REVIEW ARTICLE

Vascular Ultrastructural Changes in Hypertensive Rodent Models: A 15-Year Scoping Review

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ABSTRACT

Understanding ultrastructural changes in vascular tissue provides critical insights into the pathophysiology of hypertension, a leading global cause of mortality. This scoping review aims to offer a comprehensive overview of vascular ultrastructural changes in hypertensive rodent models over the past 15 years. Following the Arksey and O'Malley protocol, we conducted a scoping review of relevant literature. This involved defining research questions, identifying and selecting pertinent studies, data extraction, synthesis, and reporting. Searches encompassed Google Scholar, PubMed, Scopus, and ScienceDirect. Thirty studies were included, showcasing diverse methodologies, objectives, and findings. These studies investigated various hypertensive models, different vessels, and multiple quantitative, semi-quantitative, and qualitative parameters of vascular ultrastructure, along with different intervention strategies. This review provides a synthesis of existing knowledge on vascular ultrastructural changes in hypertensive rodent models and discusses relevance of rodent models to human hypertension, functional implications of ultrastructural changes and pharmacological interventions targeting these changes thus serving as a resource for researchers studying hypertension pathophysiology to identify therapeutic targets or assess novel interventions.
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INTRODUCTION

Hypertension is the leading cause of death globally, accounting for 10.4 million deaths per year (1). An estimated 1.39 billion people had hypertension in 2010 (2). Tackling this multifactorial disease requires an understanding of its pathophysiology to establish evidence-based guidelines for treatment.

Studying ultrastructural changes in vascular tissue offers valuable insights into the pathophysiology of various vascular diseases, including hypertension. Ultrastructural changes often precede macroscopic manifestations of vascular diseases. Detecting these changes at a cellular and subcellular level can provide early indications of disease progression, enabling timely intervention and preventive measures (3). These ultrastructural alterations can reveal underlying molecular and cellular mechanisms involved in the development and progression of vascular diseases such as hypertension (4).

Histological and ultrastructural results are often qualitative, categorical, and descriptive. They include changes in cell shape and arrangement, nuclear orientation, and irregularity. In contrast, semi-quantitative and quantitative data have a numerical value and may include measurements of thickness, proportions, and density of cell distribution (5–7).

The purpose of this scoping review is to provide a comprehensive overview of the current state of knowledge regarding vascular ultrastructural changes in hypertensive rodent models, to inform future research, advance understanding of hypertension pathophysiology, and ultimately improve clinical management of hypertensive vascular diseases. A 15-year span was selected to capture the most recent advancements in the field, ensuring that the review reflects the latest research trends and technological innovations, which are crucial for a thorough understanding of these vascular changes.

MATERIAL AND METHODS

Scoping Review Protocol

The protocol adopted for this scoping review follows the framework established by Arksey and O'Malley (8), encompassing five phases:
i. identification of research questions
ii. identification of relevant articles
iii. selection of relevant articles
iv. data charting
v. collating, summarising, and reporting the findings.

Identification of Research Questions

The fundamental aim of the scoping review is to identify the research question(s) essential for constructing a robust search strategy. This scoping review aimed to find the answer to one research question: "What is known from existing literature regarding research of vascular ultrastructural changes in hypertensive rodent models in the past 15 years?"

Identification and Selection of Relevant Articles

An extensive search of original peer-reviewed English articles published between 2010 and 2024 was conducted across seven databases, namely AHA Journals, Google Scholar, OVID, PubMed, Scopus, ScienceDirect, and Semantic Scholar. Nine primary search terms were employed, utilizing Boolean operators, and derived from Medical Subject Headings (MeSH) and Education Resources Information Centre (ERIC) databases. The ultimate search terms utilised were "electron microscopy" AND "vessel hypertension" and "ultrastructure" AND "rat hypertension" OR "vessel hypertension".

The articles sourced from the seven databases were downloaded and manually transferred to Google Drive. The initial search spanned from April 2023 to December 2023. Following the removal of duplicates, the remaining articles underwent scrutiny based on predetermined inclusion and exclusion criteria based on title, abstract, and full text. Subsequently, two separate researchers independently reviewed the shortlisted articles, with consensus determining acceptance or rejection according to the predefined criteria. In the event of disagreement, a third independent researcher would conduct further assessment.

