

Mechanisms in hypertension and target organ damage: Is the role of the thymus key? (Review)

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Abstract. A variety of cells and cytokines have been shown to be involved in the whole process of hypertension. Data from experimental and clinical studies on hypertension have confirmed the key roles of immune cells and inflammation in the process. Dysfunction of the thymus, which modulates the development and maturation of lymphocytes, has been shown to be associated with the severity of hypertension. Furthermore, gradual atrophy, functional decline or loss of the thymus has been revealed to be associated with aging. The restoration or enhancement of thymus function via upregulation in the expression of thymus transcription factors forkhead box N1 or thymus transplantation may provide an option to halt or reverse the pathological process of hypertension. Therefore, the thymus may be key in hypertension and associated target organ damage, and may provide a novel treatment strategy for the clinical management of patients with hypertension in addition to different commercial drugs. The purpose of this review is to summarize and discuss the advances in our understanding of the impact of thymus function on hypertension from data from animal and human studies, and the potential mechanisms.

Contents

1. Introduction
2. Potential role of the thymus in hypertension
3. Aging, thymosin β 4 and hypertension
4. Conclusion and prospects

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1. Introduction

Hypertension is characterized by the elevation of arterial pressure, and can be complicated by damage and metabolic changes in the heart, blood vessels, brain, kidney, retina and other target organs. It is a multifactorial disease and various immune cells and factors have been shown to be involved (Fig. 1) (1). There have been increases in the incidence and mortality rates of patients with heart and cerebrovascular disease; therefore, reducing the incidence and mortality rates of heart and cerebrovascular disease in patients with hypertension is the ultimate goal of antihypertensive therapy. However, even when blood pressure is under control, organ damage and abnormal metabolism may not be completely resolved, which suggests that other mechanisms may be involved in, or contribute to, the complex pathological processes of hypertension and may not be eliminated by current drug strategies. Antihypertensive therapy requires the establishment of blood pressure control (2). Therefore, it is of clinical and practical significance to investigate the mechanism of hypertension.

The thymus, as a key organ in T lymphocyte ontogenesis, has been shown to be crucial in optimizing immune system function throughout life (3-7), therefore, the pathological processes of high blood pressure are considered to be closely associated with the thymus. Studies have revealed that the thymus exhibits constant atrophy or hypofunction with age (8). Fukuda *et al* (9) suggested that the values of thymus weights were lower in Spontaneously hypertensive rats (SHR), compared with those in Wistar Kyoto (WKY) rats, when they investigated age-related changing in hematological values, serum biochemical constituents, and weights of various organs in both genders of SHR/Izm, Stroke-prone SHR and WKY/Izm rat strains. A previous study by Svendsen *et al* found that the salt-dependent phase of deoxycorticosterone acetate salt hypertension did not develop and the decreased perivascular infiltration of immune cells following renal infarction was not present in athymic 'nude' mice. However, if the thymus gland was transplanted into these athymic mice, then the capacity for developing salt-driven hypertension was restored (10-13). Ba *et al* showed that the thymus transplanted from neonatal normotensive Wistar rats to the prehypertensive SHR strain delayed the onset of hypertension from 5 to 32 weeks and decreased blood pressure in hypertensive adults; it is known that the SHR strain has normal blood pressure at birth and

gradually develops high blood pressure from ~5 weeks of age, reaching maximal levels at ~15-20 weeks of age (14). Therefore, the thymus may be involved in the process of hypertension. However, the mechanism of thymus function in the process of hypertension remains to be fully elucidated. The purpose of this review was to summarize and discuss advances in our knowledge of hypertensive vascular disease by the effect of thymus function on hypertension, with a particular focus on the mechanism underlying the effect of thymus function on hypertension.

