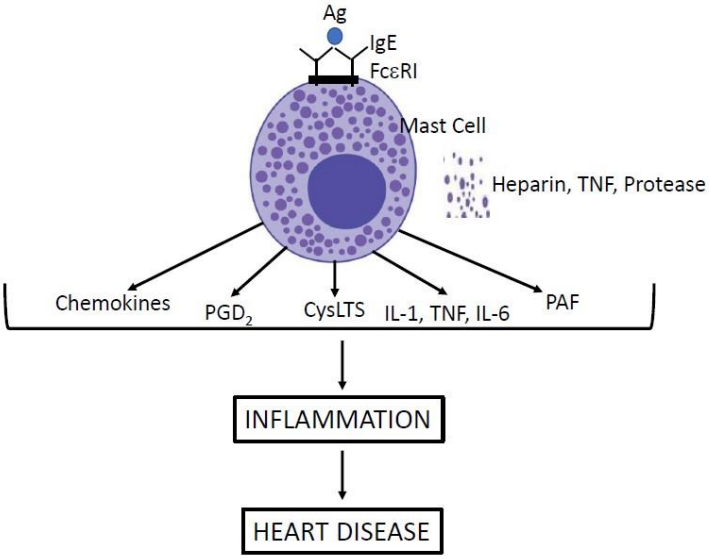

Fig. 1. *Activation of mast cells through its receptor (FcεRI) leads to the generation of chemical mediators such as heparin, TNF and protease, and other inflammatory compounds including chemokines, PGD_2, CysLTS, IL-1, TNF, IL-6 and PAF, that together, provoke inflammation and mediate heart disease.*

These studies demonstrate that innate immunity mediated essentially by macrophage cells producing IL-1 and other pro-inflammatory molecules, results in hypertension. In addition, immune cells such as innate lymphoid cells (ILCs), and gamma delta T cells that produce IL-17A, can damage organs and induce hypertension (8). Furthermore, the activation of lymphocytes and macrophages generates TNF, another very potent inflammatory cytokine. ILC cells produce inflammatory cytokines such as IFNγ, IL-17, and granulocyte-macrophage colony-stimulating factor (GMC-SF), also involved in hypertensive inflammation. CD4+ and CD8+ lymphocytes also participate in the pathological process in hypertension, producing inflammatory cytokines, while Treg lymphocytes (CD25), which have an immunosuppressive function and the ability to promote immunological tolerance, may play a protective role (9). In experimental mouse models where a Treg cell deficit was induced in the circulatory system and therefore in the organs, the animals showed an increase in blood pressure, demonstrating the importance of the activation of T lymphocytes in mediating hypertension (10).

Cardiovascular disorder is an inflammatory disease that can lead to myocardial infarction and stroke. Heart failure due to hypertension leads to ventricular hypertrophy and diastolic dysfunction.

Neuroinflammation in the central nervous system (CNS) is mainly fueled by microglia and contributes to the pathogenesis of many brain diseases. Therefore, microglia are protective immune cells similar to macrophages that reside in the CNS, but when activated by releasing substances such as cytokines that can inflame surrounding tissue, they can also enter the bloodstream (11).

Mast cells in cardiovascular disease

Cardiac tissue includes fibroblasts, pericytes, smooth muscle cells, endothelial cells, and cardiomyocytes, but immune cells are also present including macrophages, dendritic cells, T and B lymphocytes, and mast cells (MCs), which play an important role in maintaining proper regeneration and the healthy tissue physiological state (12). MCs are in the perivascular and participate in vascularized tissue reactions causing inflammation (13). Mast cells are bone marrow hematopoietic cells that are formed from CD34+ cells that are capable of migrating to all tissues including the heart where they reside near vessels. Histamine, released by MCs, acts on the endothelium, mediates vascular permeability, and promotes adhesion of platelets through the adhesion molecule. Activation of the FcεRI receptors of MCs can provoke the release of various pro-inflammatory compounds including IL-1 and other inflammatory cytokines and chemokines, which contributes to chronic inflammation. Antigen binding c-kit/CD117 receptor in cardiac mast cells also results in histamine secretion (14). Increased heart rate, mast cell count, and histamine levels mediate cardiac ischemia and cardiovascular spasm with myocardial damage (15).

