

# Inflammation, Immunity, and Hypertension

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## **ABSTRAK**

*Sistem imun, proses inflamasi serta hipertensi saling berkaitan. Sistem imun alamiah dan adaptif memicu proses inflamasi, mengakibatkan peningkatan tekanan darah yang merangsang kerusakan organ. Sel pada sistem imun alamiah memproduksi ROS seperti superoksida dan hidrogen peroksida yang bertujuan membunuh patogen. Proses inflamasi jangka-panjang meningkatkan produksi ROS, menyebabkan stress oksidatif, mengakibatkan disfungsi endotel. Endotel berfungsi mengatur tonus dan struktur pembuluh darah. Saat inflamasi, bioavailabilitas NO menurun, mengganggu fungsi utamanya, sehingga mencegah relaksasi dan vasodilatasi pembuluh darah. Sel T efektor dan limfosit regulatori, bagian dari sistem imun adaptif, berperan pada konstriksi pembuluh darah pada hipertensi. Sinyal dari sistem saraf pusat dan APC mengaktifasi diferensiasi limfosit T efektor, dan mempercepat melalui Th-1 dan fenotip Th-17. Efektor Th-1 dan Th-17 berpartisipasi dalam inflamasi, mengakibatkan peningkatan tekanan darah. Salah satu bagian CD4<sup>+</sup> adalah regulatory T cells (Tregs) yang menekan aktivasi respons imun dengan memproduksi sitokin immunosupresif seperti TGF- $\beta$  dan IL-10. Transfer adoptif dari sel Tregs menurunkan stres oksidatif pada pembuluh darah, disfungsi endotel, infiltrasi dari makrofag aorta dan sel T serta kadar sitokin proinflamasi dalam sirkulasi plasma.*

**Kata kunci:** *aktifasi sistem imun, proses inflamasi, disfungsi endotel, hipertensi.*

## **ABSTRACT**

*The immune system, inflammation and hypertension are related to each other. Innate and adaptive immunity system triggers an inflammatory process, in which blood pressure may increase, stimulating organ damage. Cells in innate immune system produce ROS, such as superoxide and hydrogen peroxide, which aimed at killing pathogens. Long-term inflammation process increases ROS production, causing oxidative stress which leads to endothelial dysfunction. Endothelial function is to regulate blood vessel tone and structure. When inflammation lasts, NO bioavailability decreases, disrupting its main function as vasodilator, so that blood vessels relaxation and vasodilatation are absent. Effector T cells and regulatory lymphocytes, part of the adaptive immune system, plays role in blood vessels constriction in hypertension. Signals from central nervous system and APC activates effector T lymphocyte differentiation and accelerate through Th-1 and Th-17 phenotypes. Th-1 and Th-17 effectors participate in inflammation which leads to increased blood pressure. One part of CD4<sup>+</sup> is the regulatory T cells (Tregs) that suppress immune response activation as they produce immunosuppressive cytokines, such as TGF- $\beta$  and IL-10. Adoptive transfer of Tregs cells can reduce oxidative stress in blood vessels, endothelial dysfunction, infiltration of aortic macrophages and T cells as well as proinflammatory cytokine levels in plasma circulation.*

**Keywords:** *immune system activation, inflammation process, endothelial dysfunction, hypertension.*

## INTRODUCTION

Hypertension is a major risk factor for cardiovascular disease events that contribute broadly to morbidity and mortality worldwide. Hypertension is a complex condition, with 90% of the cases are classified as essential hypertension with the exact cause is unknown. It is known that hypertension is associated with inflammatory processes. However, until then it has not been known for certain whether the inflammation is a cause or consequence of hypertension.<sup>1</sup>