2. Potential role of the thymus in hypertension

Thymus function and inflammatory procedure. The thymus is known to be essential in T cell development and maturation. The thymus is where the T cell repertoire is generated, and where T cells undergo positive and negative selection, leading to a wide functional MHC-restricted naïve T cell receptor $\alpha\beta$ repertoire (15,16). In the development of T cells, they migrate within distinct thymus microenvironments, where they interact with stromal cells to provide signals crucial to the survival, proliferation, differentiation and selection of thymocytes (17-19). Naïve T cells can differentiate into helper T cells (Th), regulatory T cells (Tregs) and cytotoxic T cells. The generation and maturation of the specific T cell lineage involves specific and complex processes within the thymus, and several signaling pathways are involved in these processes. If thymocytes respond spontaneously to these antigens, they undergo negative selection, through apoptosis, or into Treg lineages (17). It is now well established that Tregs are produced via two main pathways *in vivo*. The majority of functionally mature Treg cells are produced in the thymus, where recognition of self-antigen by certain clones leads to their deviation into the thymus-derived forkhead box (Fox)p3⁺ Treg cell lineage (20,21). Th cells can secrete interleukin (IL)-4, IL-17 and interferon (IFN)- γ . In addition, Tregs can secrete IL-10. IL-4 regulates the proliferation of activated B-cells and mast cells (22-25). In the absence of vascular tissue, the presence of IL4 promotes the substitution of activated macrophages into M2 cells and inhibits the activation of classical activated macrophage M1 cells. Increased macrophage repair (M2) combined with the secretion of IL-10 and transforming growth factor (TGF)- β results in a reduction of pathological inflammation (26-28). IL-17 is involved in the induction and regulation of pro-inflammatory responses. IL-17 induces the production of other cytokines, [IL-6, TGF- β , tumor necrosis factor (TNF)- α , granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor and IL-1 β], chemokines (IL-8, growth regulated oncogene- α and monocyte chemoattractant protein-1), and prostaglandin, including prostaglandin E2, from fibroblasts, endothelial cells and several other cell types (29-33). All of these cytokines, chemokines and inflammatory cells are involved in the inflammatory procedure (34,35). By contrast, these factors and cytokines also promote the inflammatory response. Therefore, changes in thymus function can affect the inflammatory response.

Low-grade inflammation has been shown to be crucial in the pathogenesis of hypertension and involved in several processes that promote the development of blood pressure (36-39). Inflammatory factors in the process of inflammation can

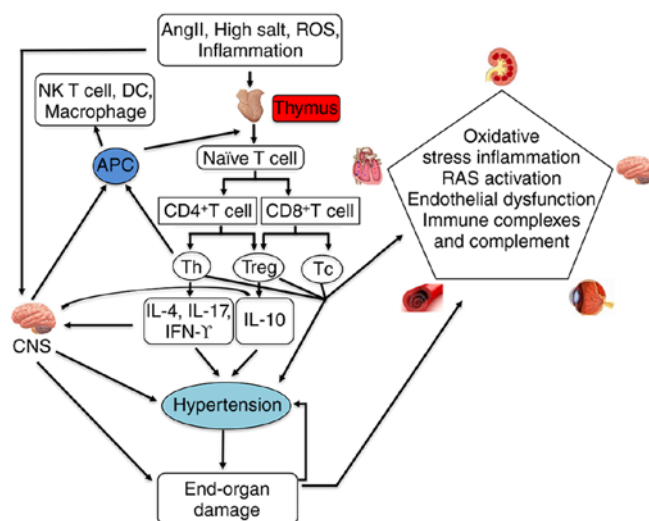


Figure 1. Factors involved in hypertension. Various types of cells and cytokines and the autonomic nervous system are affected by thymus function, and may be involved in the process of hypertension and target organ damage. Ang II, angiotensin II; ROS, reactive oxygen species; NK, natural killer T cell; DC, dendritic cell; APC, antigen-presenting cell; Th, T helper; Treg, regulatory T cell; Tc, cytotoxic T cell; IL, interleukin; IFN, interferon; CNS, central nervous system; Ras, renin-angiotensin system.

cause endothelial damage and activate the renin system, and studies have demonstrated that activation of the intrarenal renin-angiotensin system (RAS) and endothelial dysfunction are important in the development of hypertension (40-42). Nitric oxide (NO) and superoxide may cause endothelial dysfunction in hypertension, and the balance between them may be more important than the absolute levels of either alone (43,44). Other cross-sectional studies have shown a correlation between C-reactive protein (CRP), TNF and IL-6 and essential hypertension (37,45-47). Elevation of the serum concentrations of CRP and cytokines demonstrates that low-grade inflammation is present in hypertension (48,49). The association between CRP and systemic hypertension has been established in multiple cross-sectional studies, particularly following the emergence of the high sensitivity CRP assays capable of detecting levels that were earlier considered to be normal (39,50-54). Higher levels of CRP may contribute to the development of systemic hypertension by reducing the production of NO in endothelial cells, increasing the production of endothelin 1 and leading to vasoconstriction (39,55-57).