MCs produce cytokines and proteases such as tryptase and chymase, promoting leukocyte infiltration into cardiac tissue and causing inflammation (Fig.2).

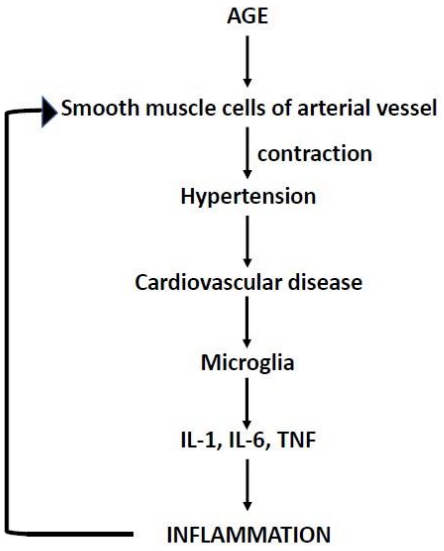

Fig. 2. *Smooth muscle cells of arterial vessel contraction in age can lead to hypertension and vascular disease, involving microglia which release inflammatory cytokines such IL-1, IL-6, and TNF causing inflammation which mediates hypertension.*

Activated MCs release tryptase from their granules which stimulates activate protease-activated receptors (PARs) present in sensory neurons near the MCs. This activation leads to the release of substance P from the afferent nerves, causing inflammation. MCs can proliferate in cardiac tissue and play an important role in heart failure and ischemia (15). However, it appears that no increase in the number of MCs results in myocardial infarction. They can proliferate in cardiac tissue and play an important role in heart failure and ischemia, although it has been reported that these cells may also play a protective role in cardiac tissue remodeling (16).

Hypertension, cardiovascular disease, and microglia

Hypertension, associated with cardiovascular morbidity, can lead to organ specific microvascular disease, mediated by sterile inflammatory processes. For instance, the activation of immune cells by an ischemic process leads to the recruitment of leukocytes with production of cytokines that mediate the sterile inflammatory process in cardiac tissue. Innate immunity, represented by monocytes CD14 and CD16 that maintain homeostasis, plays an important role in cardiovascular disease which is associated with various pathologies such as endocarditis, atherosclerosis, peripheral vascular disease, ischemic heart disease, hypertensive heart disease, hemorrhagic stroke, cardiomyopathy, and others (17).

Activated monocytes can generate several pro-inflammatory vasoactive mediators such as cytokines (IL-1, IL-6, and TNF), prostaglandins PGD2, cysteinyl leukotrienes (LTC4, D4, E4), platelet-activating factor (PAF), and chemokines. CD4+ immune T cells have a protective function in cardiovascular disease, as most of them resident in heart tissue are T regulatory (Treg) cells that produce IL-10, an anti-inflammatory cytokine that opposes heart disease (18). CD4+ cell intervention improves diseased heart tissue through monocyte/macrophage regulation.

In response to hypertensive insults, cardiovascular inflammation and neuroinflammatory processes can occur involving microglia which mediate the immune response in cooperation with neuronal cells and astrocytes. Glial cells are cells of mesodermal origin and non-neuronal cells of the nervous system. Glia is a word of Greek origin and means "glue" because these cells were thought to function only to hold the nervous system together. Glial cells are now known to play an important role in the nervous system such as astrocytes, which are glial cells responsible for regulating the levels of neurotransmitters, such as inflammatory substance P, around neurons (19). In addition, microglia, which are innate immune cells, are tissue-resident macrophages in the brain and perform their immunological function through phagocytosis, removing dead neurons and other harmful substances (Fig.3).