Data

Once the articles were selected, several important data were extracted to provide a good summary of the content. Among the data extracted included (i) author(s), (ii) date of publication, (iii) title, (iv) purpose of study, (v) type of model, (vi) characteristics of animals used, (vii) types of vessels harvested and processing methods, (viii) modalities used, (ix) outcomes and (x) ultrastructural findings.

Collating, summarising, and reporting the findings

A content analysis was used to determine each study's primary criteria and to summarise its scope. We studied the selected articles to gain a general understanding of parameters to study ultrastructural changes in hypertensive rodent models. The extracted data were subcategorised. The independent researchers then accepted or reformulated each subcategory. Figure 1 depicts the study's scoping review process.

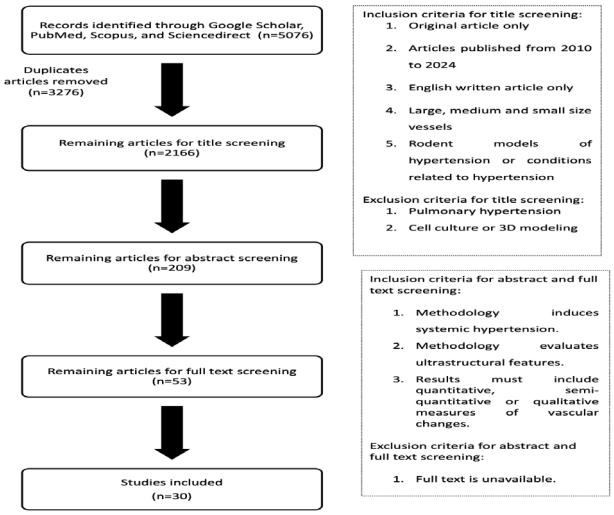

Figure 1: Articles identification and screening process.

RESULTS

Literature Search

From the keyword search, 5076 articles were obtained. Articles that were duplicates and found in multiple databases were removed. The eligibility of 2166 titles were evaluated based on the study inclusion and exclusion criteria. Articles that did not fulfil the determined criteria were removed. A total of 209 articles were screened according to the eligibility criteria for abstract selection. Based on these criteria, 53 articles were selected and screened according to the eligibility criteria for full article selection. Thirty articles were selected for the final review.

Study Characteristics

Hypertensive Rat Models

Eighteen studies focused on spontaneously hypertensive rats (SHR), a well-established model for hypertension. Hayden et al. (2012) used transgenic heterozygous (mRen2)27 (Ren2) rats that overexpressed the mouse renin gene. These rats have increased local tissue levels of angiotensin II, low plasma renin activity, and increased plasma levels of aldosterone (7).

The most common pharmacologically induced model was through L-NAME and NO synthase blockade, which was used in six studies. This model causes a reduction in NO synthase activity, which leads to hypertension and

increased vascular dysfunction (9-11).

Other pharmacologically induced models included the Angiotensin II infusion model, which showed impaired endothelial-dependent relaxation and ADMA administration, causing inhibition of NO synthesis (12,13).

Xian et al. (2012) were able to produce a hypertensive model using the consumption of repeatedly heated palm oil because free radicals generated by repeated heating might impair the nitric oxide bioavailability (14). The two other diet-induced models were the high fat-induced model and high salt diet in Dahl salt-sensitive rats (14, 15). Dallak et al. (2019) used a high carbohydrate and fat diet (HCFD) + streptozotocin (STZ) induction to produce a rat model that was diabetic and hypertensive (4).

Additionally, Moustafa (2010) noted premature morphological changes in the thoracic aorta in a menopause-induced rat model, and Olgar et al. (2018) demonstrated that reactive oxygen species (ROS) plays a major role in the impairment of electrical and mechanical dysfunction in the cardiovascular system of the aging rat model (17,18).

Types of vessels & harvesting techniques

The majority of the studies used the thoracic aorta and mesenteric arteries. Han et al. (2013) used the caudal artery, and Kristek et al. (2017) used the iliac arteries as well as the thoracic aorta (13,19). All arteries were harvested and fixed in a similar fashion using standard fixation techniques.

Parameters used to assess ultrastructural changes

We first defined qualitative parameters as those yielding non-numerical or observational results and semi-quantitative parameters as those that provide estimated or derived quantities, whereas quantitative parameters yielded numerical results (5).