The role of inflammation and immunity in the pathogenesis of hypertension has been widely known. Infiltration of cells in innate and adaptive immune system to the kidneys, blood vessel wall and area around the blood vessels that occurs simultaneously with the stages of inflammatory process, such as an increase in cytokines release, reactive oxygen species (ROS) production and the emergence of adhesion molecules, are hallmarks which are always found in hypertension.<sup>2</sup> The study by Yao et al shows an interesting fact about the relationship between interleukin-17 (IL-17) and hypertension using cross-sectional data adjusted for other factors involved in heart disease and blood vessels. The data support Harrison and his colleagues hypothesis' stating that Angiotensin II stimulation can increase blood pressure associated with the activation of the immune response and inflammation.<sup>3</sup>

## BASIC CONCEPT OF IMMUNITY

Defense against microbes is mediated by the initial reaction of innate immune system followed by further response by adaptive immune system. Initial mechanism of the immune system to fight pathogens are innate immune system.<sup>4</sup> Innate immunity is the front line for the body's defense against microbes. Important components of the innate immune system is physical and chemical defenses, such as chemical epithel and antimicrobials produced in epithelial surface. Another component is the phagocytic cells (neutrophils and macrophages), dendritic cells, Natural Killer cells (NK cells) and lymphocytes. Other components are blood proteins, including the members of the complement system as well

as other inflammatory mediators.<sup>5</sup>

In contrast to innate immunity, there are other immune responses that will be stimulated by the presence of microorganisms and the exposure will increase, both its magnitude and the ability to survive, if there is exposure that gives a good response to some specific microbes. The immune response is called the adaptive immune response.<sup>6</sup> The innate immune system plays an important role in the initiation of adaptive immune response. Furthermore, activation of adaptive immune response takes 4-7 days, so that the innate immune system will be activated prior to that time frame.<sup>7</sup> Early concepts related to adaptive immunity is Antigen Presenting Cell (APC) in peripheral tissues that processes foreign proteins, such as bacteria and viruses, to become a short peptide that is displayed on the Major Histocompatibility Complex (MHC).<sup>4</sup> The characteristics that must be found in adaptive immunity is extensive capabilities to identify molecules or fragments of molecules with different types, either extrinsic or with modified structure. In addition, adaptive immune system also has the ability to respond aggressively to repeated exposure to the same microbe, known as memory. Adaptive immune response is divided into two: humoral and cellular responses. Humoral response will produce antibodies reactive with a particular antigen. Antibodies are a collection of proteins with similar structures, which, if collected collectively, will be the immunoglobulin (Ig).<sup>7</sup>

In addition to cellular components, cytokines are important for the development of immune responses involving both innate and adaptive systems.<sup>6</sup> All cells of the immune system may produce a minimal number of cytokines and express receptors that signal specifically for certain types of cytokines. Structured group of cytokines that regulate the migration and movement of cells are known as chemokines.<sup>5</sup> Cytokines are a large group of proteins that dissolve and react in short term, which is produced by immune cells and blood vessels, as well as serve to activate specific receptors and modulate the function of various cells in tissues.<sup>8</sup>

Both innate and adaptive immune response are components of the integrated system derived

from the body's host defenses where a large number of cells and molecules work and support each other's function. The working mechanism of innate immunity is to provide an effective early defense against infection. However, unfortunately, many pathogens have the ability to resist innate immunity against a variety of microbes that elimination of those microbes will require stronger immune mechanism, ie adaptive immunity. There is some relationships between innate and adaptive systems. Innate immune response against microbes will stimulate adaptive immune response and affect the origin of adaptive response. In contrast, the adaptive immune response works by enhancing the protective mechanisms of innate immunity, thus making the innate immune response be effective against pathogenic microbes.<sup>5</sup> For the immune system can be activated, it takes the interaction between the phagocytic cells from innate immune system and T cells with high specificity capabilities from adaptive immune system.