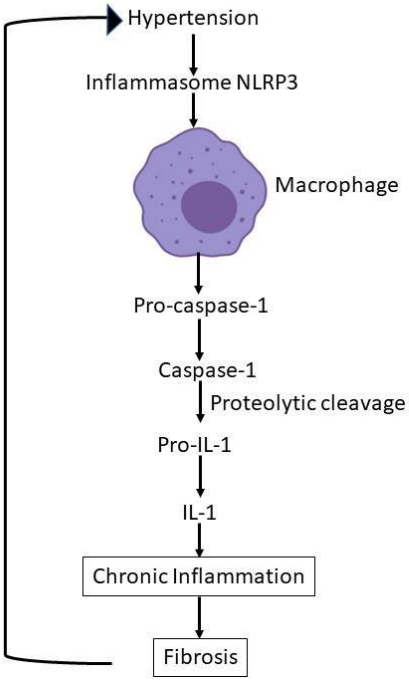

Fig. 3. *Inflammasone NLRP3 in hypertension activates macrophages to release caspase and therefore, IL-1, which mediate chronic inflammation and fibrosis involved in hypertension.*

In the nervous system, microglia also regulate synapses and the synthesis of myelin which surrounds neuronal axons. The cooperation between glial cells and neurons is important for a correct physiology of the nervous system.

The activation of microglia can occur in neurological and cardiovascular diseases and by acting on the microglia it is possible to obtain an improvement in these pathological states. In fact, microglia have been shown to mediate inflammatory diseases, including cardiovascular diseases, demonstrating a relationship between cardiac, neuroinflammatory, and hypertension diseases. The activation of microglia and the cardiovascular system leads to the production of pro-inflammatory cytokines such as IL-1, TNF, IL-6, and various chemokines (20). The M2 macrophage-like microglial phenotype produces anti-inflammatory cytokines such as IL-4 and IL-13 for tissue repair and healing. It is not yet known whether this population of M2 macrophage and microglial cells can generate the anti-inflammatory cytokines IL-37, IL-38 or IL-1Ra. Neuroinflammation affects blood pressure; In fact, infectious states activate microglia which produce pro-inflammatory cytokines, an effect that can be attenuated by inhibiting microglia activation. These reactions demonstrate a clear connection between hypertension and microglia. It has been reported that in acute hypertension, the number of synapses in contact with microglia increases, while in hypotension, the microglia decrease the number of synapses (21).

Microglia express the TLR4 receptor which can be activated by different antigens, resulting in an inflammatory response, a reaction that is downregulated by inhibiting TLR4. This demonstrates the importance of TLR4 in microglial cell response, hypertension, and cardiovascular disease, paving the way for therapeutic intervention. Myocardial infarction may also activate hypothalamic microglia with elevations of pro-inflammatory cytokines such as IL-1, IL-6, and TNF that activate the pituitary adrenal axis (22). Coronary injury with reperfusion also causes microglial activation, suggesting a connection between cardiac injury and microglial activation.