Evidence suggests that oxidative stress and angiotensin II (Ang II) are critical in the pathogenesis of hypertension and vascular endothelial dysfunction (43,44,58). Studies have shown that Ang II induces severe inflammation and activates redox-sensitive genes via the activation of nuclear factor (NF)- κ B, independent of blood pressure in double transgenic rats harboring human renin and human angiotensinogen genes (43,59-61). It is well known that these cells, inflammatory factors and oxidative stress are involved in the process of target organ damage, as mentioned above (62-64). The thymus may be involved in the process of hypertension and target organ damage by regulating the inflammatory reaction.

Thymus function and the immune system. In 1970, Ebringer and Doyle found that serum immunoglobulin levels were

significantly increased in 30% of patients with hypertension, and with the rapid development of clinical immunology, increasing evidence has shown that hypertension is always accompanied with immune dysfunction and there are immune factors involved in the complications of hypertension (65-67). Several studies have shown that, in hypertension, T cells can cause high blood pressure, vascular disorders and kidney disease, and the possible mechanisms include the release of cytokines directly affecting vascular and renal function or indirectly stimulating cells to release cytokines (68). The thymus is an important and essential site for the generation and maturation of T cells *in vivo*, as this microenvironment induces and supports lineage commitment, differentiation and the survival of thymus-seeding cells.

T cells and their subsets are involved, either directly or through the secretion of certain factors, in the process of hypertension. The selection of one of the T cells subsets, Tregs, in the thymus is essential for preventing autoimmune diseases (69). Tregs of the CD4⁺CD25⁺FOXP3⁺ phenotype are generated in the thymus, and are critical for the maintenance of immune homeostasis and the suppression of naturally occurring self-reactive T cells (70-72). Previously, it was shown that changes in the immune system are important in the SHR model and other models of hypertension; T cell activation and vascular inflammation may contribute to the formation of high blood pressure (48,73-76).

There is emerging evidence suggesting that the immune response is significant in the pathogenesis of hypertension (77-79). The classical immune system is considered to consist of two parts: Innate and adaptive immunity (77,80-82). Innate immune responses mediated by macrophages are triggered through toll-like receptors. In animal models of hypertension, the infiltration of inflammatory cells from the innate immune system, including dendritic cells (DCs), natural killer cells and predominantly monocytes/macrophages has been documented in the perivascular fat and adventitia of blood vessels, and in target organs including the kidney and heart (77,83). Various studies have suggested a role for macrophages in the pathogenesis of hypertension and vascular damage (84-87). Macrophages generate superoxide when NADPH oxidase is activated by Ang II or mineralocorticoids, and this may lead to vascular wall remodeling and contribute to blood pressure (BP) elevation (49,88). Therefore, the role of monocytes/macrophages has been expanded (89-91).

Adaptive immune responses are characterized by activated lymphocytes, and interact with innate immunity in the pathophysiology of cardiovascular disease and hypertension (92-94). Several studies have confirmed that T cells and their subsets, including effector T lymphocytes and Treg cells, are involved in the process of hypertension (95-97). Rodriguez-Iturbe and Johnson (98) showed that T lymphocytes contribute to renal changes and BP elevation in rodents, which others have since confirmed and extended (99). It has been reported that T-effector cells that mediate, in part, the pressor effects of Ang II are predominantly CD8⁺ rather than CD4⁺ (100). Studies have shown that immune cells are involved in target organ damage caused by hypertension (63,96). Possible mechanisms for their involvement in the process of hypertension have been investigated previously. The change in thymus function can affect the function of macrophages and B cells. The

monocyte-macrophage system is crucial in innate immunity and in the initiation of the adaptive immune response (101-103). Plasma cells derived from B cells are involved in the humoral immune response. In addition, DCs are significant in establishing self-tolerance and inducing antigen-specific immunity through their ability to present self-antigens to developing T cells in the thymus (104-106). Therefore, the thymus may be involved in the process of hypertension via the immune system.

Thymus function and the renal system. Inflammation is associated with several hypertensive models in the kidney, including two-kidney-one-clip hypertension and salt-sensitive hypertension (107). T lymphocytes and macrophages infiltrate the kidneys in various models of hypertension (108-111). Changes of thymus function can also affect the function of macrophages and T lymphocytes; therefore, changes in thymus function can affect kidney function. The effects of RAS activation on kidney function and its role in hypertension have been investigated extensively (112). Here discusses the role of immune cells, induced by changes in thymus function in the kidney, in hypertension.