The studies used quantitative, semi-quantitative, and qualitative parameters to describe the vascular ultrastructural changes in hypertensive rodent models. Quantitative measurements included intimal wall thickness, endothelial cell volume density, tunica media thickness, young collagen production, and the volume densities of smooth muscle cells, extracellular matrix, collagen fibre size, and lumen size. Semi-quantitative parameters focused on the number of fibroblast-like cells in the intima and the density of cytoplasmic vacuoles and processes in the media. Qualitative evaluations examined endothelial architecture, basement membrane structure, interstitial collagen accumulation, subendothelial space, internal elastic lamina, aortic wall remodelling, and the organisation of the extracellular matrix. All studies used either a scanning electron microscope or a transmission electron microscope to view these ultrastructural changes.

Key Qualitative Findings of Ultrastructural Changes

Normal vascular ultrastructure (Figure 2A) is characterised by a well-organised and consists of three main layers: the tunica intima, tunica media, and tunica adventitia. The tunica intima features a smooth endothelial lining. Beneath this layer, the internal elastic lamina provides structural support, while the tunica media comprises smooth muscle cells (SMCs) that maintain vascular tone and regulate blood pressure through contraction and relaxation. The tunica adventitia consists of connective tissue that houses nerves and blood vessels, providing further structural integrity. Figure 2B shows some examples of common hypertensive ultrastructural changes, which will be discussed further.

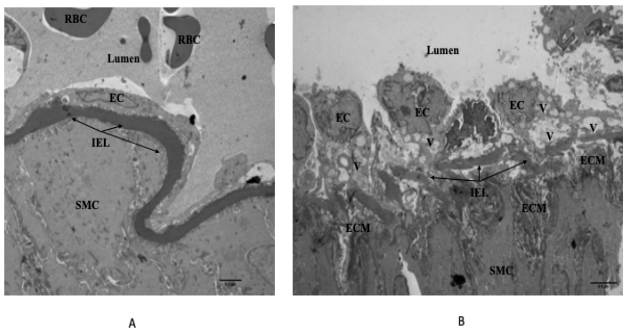

Figure 2: Electron microscopic photomicrographs of rat vessel at a magnification of x 3.2K. (A) Normal vascular ultrastructure (B) Ultrastructural findings in a hypertensive rat model (L-NAME induced) EC: Endothelial cell, IEL: Internal elastic lamina, V: Vacuole, ECM: Extra cellular matrix, SMC: Smooth muscle cell

Common features of ultrastructural changes found in the hypertensive rat models include various aspects of endothelial dysfunction seen in the tunica intima (7,10-11,17,20–22), such as decreased adhesion, irregular morphology, damage to the luminal surface, and leukocyte adhesion (4,7,9,11,15,23–25). Leal (2019), Moustafa (2010), and Zerbinati (2014) also note the presence of inflammatory cells, such as leukocytes, mononuclear leukocytes, or macrophages, within the vessel wall, indicating inflammation (17,22,26).

In the tunica media, changes in the internal elastic lamina and alterations in smooth muscle cell (SMC) morphology, including changes in shape, orientation, and phenotype, were noted (4,7,9,11,15,23–25). Other studies highlighted intracellular and extracellular damage, including damaged mitochondria, irregularities in nuclear morphology, and the presence of vacuoles (4,9,13,14,27).

Hannan et al. (2011) also highlighted the differences between young SHR and old SHR in terms of SMC phenotype, organelle distribution, and composition, as well as actin filament distribution. In young SHR, SMC in the media demonstrates a contractile phenotype, characterized by elongated nuclei and parallel-aligned actin filaments, with organelles such as mitochondria, Golgi complex, and endoplasmic reticulum located

near the nucleus. Conversely, older SHR exhibit SMC with a synthetic phenotype, appearing round in shape, accompanied by an increase in the endoplasmic reticulum, mitochondria, Golgi complexes, and well-developed vesicles. Additionally, older SHRs display fewer actin filaments near the cell's edges compared to their younger counterparts. These findings suggest a transition in SMC phenotype and organelle distribution with aging in SHR, indicative of vascular remodelling processes associated with hypertension and aging (24). Another study observed consistent proportions and cross-sectional areas of smooth muscle cells (SMCs) between younger and older SHRs when determined by the point counting method. However, they found that the extracellular matrix in the intima and media of older SHR was thicker (6).

