# Immune system and Arterial Hypertension

Subjects: Pathology

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It is well-accepted that immune system and some cells from adaptive and innate immunity are necessary for the initiation/perpetuation of arterial hypertension (AH). However, whether neutrophils are part of this group remains debatable. There are evidences showing that neutrophil/lymphocyte ratio correlates with AH and is higher in non-dipper patients. On the other hand, the experimental neutrophil depletion in mice reduces basal blood pressure, nevertheless, their participation in AH is still controversial. Apparently, neutrophils may modulate the microenvironment in blood vessels by increasing oxidative stress favor the endothelial disfunction. In addition, neutrophils may contribute to the tissue infiltration of immune cells, secreting chemoattractant chemokines/cytokines and promoting the pro-inflammatory phenotype driving to the AH development. In this work, we discuss the potential role of neutrophils in AH by analyzing different mechanisms proposed from clinical and basic studies, with a perspective upon cardiovascular and renal damages relating to the hypertensive phenotype.

Keywords: Arterial Hypertension ; Immune System ; Kidney Disease ; Cardiovascular Risk ; neutrophils

## 1. Introduction

Arterial hypertension (AH) is a worldwide health problem and a huge economic burden in developing and developed nations, where the projected cost for 2030 in the United States of America (USA), for example, could reach values upward of USD 200 billion[1]. AH affects 31.1% of the population[2] and its inappropriate handling represents the leading risk factor for mortality worldwide[3][4]. In this sense, AH can promote chronic kidney disease, another critical cardiovascular (CV) risk factor, affecting ~13% of the population, and this remains one of the leading causes for progression to end-stage renal disease requiring renal replacement therapies. Therefore, AH, renal, and CV diseases are complex conditions with a demonstrated causal relationship, supporting the need of new alternatives for earlier detection and adequate treatment.

Above 70% of AH patients have no etiology and they remain categorized as “essential” or “primary”. The origin of this situation is complex and multifactorial, and it involves the interaction of several physiological systems boosted by exposure to lifestyle risk factors[2].

## 2. Role of Immune System in Hypertension

The evidence linking the immune system and AH dates from the 1960s[5][6]; however, the hypothesis of a causal role of the immune system in AH was proposed years later by Okuda and Grollman, where the transference of lymph node cells from rats with unilateral renal artery ligation induced AH in recipient rats[7]. Likewise, splenocytes from rats treated with deoxycorticosterone acetate (DOCA) salt induced AH in normotensive animals[8]. Conversely, the absence of thymus was sufficient to protect against AH development in the DOCA salt and genetic models[9][10], while thymus grafting from wild-type mice (WT) into nude mice (resistant to AH generation) restored their sensitivity to DOCA salt-dependent AH[9]. In this context, the most recent evidence suggests that the autonomic nervous system may control the immune system[11], since there is a neuroimmune boost at the splenic level during AH[12]. This emerging evidence proposes the autonomic nervous system as a modulator of the immune system in AH, beyond its classic effects on heart rate, vascular tone, and sodium excretion.

Guzik et al. found that T lymphocytes and not B lymphocytes were necessary for AH development and vascular dysfunction, as a result of DOCA salt or angiotensin II (AngII)[13]. Years later, these findings were confirmed by other groups and in other experimental settings of AH that included salt sensitivity[14][15]. In addition, it was suggested that T lymphocytes can be activated by a cholinergic impulse, through a vagus nerve connection to the spleen, promoting their migration to the target organs and contributing to AH[12].

In the last 10 years, different lymphocytes have been studied in order to establish their role in blood pressure control. On the adaptive immunity side, $CD8^+$ T cells apparently participate in AH by increasing renal sodium reabsorption through the activation of specific transporters[16][17]. On the other hand, $CD4^+$ lymphocytes, both T helper 1 ($T_H1$) cells and $T_H17$ cells, accumulate in the vessels, spleen, and kidney during AH[18][19]. Causal involvement of $CD4^+$ cells was demonstrated by blood pressure modulation in various studies using genetically lacking $CD4^+$ lymphocytes animals or knockout (KO) animals for cytokines from $T_H1$ or $T_H17$ cells[20][21][22]. However, since other cells can also secrete these cytokines, the involvement of $T_H1$ and $T_H17$ has not been entirely clarified. Contrarily, it has been proposed that the activity of regulatory T (Treg) cells, a subpopulation of $CD4^+$ lymphocytes, could be decreased in AH. Different studies have shown a decreasing Treg cell population in plasma, spleen, or kidney during AH, while the selective depletion of Treg cells raises blood pressure and exacerbates target organ damage in experimental models[23][24]. In all these studies, the adoptive transfer (or activation) of Treg cells prevented AH and CV damage in response to AngII or aldosterone, supporting their promissory use in cell therapy strategies.

Regarding the innate immune cells, unconventional γδ T cells that present a rapid innate-like response initiating immune response are involved in AH development by regulating vasoconstriction and by secreting large amounts of interleukin (IL)-17[25]. These observations delineated new perspectives for IL-17, beyond $T_H17$ lymphocytes. On the other hand, dendritic cells (DCs) are considered as critical for the AH since there is evidence showing that they participate in $T_H1$ and $T_H17$ cell activation, by taking up neoantigens and through isoketal formation after Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation[26][27]. Moreover, van Beusecum et al. demonstrated that the specific deletion of serum glucocorticoid kinase 1 (SGK1) in DCs prevents AH, vascular dysfunction, and kidney inflammation induced by *N*-Nitro-l-arginine methyl ester (L-NAME) plus a high-salt diet[28]. Apparently, SGK1 may function as a sodium sensor, allowing DC activation; this effect was also observed in $CD4^+$ lymphocytes[29]. The orchestrated responses by DCs are supported by a recent study showing that the absence of DCs protects against renal dysfunction, kidney damage, and CV inflammation/fibrosis in an AngII-dependent hypertensive model[30]. The protective effect of DC depletion for AH development was also corroborated in the nephrectomy aldosterone salt (NAS) model, which involved the prevention of cardiac hypertrophy and fibrosis[31]. Finally, monocytes and macrophages have also been implicated, principally due to their increase and the phenotypic changes in vasculature, kidney, heart, and brain during AH[32], promoting fibrosis and maintaining AH through NADPH oxidase-dependent mechanisms in vascular tissue[33][34]. In general, the accumulative evidence suggests that innate and adaptive immunity are involved in the pathophysiology of AH and in associated end-organ damage. However, the specific immune cells that promote AH and tissue damage are still under study, where the role of neutrophils remains to be addressed.

## References


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