As early as 1964, the injection of kidney extract in normal rat hypertension confirmed the role of autoimmunity in the renal infarct model (113). It was observed that the infiltration of immune-cells and increased activity of NF- κ B in the kidney occurred at a prehypertensive age and progressively increased with age in the SHR model, which was inhibited by a broad-spectrum inhibitor, pyrrolidine dithiocarbamate (114,115). Other studies have shown that hypertension induced by Ang II or high salt can lead to the activation of T cells and the subsequent entry of activated T cells into the peripheral blood vessels and kidney (96,116). Studies have also shown that the cells which accumulate in the kidneys and blood vessel release pro-inflammatory cytokines, and promote vasoconstriction and sodium retention, leading to high BP (64,96,117,118).

Yang *et al* (119) found that modulation of NADPH oxidase-derived oxidative stress and immune cell function via A3 receptor signaling may be critical mechanisms in the development of hypertension and associated target organ damage. Their data showed that these changes in the innate and adaptive immune systems in A3^{-/-} mice assisted in eliminating pathological changes in the renal and cardiovascular systems following uninephrectomy-high salt and protected the A3^{-/-} mice from developing hypertension. This finding is consistent with previous studies of the role of T cells in renal injury and hypertension (63,120).

Thymus function and the autonomic nervous system (ANS). The ANS, which is composed of sympathetic and parasympathetic (vagal) innervation of the heart and predominantly sympathetic innervation of the vascular system, controls and regulates the secretion and activity of various organs, blood vessels, smooth muscles and glands, and is involved in the endocrine regulation of glucose, fat and fluid, electrolyte metabolism, body temperature, sleep and BP (121,122). There is evidence that the ANS is key in regulating the immune system (123-127), and there is substantial evidence that the thymus receives dense sympathetic innervation, which

originates from postganglionic neurons in the upper paravertebral ganglia of the sympathetic chain, particularly the superior cervical and stellate ganglia (128-131). The importance of the ANS has been recognized to be of main clinical and therapeutic significance in the progression of chronic cardiovascular disease, primarily as a result of changes in the immune system (132-134). Previous studies have shown that thymocytes and thymic epithelial cells express functional adrenergic receptors (135,136). Norepinephrine (NE) released from the sympathetic nervous system (SNS) can influence immune responses and innervate the thymus (137,138). Thymus involution is associated with increased noradrenergic nerve fiber density and NE concentration, accompanied with immunosuppression in male rats and mice (139). Several studies have also shown that the effect of the SNS on thymic cell maturation and development is the outcome of multiple interactions between sympathetic and other neurotransmitters and the endocrine system, and may also depend on the immunological status of the host, under physiological conditions (22,131,140,141).

The SNS is also activated in hypertension, influencing renal perfusion and oxygenation (142). In the majority of studies in humans and animal models of hypertension, drugs and interventions can reduce BP and prolong survival rates by activating the parasympathetic nervous system (vagal), by blocking or inhibiting the SNS and the RAS (143-149). Early studies have shown that experimental lesioning of specific circumventricular organs of the forebrain, including the subfornical organ, the anteroventral third ventricle region involving the inferior aspects of the lateral terminalis, prevents the formation of several forms of experimental high BP (150,151). Increasing evidence indicates that the cardiovascular damage caused by overstimulation of the SNS and RAS, their α - and β -adrenergic receptors, and Ang II AT1 receptors is mediated through proinflammatory activation of the immune system (152-155).

Resistant hypertension refers to the case of patient BP remaining $>140/90$ mmHg following the use of a variety of antihypertensive drugs (156-158). Traditional treatments are not effective, therefore, it is necessary to develop novel therapeutic approaches, and highly selective renal denervation (RDN) is one of these approaches (159-161). RDN, a catheter-based approach developed to disrupt the renal sympathetic nerves using radiofrequency energy, is a promising therapy for resistant hypertension (142). Studies have shown that the efficacy of RDN in different models of hypertension requires examination as a method that matches the causal mechanisms of the hypertension (161-165). Reported for the first time in 2009, the ablation of renal artery denervation technology, as a sympathetic nerve and RAS activity non-drug block technique, has been successfully applied to the clinical treatment of resistant hypertension (166). In a relatively small number of patients, the first clinical study showed that this technique appeared to be safe and effective (166-168). Systolic BP and diastolic BP were reduced by 22/11 and 27/17 mmHg at 6 and 12 months post-RDN, respectively, and no serious adverse events had occurred at the follow-up at 1 year. Worthley *et al* (169) adopted a single electrode radiofrequency ablation catheter for RDN treatment in a prospective, multicenter, nonrandomized cohort study, which showed that the patient BP was also significantly reduced at 6 months by