As for the adventitia layer, many studies also noted changes in the extracellular matrix, such as collagen deposition and changes in connective tissue density (9,15,22–25).

The studies also examined various vessel types, including aorta, mesenteric arteries, and pudendal sections, which exhibited slightly different patterns of ultrastructural alterations. Moustafa (2010) noted the presence of irregular luminal surfaces, endothelial projections, erosions, and thrombus in the aorta (17). Abnormal endothelial ultrastructure with swollen nuclei and disappearance of microvilli on the endothelial surface in mesenteric arteries was reported by Ye et al. (2019) (20). Hannan et al. noted an increase in endoplasmic reticulum, mitochondria, Golgi complexes, and vesicles in pudendal vessels (24). These differences may illustrate the varying ultrastructural changes observed in different vessel types, reflecting the diverse responses of the vascular system to hypertensive conditions. The summary of these findings is listed in Table I.

Table I: Summary of qualitative key findings

Vascular layer	Key findings	Authors
Tunica intima	**Endothelial changes** Decreased adhesion, irregular morphology, damage to the luminal surface, and leukocyte adhesion.	Dallak et al., 2019 [4]; Hayden et al., 2012 [7]; Li et al., 2015 [10]; Kumar et al., 2014 [9]; Neto-Ferreira [11]; Billaud et al., 2012 [15]; Deres et al., 2019 [23]; Hannan et al., 2011 [24]; Zerbinati et al., 2014 [22]
	Presence of Inflammatory Cells Presence of leukocytes, mononuclear leukocytes, or macrophages within the vessel wall.	Leal et al., 2020 [26]; Moustafa et al., 2010 [17]; Zerbinati et al., 2014 [22]
Tunica media	**Changes in Internal Elastic Lamina and SMC Morphology** Alterations in SMC morphology including shape, orientation, and phenotype.	Dallak et al., 2019 [4]; Hayden et al., 2012 [7]; Kumar et al., 2014 [9]; Billaud et al., 2012 [15]; Deres et al., 2019 [23]; Hannan et al., 2011 [24]; Zerbinati et al., 2014 [22]
	Intracellular and Extracellular SMC Damage Mitochondrial damage, nuclear irregularities, vacuole presence, actin filament disruption, and changes in organelle distribution.	Dallak et al., 2019 [4]; Kumar et al., 2014 [9]; Neto-Ferreira [11]; Han et al., 2013 [13]; Xian et al., 2012 [14]; Hannan et al., 2011 [24]; Bakker et al., 2014 [27]
Adventitia	**Extracellular Matrix Changes** Changes in extracellular matrix, such as collagen deposition and connective tissue density.	Cebova et al., 2011 [6]; Kumar et al., 2014 [9]; Billaud et al., 2012 [15]; Zerbinati et al., 2014 [22]; Deres et al., 2019 [23]; Hannan et al., 2011 [24]

*SMC: Smooth Muscle Cell

Non-interventional and Interventional studies

A total of 11 studies were non-interventional and focused on the effect of the various hypertension rodent models on the vascular ultrastructure. The remainder of the studies studied the effect of an intervention on the vascular ultrastructure and other studied parameters (Table II).

Table II: Summary of non-intervention and interventional studies

No intervention	Interventional studies					
	Pharmacological		Natural products		Others	
	Study	Intervention	Study	Intervention	Study	Intervention
Cebova et al., 2012 [6]	Dallak et al., 2019 [4]	Metformin	Kumar et al., 2014 [9]	Vanillic acid	Palao, 2016 [12]	Thrombospondin-4 knockout
Hayden et al., 2011 [7]	Neto-Ferreira et al., 2011 [11]	Rosuvastatin	Li et al., 2015 [10]	*Uncaria rhynchophylla & semen raphani*	Ye, 2019 [20]	Exercise
Xian et al., 2012 [14]	Han et al., 2013 [13]	Apelin13	Moustafa, 2010 [17]	Ginger	Jordro, 2011 [25]	Exercise
Billaud et al., 2012 [15]	Olgar et al., 2018 [18]	mitoTEMPO	Zerbinati et al., 2014 [22]	Fish egg homogenate	Moraes-texeira, 2010 [35]	Exercise
Mensah et al., 2022 [16]	Yildirim et al., 2015 [21]	Barnipidine	Liang et al., 2011 [32]	Green tea		
Kristek et al., 2017 [19]	Leal et al., 2019 [26]	Sildenafil	Liang et al., 2016 [33]	Grape seed		
Deres et al., 2019 [23]	Kristek et al., 2011 [30]	Prazosin	Takemori et al., 2015 [34]	Fish elastin peptide		
Hannan et al., 2011 [24]	Ruseva et al., 2012 [31]	Selenium				
Bakker et al., 2014 [27]						
Felix et al., 2012 [28]						
Ma et al., 2013 [29]						