CONCLUSIONS

In this article, we have shown the interrelationship between hypertension, vascular disease, and neuroinflammation, demonstrating that the human body works as an orchestra where each instrument plays together to perform the correct music.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Peixoto AJ. Acute Severe Hypertension. *N Engl J Med*. 2019;381(19):1843-1852. doi:10.1056/NEJMcp1901117
2. Latic N, Erben RG. Vitamin D and Cardiovascular Disease, with Emphasis on Hypertension, Atherosclerosis, and Heart Failure. *Int J Mol Sci*. 2020;21(18):6483. doi:10.3390/ijms21186483
3. Touyz RM, Alves-Lopes R, Rios FJ, et al. Vascular smooth muscle contraction in hypertension. *Cardiovasc Res*. 2018;114(4):529-539. doi:10.1093/cvr/cvy023
4. Agita A, Alsagaff MT. Inflammation, Immunity, and Hypertension. *Acta Med Indones*. 2017;49(2):158-165.
5. Madhur MS, Elijovich F, Alexander MR, et al. Hypertension: Do Inflammation and Immunity Hold the Key to Solving this Epidemic? *Circ Res.* 2021;128(7):908-933.
6. Griendling KK, Camargo LL, Rios FJ, Alves-Lopes R, Montezano AC, Touyz RM. Oxidative Stress and Hypertension. *Circ Res*. 2021;128(7):993-1020. doi:10.1161/CIRCRESAHA.121.318063
7. Conti P, Caraffa A, Mastrangelo F, et al. Critical role of inflammatory mast cell in fibrosis: Potential therapeutic effect of IL-37. *Cell Prolif*. 2018;51(5):e12475. doi:10.1111/cpr.12475
8. Zhang RM, McNerney KP, Riek AE, Bernal-Mizrachi C. Immunity and Hypertension. *Acta Physiol (Oxf)*. 2021;231(1):e13487. doi:10.1111/apha.13487
9. Huang N, Zhou R, Chen H, et al. Splenic CD4+ and CD8+ T-cells highly expressed PD-1 and Tim-3 in cirrhotic patients with HCV infection and portal hypertension. *Int J Immunopathol Pharmacol*. 2021;35:20587384211061051. doi:10.1177/20587384211061051
10. Radwan E, Mali V, Haddox S, et al. Treg cells depletion is a mechanism that drives microvascular dysfunction in mice with established hypertension. *Biochim Biophys Acta Mol Basis Dis*. 2019;1865(2):403-412. doi:10.1016/j.bbadis.2018.10.031
11. Richards EM, Li J, Stevens BR, Pepine CJ, Raizada MK. Gut Microbiome and Neuroinflammation in Hypertension. *Circ Res*. 2022;130(3):401-417. doi:10.1161/CIRCRESAHA.121.319816
12. Salei N, Rambichler S, Salvermoser J, et al. The Kidney Contains Ontogenetically Distinct Dendritic Cell and Macrophage Subtypes throughout Development That Differ in Their Inflammatory Properties. *J Am Soc Nephrol*. 2020;31(2):257-278. doi:10.1681/ASN.2019040419
13. Conti P, Caraffa A, Ronconi G, et al. Impact of mast cells in depression disorder: inhibitory effect of IL-37 (new frontiers). *Immunol Res*. 2018;66(3):323-331. doi:10.1007/s12026-018-9004-9
14. Galli SJ, Kalesnikoff J, Grimbaldeston MA, Piliponsky AM, Williams CM, Tsai M. Mast cells as "tunable" effector and immunoregulatory cells: recent advances. *Annu Rev Immunol*. 2005;23:749-786. doi:10.1146/annurev.immunol.21.120601.141025
15. Marone G, De Crescenzo G, Florio G, Granata F, Dente V, Genovese A. Immunological modulation of human cardiac mast cells. *Neurochem Res.* 1999;24: 1195–1202.
16. Clejan S, Japa S, Clemetson C, Hasabnis SS, David O, Talano JV. Blood histamine is associated with coronary artery disease, cardiac events and severity of inflammation and atherosclerosis. *J Cell Mol Med*. 2002;6: 583–592.
17. Vegting Y, Vogt L, Anders HJ, de Winther MPJ, Bemelman FJ, Hilhorst ML. Monocytes and macrophages in ANCA-associated vasculitis. *Autoimmun Rev*. 2021;20(10):102911. doi:10.1016/j.autrev.2021.102911
18. Granowitz EV, Clark BD, Vannier E, Callahan MV, Dinarello CA. Effect of interleukin-1 (IL-1) blockade on cytokine synthesis: I. IL-1 receptor antagonist inhibits IL-1-induced cytokine synthesis and blocks the binding of IL-1 to its type II receptor on human monocytes. *Blood*. 1992;79(9):2356-2363.
19. Zhang YY, Song N, Liu F, et al. activation of the RAS/B-RAF-MEK-ERK pathway in satellite glial cells contributes to substance p-mediated orofacial pain. *Eur J Neurosci*. 2020;51(11):2205-2218. doi:10.1111/ejn.14619
20. Wang M, Pan W, Xu Y, et al. Microglia-Mediated Neuroinflammation: A Potential Target for the Treatment of Cardiovascular Diseases. *J Inflamm Res*. 2022;15:3083-3094.
21. Kapoor K, Bhandare AM, Nedoboy PE, et al. Dynamic changes in the relationship of microglia to cardiovascular neurons in response to increases and decreases in blood pressure. *Neuroscience*. 2016;329:12–29.

22. Francis J, Chu Y, Johnson AK, et al. Acute myocardial infarction induces hypothalamic cytokine synthesis. *Am J Physiol Heart Circ Physiol*. 2004;286(6):H2264–71.