26/10 mmHg, compared with preoperative BP. The early stage of the preliminary results of transcatheter renal artery ablation treatment technology show it can safely and effectively reduce BP levels in patients with resistant hypertension. Consequently, it is suggested that RDN decreases sympathetic activity and may potentially improve renal oxygenation, resulting in altered sodium handling by the kidneys and a decrease in peripheral vascular resistance, thereby removing the trigger for hypertension.

Taken together, the ANS may be involved in the process of hypertension by regulating the function of the thymus.

3. Aging, thymosin $\beta 4$ and hypertension

The thymus is the main immune organ capable of generating T cells throughout life, and is crucial for the development, selection and maintenance of peripheral T cells. It is well documented that aging leads to an increase in infection and mortality rate, which has a negative impact on the immune response. Aging reduces immune function, partly due to thymic involution leading to a marked loss of progenitors, epithelial cells and differentiating thymocytes, causing a decline in the production of naïve T cells by the thymus (170-176).

The thymus transcription factor forkhead box N1 (Foxn1) is the most important factor for complete physiological function of the thymus (174,177-179). With atrophy of the thymus, the expression of the thymus aging-associated gene Foxn1 decreases, which leads to the downregulation of Foxn1 with age. Increasing the expression of Foxn1 can improve the function of the thymus, and even promote regeneration of the thymus by increasing the expression of Foxn1 (180). Žuklys *et al* (181) reported that Foxn1 regulates the expression of genes involved in antigen processing and thymocyte selection, in addition to the transcriptional control of genes involved in the attraction and lineage commitment of T cell precursors. Therefore, there is evidence to suggest that the thymus Foxn1 may be involved in the process of high BP. In previous studies, the atrophy of thymus organs in hypertensive mice has been confirmed, however, the specific change in thymus function remains to be fully elucidated.

Thymosin $\beta 4$ (T $\beta 4$), a peptide of 43 amino acids first identified by extraction from the calf thymus, is the most abundant member of the highly conserved β -thymosin family (182,183). It is part of the thymosin fraction 5, a partially purified thymic preparation, which is involved in thymus-dependent lymphocyte regulation (184,185). The functions of T $\beta 4$ include the involvement of thymus-dependent lymphocyte maturation and a variety of cellular processes, including cell migration, chemotaxis, maintenance of cell shape and cell division (186-189). It is well documented that T $\beta 4$ can prevent inflammation and fibrosis, promoting healing in the eye, skin, and heart, and can control cell morphogenesis and motility by regulating the dynamics of the actin cytoskeleton (190-193). In addition, T $\beta 4$ can promote repair and reduce late fibrosis in kidney injury, and is increased in vascular, tubulointerstitial and myocardial fibrosis (194-199). T $\beta 4$ can also enhance endothelial cell differentiation and angiogenesis (200).

Cavasin *et al* found that a cytosolic enzyme prolyl oligopeptidase (POP) involved in the metabolism of several peptidic hormones and neuropeptides is widely distributed

in the CNS, peripheral tissues and body fluids, and is responsible for the release of N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) from its precursor T β 4 (201-205). Ac-SDKP can reduce collagen deposition, and reverse inflammation and fibrosis in the heart and kidneys when it is chronically infused into rats with hypertension and myocardial infarction (206-211). In addition, decreased endogenous levels of Ac-SDKP promote organ fibrosis, including the vasculature, heart and kidneys (1,196,208,212-214). Previous studies have shown that oral administration of POP inhibitors significantly reduced endogenous levels of Ac-SDKP in the heart and kidney in normal rats, and Ac-SDKP assisted in regulating collagen protein content, through promoting collagen deposition, vascular fibrosis and glomerular sclerosis.