DISCUSSION

Relevance of rodent models to human hypertension

Cebova & Kristek (2011) justified their choice of SHR by noting its widespread use in modelling human essential hypertension (6). Ruseva et al. (2012) asserted that SHR are the most suitable genetic models for essential hypertension research (31). Zerbinati et al. (2014) concurred, highlighting SHR as a genetic model that closely mimics idiopathic hypertension in humans (22). Hayden et al. (2012) studied young transgenic heterozygous (mRen2)27 (Ren2) rats, which exhibit an activated renin-angiotensin-aldosterone system (RAAS) and altered autonomic nervous system regulation. These rats lack a developed subendothelial space or intima. The study aimed to visualize the earliest changes occurring in hypertension (HTN) and the associated accelerated atherosclerosis, in patients with cardiorenal syndrome and type II diabetes mellitus (7).

Kumar et al. (2014) demonstrated that chronic blockade of NO synthase in L-NAME hypertensive rats significantly increased blood pressure and downregulated eNOS mRNA expression (9). Li et al. (2015) found that the L-NAME hypertensive rats had increased expression of CD54 and CD62P, which are used as molecular markers of endothelial dysfunction (10). Han et al. (2013) used an ADMA induced hypertensive rat model since this endogenous competitor of NOS has been found to accumulate in patients with chronic kidney disease related hypertension (13).

Diet-related hypertensive models offer valuable insights into the role of dietary factors in the pathogenesis of hypertension and provide platforms for evaluating dietary interventions and pharmacological treatments for hypertension and related metabolic disorders. Xian et al. (2012) used reheated oil palm, mirroring common practice in Asia when frying foods (14). High salt diet is used to induce salt-sensitive hypertensive models in salt-sensitive strains, such as Dahl salt-sensitive rats. While both abnormal vasoconstriction and vasodilation have been described in blood vessels of this strain, they also display distinct rapid and slow phases for elevation in blood pressure (16). Obesity related hypertensive models mimic aspects of metabolic syndrome often observed in obese individuals with hypertension, such as insulin resistance. Dallak et al. (2019) used a high carbohydrate and fat diet (HCFD) + STZ induction to produce a rat model that was both diabetic and hypertensive (4).

Since increase in age also increases risk of hypertension, aging-related hypertensive models may highlight age-related changes in cardiovascular physiology due to vascular stiffness, endothelial dysfunction, mitochondrial oxidative stress and alterations in hormonal regulation (17-18).

Functional Implications of Ultrastructural Changes

Irregularities in endothelial morphology, including decreased adhesion, irregular arrangement, and damage to the luminal surface, compromise the endothelial barrier function and impair vasomotor regulation, leading to endothelial dysfunction. This dysfunction is associated with reduced nitric oxide bioavailability, increased vascular tone, enhanced inflammation, and

impaired vascular repair mechanisms, contributing to hypertension, atherosclerosis, and other cardiovascular diseases (10,20,26).

Changes in SMC phenotype, such as transition from a contractile to a synthetic state, affect vascular tone regulation and extracellular matrix remodelling. Synthetic SMCs exhibit increased proliferative and migratory capacities, contributing to vascular remodelling, neointimal hyperplasia, and arterial stiffening, which are hallmarks of hypertensive vascular pathology (15,16,27).

Alterations in the extracellular matrix composition, including collagen deposition, thinning or thickening of the internal elastic lamina, and disruption of elastin fibres, impact vascular biomechanics and structural integrity. Excessive collagen accumulation and disruption of elastic fibres promote vascular stiffness, impair elasticity, and increase susceptibility to mechanical stress and vessel wall remodelling, exacerbating hypertension and arterial dysfunction (6,16).