All of these are highly correlated with cardiovascular disease since pathogenic microbes mentioned above can lead to dramatic changes in communication between the cells involved to change the function of heart and blood vessels. ROS and Reactive Nitrogen Species (RNS), which plays an important role in the cardiovascular system, are important parts of innate immunity.<sup>4</sup>

### **BASIC CONCEPT OF INFLAMMATION**

Inflammation is a protective response to damage or infection of a cell. Inflammation is a complex process and involves inflammatory cells that will essentially identify the tissues involved, then recruit leukocytes to the tissues, eliminating the cause of inflammation and repair damaged parts of the cell.<sup>1</sup>

In infection area, macrophages that have been dealing with the microbes, will produce cytokines (such as tumor necrosis factor (TNF) and IL-1) and activate endothelial cells to produce selectins, integrins and chemokines.<sup>5</sup> To be able to enter into the inflamed tissue, the circulating leukocytes must stick to endothelial layer of the blood vessels walls. This process is called extravasation. Leukocyte-specific cell-adhesion

molecules (CAMs), which is expressed on cell surface, serves to regulate the travel path of the leukocytes from blood to the tissues around. Production of proinflammatory cytokines and other inflammatory mediators in inflammatory regions will initiate the emergence of CAMs. Vascular endothelium, which is known to have been inflamed, will experience an extravasation process, ie. the displacement of leukocytes to the endothelial tissue. In the event of the creation of leukocytes interaction with endothelium, neutrophils are the first cells that are activated by the inflammatory response, which causes the neutrophil to stick to the inflamed endothelium. Then, they will penetrate the endothelium and eventually migrate toward extravascular tissue. The process of neutrophil extravasation can be divided into four stages, ie. attachment-rolling, activation, arrest-adhesion and extravasation.<sup>9</sup>

In immune system-mediated inflammation, the T-helper 1 (Th-1) and T-helper 17 (Th-17) cells secrete cytokines that recruit and activate leukocytes. IL-17, produced by Th-17 cells, activates neutrophils withdrawal. Whereas, Interferon- $\gamma$ , produced by Th-1 cells, activates macrophages and TNF as well as chemokines, which are produced by T-lymphocytes and other cells, and is involved in withdrawal and activation of various types of leukocytes. Although it has been emphasized that the TH-1 and TH-17 cells are the initial source of these cytokines, in cell injury there will be other cells that produce similar cytokines. Tissue damage is the result of neutrophil and macrophage products that have been drawn and activated, such as lysosomal enzymes, ROS, nitric oxide (NO) and proinflammatory cytokines.<sup>5</sup>

There is some evidence related to the phenotype of proinflammatory cells through a vascular triangle illustrating paralleled vascular dysfunction by oxidative stress, both at the tissue and at cellular level (**Figure 1**). The vascular dysfunction may occur through several mechanisms, including decreased NO level, modified LDL, as well as an increase in circulating leukocytes adhesion. The inflammatory process is an integrated process involving oxidative processes and vascular dysfunction, which is primarily mediated by transcription factors