According to the above findings and previous studies, it appears that the expression of Ang II type 1 receptor-associated protein (ATRAP) is downregulated, due to the increase of Ang II, resulting in a decline in function of the thymus and a decrease in expression of the thymus transcription factor Foxn1, causing an imbalance of T cell subsets. ATRAP is a transmembrane protein localized in intracellular trafficking vesicles and the plasma membrane (215,216). In addition, the secretion of thymosin prevents target organ damage and fibrosis, which slows or reverses the process of hypertension. T β 4 is decomposed into Ac-SDKP under the action of POP, which can reduce the damage to the target organ, ameliorating or improving BP. Based on the above, a proposed mechanism of thymic function involved in the process of hypertension has been hypothesized (Fig. 2). The change in thymus function provides a novel target for the treatment of hypertension.

4. Conclusion and prospects

Inflammatory and immune system mechanisms are crucial in the pathophysiology of hypertension and cardiovascular disease. T lymphocytes mature in the thymus and are important in the inflammatory response and the immune response, which can induce hypertension. The important mechanism for regulating the inflammatory response involves tissue and circulating leukocytes and macrophages. T lymphocytes are involved in the pathogenesis of hypertensive vascular remodeling. An imbalance between Tregs and T effector lymphocytes may be the cause of elevated BP and the progression of vascular damage.

T lymphocytes and macrophages infiltrate the kidneys in various models of hypertension. The aggregation of inflammatory factors, complement and immune response in the kidney and renal vascular injury can cause hypertension. The ANS is involved in the process of hypertension by modulating the immune response.

Based on previous studies, the changes in thymus function appear to have an effect on the process of hypertension. The proposed mechanism underlying the involvement of the thymus in the process of hypertension is as follows: Ang II may affect the function of the thymus and expression of the thymus transcription factor Foxn1 through the downregulated expression of ATRAP, and then affect the balance of T lymphocytes, which causes endothelial dysfunction and target organ damage, including fibrosis, thereby leading to hypertension.

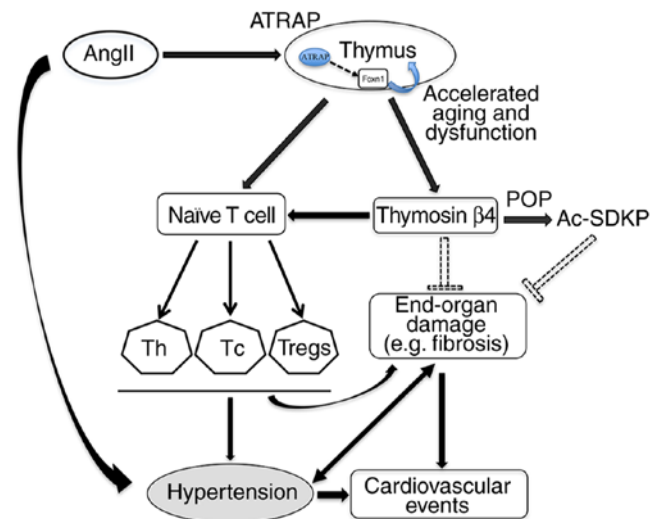


Figure 2. Role of the thymus in hypertension and target organ damage. Thymus dysfunction leads to the imbalance of T cell subsets and a change in the secretion of T β 4, thereby aggravating the progression of hypertension and target organ damage, in addition to other cardiovascular events. T β 4, thymosin β 4; Ang II, angiotensin II; ATRAP, Ang II type 1 receptor-associated protein; Foxn1, forkhead box N1; POP, prolyl oligopeptidase; Ac-SDKP, N-acetyl-seryl-aspartyl-lysyl-proline; Th, T helper; Tc, cytotoxic T cell; Tregs, regulatory T cells.

In conclusion, novel data increasingly suggests the potential for novel targets involved in thymus function for therapeutic intervention to modify the course and reduce events in cardiovascular disease and hypertension, as evidence has increasingly implicated thymus-related mechanisms. Further investigations on the changes of thymus function are likely to assist in the development of novel therapeutic targets that may improve outcomes in hypertension and cardiovascular disease, and assist in identifying novel approaches for the treatment of hypertension and vascular disease.

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Availability of data and materials

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Authors' contributions

XD, ZW and CL conceived and designed the paper. XD, LH and YC analyzed the relevant literature. XD, JW, JL, FW, JS and YZ drew the figures and XD wrote the paper.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no competing interests.

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