Changes in organelle distribution and composition, such as increased endoplasmic reticulum, mitochondria, and Golgi complexes, reflect cellular metabolic adaptations and increased synthetic activities associated with vascular remodelling and hypertrophy (17,24).

Overall, these ultrastructural changes collectively contribute to vascular dysfunction, arterial remodelling, and the progression of hypertension, ultimately increasing the risk of cardiovascular events such as myocardial infarction, stroke, and heart failure.

Pharmacological interventions to ameliorate hypertension and improve vascular ultrastructure

The observed ultrastructural changes in the vessels following pharmacological interventions suggest promising outcomes. For instance, Yildirim et al. (2015) reported that barnidipine, administered over three weeks, potentially prevented the usual hypertensive-induced morphological changes in resistance arteries, possibly indicating a protective role in maintaining vascular integrity (21). Similarly, metformin, a widely used treatment, may have protected against hypertensive aortic injury in rats with type 2 diabetes, suggesting its potential to stabilise or reverse ultrastructural damage (4). Additionally, Neto-Ferreira et al. (2011) also found that rosuvastatin administration was capable of attenuating ultrastructural aortic wall remodelling in NO-deficient rats (11).

Other treatments, such as prazosin and sildenafil, appeared to enhance endothelial cell development and improve the structural architecture of the endothelial surface in spontaneously hypertensive rats (SHR), potentially preventing further deterioration (19,26). Apelin-13, by directly stimulating vascular smooth muscle cells (SMCs), might prevent or reverse the ultrastructural changes associated with hypertension, though this effect warrants further exploration (13).

Furthermore, selenium supplementation may have slowed elastin degradation and reduced degenerative changes within the vessel wall, implying a potential to counteract the stiffening and weakening of arteries commonly seen in hypertension (31).

Natural products also appear to hold speculative promise. Green tea, grape seed extract, and vanillic acid demonstrated potential in inhibiting arterial wall remodelling and protecting against oxidative stress-induced damage, suggesting they could play a role in preventing or mitigating hypertensive ultrastructural changes (9,10,32¬–33). Ginger's efficacy in reducing morphological changes in rat aorta induced by premature menopause raises the possibility of its use in vascular protection (17). Marine-based compounds, such as fish elastin peptide and fish egg homogenate, showed potential in suppressing endothelial damage and modulating vascular hypertrophy (22,34).

Exercise, particularly moderate and high-intensity, may also have restorative effects on hypertensive-induced changes in elastic tissue and endothelial ultrastructure, offering a non-pharmacological approach to maintaining or improving vascular health (20,25,35).

These findings indicate various avenues through which interventions could potentially alter, prevent, or even reverse hypertensive ultrastructural changes, although further research is needed to confirm these effects.

CONCLUSION

This scoping review has reviewed the available knowledge of vascular ultrastructural changes in hypertensive rodent models spanning from 2010 to 2024. Over the past 15 years, significant advancements have been made in understanding the ultrastructural changes in hypertensive blood vessels, particularly through the use of various rodent models. Compared to earlier research, recent studies have included new diet-induced models and transgenic rats that more closely mimic human hypertensive conditions.

The findings highlight several critical vascular changes due to hypertension, including endothelial damage, SMC transition from a contractile to a synthetic phenotype, and significant modifications in the extracellular matrix, such as collagen deposition and elastin fibre disruption. These changes collectively impair vascular function and contribute to the progression of hypertensive pathology, ultimately increasing the risk of cardiovascular events.
In addition to non-interventional studies, recent research has also explored various pharmacological and natural interventions aimed at reversing or mitigating

these ultrastructural changes. Promising results have been reported with compounds such as metformin, barnidipine, and natural products like green tea and ginger, which have shown potential in protecting against or even reversing the vascular damage caused by hypertension.

Overall, the past 15 years have seen a deeper understanding of hypertensive vascular ultrastructural changes, driven by innovative models and a focus on both pharmaceutical and natural therapeutic interventions. This progress not only enhances our comprehension of hypertension's pathophysiology but also opens new avenues for clinical management and treatment strategies. These findings should serve as a valuable guide for researchers aiming to leverage rodent models of hypertension, whether to better understand the pathophysiology to identify therapeutic targets or evaluate novel interventions.

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