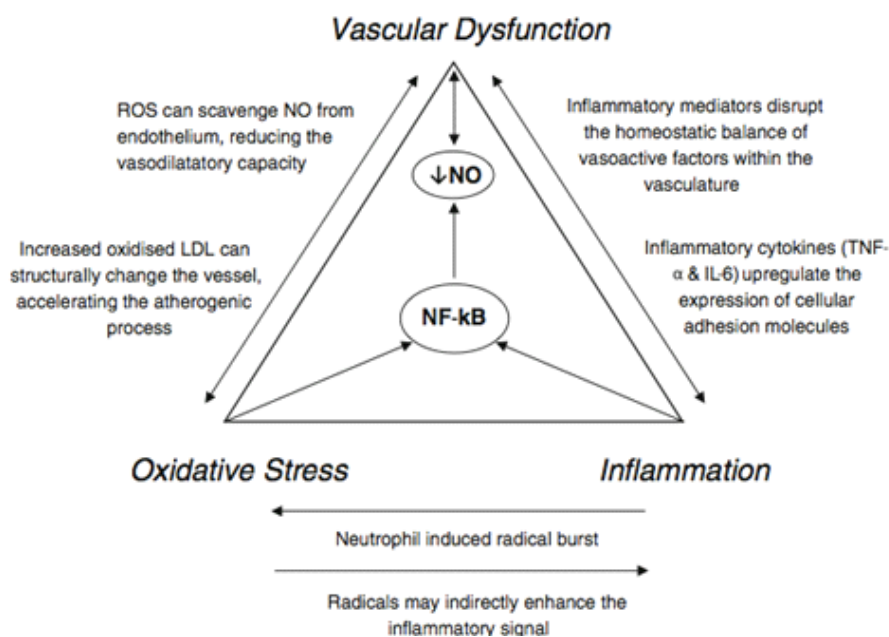


Figure 1. Vascular Triangle<sup>10</sup>

such as NFkB, with the target of reducing NO bioavailability. This cycle occurs naturally, in which the stages of vascular dysfunction would create an environment that aggravate the ongoing inflammation and oxidative stress. In 2004, Clapp and colleagues conducted a study to learn this cycle by inducing an inflammatory response in healthy subjects and observed a decrease in antioxidant status and endothelial function reduction. This study concluded that oxidative stress can decrease endothelial function by decreasing NO bioavailability.<sup>10</sup>

It has been recognized that proinflammatory cytokines are produced by activated dendritic cells, such as IL-1, IL-6 and TNF. These proinflammatory cytokines will cause vasodilation that increases blood flow to the tissues. In addition, inflammatory chemokines will also cause some cells to migrate into the tissue. IL-1 is used to stimulate lymphocytes and macrophage proliferation. Whereas, IL-6 stimulates the production of acute phase proteins derived from liver cells and TNF serves to activate neutrophils, endothelial cells, lymphocytes and acute phase proteins.<sup>7</sup>

## BASIC CONCEPT OF HYPERTENSION

Activation of the renin-angiotensin-aldosterone system is one of important mechanisms that contribute to the occurrence of endothelial dysfunction, vascular remodeling and hypertension. Renin, a protease produced by the juxtaglomerular cells of the kidney, will break angiotensinogen (substrate of renin produced in the liver) to angiotensin I, which is converted to angiotensin II by the angiotensin converting enzyme (ACE). Interactions between angiotensin II and receptor G protein-coupled Angiotensin 1 activates a number of cellular processes that contribute to the onset of hypertension and accelerate the occurrence of end-organ damage associated with hypertension. There is strong evidence showing that either aldosterone, angiotensin II or even renin, activate several signaling pathways that can reduce blood vessels function and cause hypertension. Changes of structure and function, both from small and large arteries, have a major role in hypertensive pathogenesis and progress. Endothelial layer in the blood vessels is an important component for the health of the blood vessels and lead to a solid defense to prevent hypertension.<sup>11</sup>



The important role of the kidneys in the long-term control of blood pressure is through the regulation of body fluids and salt homeostasis. This is supported by the fact that the ability of the kidneys to excrete salt would still be decreasing without relying on the causes of hypertension, either through the blood, kidneys and sympathetic vessels. Relationship between the activation of innate and adaptive immune system that causes inflammation of the kidneys and hypertension have been widely studied. Some are by Harrison et al<sup>4</sup> and Khodja et al<sup>2</sup>. One characteristic that is frequently found is an increase in infiltration of immune cells, including macrophages and T lymphocytes, in renal interstitial. In addition to the kidney, core regulation of blood pressure can be achieved through a balance between sympathetic and parasympathetic nervous innervation of the kidneys and blood vessels, in addition to the hypothalamic hormone that regulates thirst, renal sodium treatment and the functions of peripheral blood vessels and kidneys.<sup>12</sup>

Over time, endothelial dysfunction, neurohormonal activation and an increase in blood pressure would lead to remodeling of blood vessels. This condition will worsen the condition of hypertension. Increasing thickness of the medial to lumen part of the blood vessel (medial to lumen ratio) is a sign of vascular remodeling caused by hypertension, either in small arteries or large arteries. Vasoconstriction will initiate remodeling of small arteries. Normal smooth muscle cells would reconstitute themselves around the diameter of the lumen of small arteries so that medial portion to the blood vessel lumen (medial to lumen ratio) will thicken. However, medial cross-sectional area will not change. By reducing the diameter of the lumen in peripheral circulation, systemic vascular resistance will increase so that it will lead to the occurrence of hypertension. Instead, lumen remodeling of large arteries are characterized by the appearance of hypertrophic genes that will stimulate an increase in the thickness of medial to lumen ratio. The incidence of remodeling associated with this hypertrophy will cause an increase in the size of vascular smooth muscle cells and the accumulation of extracellular matrix

proteins in smooth muscle, such as collagen, due to the activation of the transforming growth factor beta (TGF- $\beta$ ).<sup>11</sup>

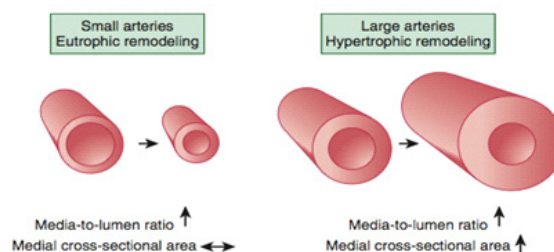


Figure 2. Vascular remodelling in hypertension<sup>11</sup>

## IMMUNITY AND INFLAMMATION IN HYPERTENSIVE PHYSIOLOGY

### Oxidative Stress in Hypertension

Oxidative stress contribution to disrupt renal hemodynamic and tubular function has been widely studied. Oxidative stress in the kidney is commonly found in the study of hypertension. These studies affirm that ROS is an important media for the occurrence of hypertension caused by exposure to angiotensin II.<sup>13</sup>

There are many factors involved in hypertension, including angiotensin II, aldosterone, cytokines and changes in mechanical stress in blood vessels, such as stretching and tearing, which will stimulate the sources of enzymes, such as Nicotinamide Adenine Dinucleotide Phosphate (NADPH) Oxidase, uncoupled Nitric Oxide Synthase and mitochondria, which will produce ROS that contribute to hypertension.<sup>4</sup> Cells derived from innate immune system, such as neutrophils and macrophages, will produce ROS such as superoxide ( $O_2^-$ ) and hydrogen peroxide ( $H_2O_2$ ), which aims to kill pathogens. NADPH oxidase is a major source of ROS production in the vasculature.<sup>1</sup>

Vascular dysfunction is the damage of blood vessel function, which is caused by an imbalance of different factors in endothelial vasoactive substances. One endothelial cell within the blood vessels, which is for the protection of outer layer, is responsible for the release of several vasoactive substances, especially NO. NO is a

vasodilator which can cause direct relaxation of smooth muscle, blood flow and the delivery of the substrate to the tissues. NO also has anti-atherogenic components that can prevent the adhesion of leukocytes and platelets to blood vessel walls. The balance between vasodilation factors such as NO, with vasoconstriction factors, such as endothelin-1 (ET-1), will affect blood circulation. The decrease of NO bioavailability and/or synthesis of oxide synthase (eNOS) will significantly reduce endothelium-dependent dilatation (EDD), which will result in varied process over time, will reduce the function of blood vessels and initiate complications of the heart and blood vessels.<sup>10</sup>

An inflammatory process will continue until the inflammation-causing microorganisms can be destroyed or tissue repair process has been completed. However, chronic inflammatory process can trigger excessive ROS produced. Oxidative stress is defined as an unbalanced condition between ROS production and breakdown, which may cause endothelial dysfunction. In normal circumstances, kidneys will produce ROS, including anions  $O_2^-$ ,  $H_2O_2$ , peroxynitrite ( $ONOO^-$ ) and hydroxyl radical (OH), which will be efficiently eliminated by catalase enzymatic superoxide dismutase (SOD), glutathione peroxidase (GPX) and non-enzymatic systems (glutathione, vitamin C and E). ROS Overproduction is related to  $O_2$  and will culminate in a state of oxidative stress that will reduce the biological effects of NO.<sup>14</sup>

ROS activates transcription factors such as Nuclear factor (erythroid-Derived 2)-like 2 (NFE2L2), Nuclear Factor Kappa-B (NF $\kappa$ B) and Activator Protein 1 (AP-1). These transcription factors will modulate gene expression, including adhesion molecules and chemokines, which causes the accumulation of inflammatory cells. In the event of an oxidative damage, the permeability of the endothelium will increase. This will cause an increase in the influx into subendothelial space, which will cause oxidation and inflammation. Oxidized lipoproteins can interact with Toll Like Receptors (TLR), in particular the TLR4, which can cause impaired blood vessel function. ROS can affect the polarization of T cells and cytokine secretion.

Inflammatory cells such as macrophages and granulocytes may release ROS that can aggravate oxidative ongoing.<sup>4</sup>

### T-lymphocytes in Hypertension

As described previously, the interaction between vascular and inflammatory cells play an important role at the beginning and the development of hypertension. T cells effector that are part of the adaptive immune system, have a role in constricting blood vessels in hypertension. Signals from central nervous system and APC activate T lymphocytes effector and accelerate the differentiation through proinflammatory T-helper (Th-1) and Th-17 phenotype. Effector cells Th-1 and Th-17, produced by proinflammatory mediators, participate in inflammation that will lead to increased blood pressure and target organ damage. Meanwhile, the regulatory T lymphocytes act otherwise in hypertension by holding innate and adaptive immune responses (Figure 3).<sup>2</sup>

In addition, other than Th-17 cells, another division of CD4 +, irrespective of Th-1 and Th-2, is the regulatory T cells (Tregs). There is recent evidence related to the role of Tregs in suppressing the activation of the immune response. It is known that natural Tregs produce immunosuppressive cytokines like TGF- $\beta$  and IL-10.<sup>7</sup> Several recent studies indicate that Tregs have a protective effect on hypertension. It has been recognized that these Tregs can reduce oxidative stress in blood vessels, endothelial dysfunction, infiltration of aortic macrophages and T cells as well as the levels of proinflammatory cytokines circulating in plasma circulation. Additionally, adoptive transfer of the T-regs may also decrease the incidence of cardiac hypertrophy and fibrosis, infiltration of immune cells and remodeling effects. Therefore, it can be inferred that Tregs have a high antihypertensive effect, with regard to its ability to produce anti-inflammatory cytokines such as IL-10.<sup>2</sup>

Slight increase in blood pressure in response to hypertensive stimulus of such as angiotensin II, aldosterone, ET-1, salt diet and genetic influences, arising from signal increase in the central nervous system. This is likely to cause minor damage of the tissue and the formation of DAMPs (Damage Associated Molecular

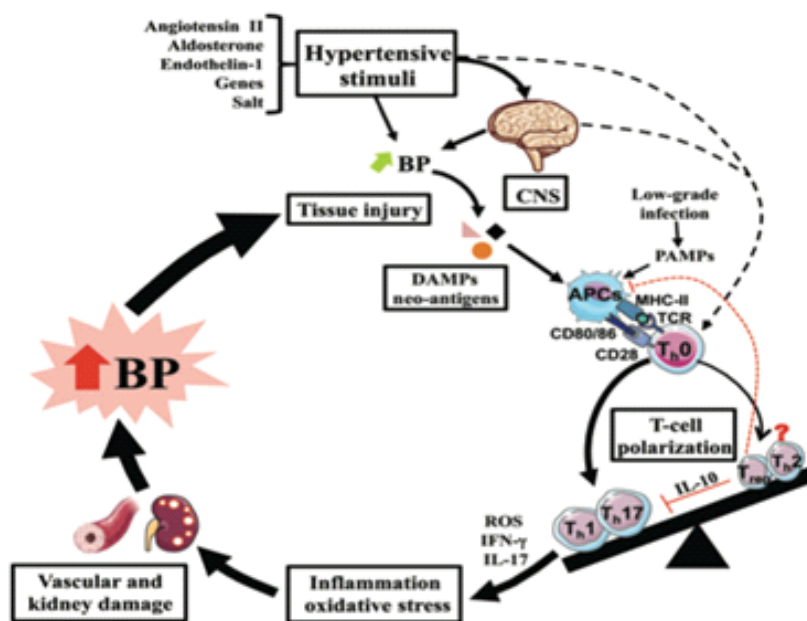


Figure 3. Role of T lymphocytes in Hypertension<sup>2</sup>

Patterns) and neoantigen. This condition may trigger APC activation and gradually also activate and polarize naïve CD4, effector T-lymphocytes via proinflammatory T-helper (Th-1) or Th-17 phenotype that contribute to damage to blood vessels and kidneys through the production of ROS, interferon- $\gamma$  and IL-17, and may trigger hypertension stability and progression of target organ damage. Whereas, regulatory T-lymphocytes provide a resistance to hypertension and related damage by producing IL-10 and suppresses innate and adaptive immune responses.<sup>1</sup>

### Proinflammatory Cytokines Release in Hypertension

In local inflammatory process, immune cells may enter into inflammation area through varied chemokines, including Monocyte Chemoattractant Protein-1 (MCP-1).<sup>12</sup> Once it is localized in the kidney, immune cells will release proinflammatory cytokines such as TNF- $\alpha$ , IL-6, IL-1 $\beta$ , IL-17 and interferon- $\gamma$ , where the number of proinflammatory cytokines will increase in the kidneys and contribute to local tissue damage. The role of proinflammatory cytokines in the pathogenesis of hypertension is supported by studies designed to test the inhibitory effect of cytokines on blood pressure. For example, when

etanercept is injected into the body to reduce biological activity of TNF- $\alpha$  in mice, it reduces the development of hypertension. It is associated with decreased expression of MCP-1 in renal cortex. The same event happens in the inhibition of IL-6. The occurrence of hypertension can be prevented and associated with decreased expression of IL-6, macrophage and T cell infiltration.<sup>15</sup>

APCs, like dendritic cells and monocytes or macrophages, will carry antigens that present in MHC-II towards naïve T cells (Th0) in the secondary lymphoid tissues, which will result in a differentiation in the form of T effector cells such as Th-1, Th-2, Th-17 and regulatory T cells that depend on the combined stimulation originating from different cytokines. Effector T cells lymphocytes and Tregs then migrate to vasculature tissues, the tunica adventitia and perivascular fat. Effector T lymphocyte cells (Th1 and Th17) will activate other immune cells and contribute to the onset of inflammation by producing proinflammatory cytokines such as interferon- $\gamma$ , IL-6 and IL-17. Whereas, regulatory T cells will suppress innate and adaptive immune response through the production of anti-inflammatory cytokines such as IL-10 and TGF- $\beta$ .<sup>2</sup>

Several studies have found that IL-6, IL-1 and TNF- $\alpha$  levels in hypertensive patients will be higher than those in patients with normal blood pressure.<sup>1</sup> In addition, in their study in 2015, Yao et al.<sup>3</sup> have concluded that cytokines play an important role in the pathogenesis of hypertension.

## CONCLUSION

Immunity, inflammation and hypertension have proven to be related to each other. The activation of those 3 factors triggers an inflammatory process, that will and increase the blood pressure and leads to organ damage. The innate immunity cells, such as neutrophil and macrophage, will produce ROS such as anion superoxide ( $O_2^-$ ) and hydrogen peroxide ( $H_2O_2$ ) that leads to reduced bioavailability of NO resulting in increase blood pressure. In addition to this, T Cell effector and regulatory lymphocyte will increase the differentiation throughout pro-inflammatory T Helper (Th-1) and Th-17 and produce the pro-inflammatory cytokines while in the contrary, the Tregs cells will suppress the activation of immune system and give protective effect against hypertension. A numerous research and study should be held to discover the relation between immunity, inflammation and hypertension in depth. So that the new methods in managing hypertension such as immunotherapy or even further might reduce the prevalence and incidence of hypertension.

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