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Research progress on denervation in cardiovascular diseases

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Abstract: Denervation is closely related to many cardiovascular diseases, such as myocardial infarction, myocardial ischemia-reperfusion injury, hypertension, arrhythmia, heart failure, atherosclerosis and ventricular remodeling. Denervation affects the patient's resting heart rate and response to exercise in the early stages of cardiac transplantation. Therefore, this article reviews the research progress of denervation in the treatment of cardiovascular disease and elaborates on the mechanism of denervation in the treatment of cardiovascular disease, intending to provide new complementary treatment methods for the treatment of cardiovascular diseases.

Keywords: Denervation; Cardiovascular diseases; Renal denervation; Cardiac transplantation; Hypertension
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Cardiovascular disease (CVD) is a significant contributor to global death and disability and a major cause of the world's disease burden. Data show that the burden of CVD has increased in most countries for decades [1]. Prevention and treatment of CVD mainly consist of pharmacologic and surgical therapies aimed at preventing risk factors, alleviating patients' clinical symptoms, and improving their quality of life. In recent years, with the continuous development of radiofrequency and ultrasound technologies, denervation treatment through interventional therapy has shown positive results in many CVDs as a new complementary treatment. The efficacy of renal denervation (RDN) in treating renal hypertension has been demonstrated in recent years. However, the efficacy and safety of denervation as a therapeutic modality in other CVDs have yet to be investigated. In addition, patients with end-stage cardiomyopathy usually need to seek cardiac transplantation, and the occurrence of denervation inevitably accompanies the implementation of cardiac transplantation. Although renal denervation occurs in the later stages of the transplanted heart, the effect of pre-transplantation denervation on the output of the transplanted heart and the mechanism of its occurrence has yet to be investigated.

1 Denervation

1.1 Overview of denervation

Denervation is caused by injury, disease, or surgery, and can be the outcome of nerve damage. According to Seddon's classification, the three main types of nerve injury are nerve disuse, axonal dissection, and nerve rupture [2]. In addition, denervation may be caused by certain diseases. Patients with post-polio syndrome continue to experience denervation and reinnervation, with an increase in motor units compensating for the

denervation to a certain extent, and loss of muscle strength complicated by muscle atrophy following the loss of compensation. Finally, reinnervation is associated with surgical procedures. Denervation is used in treating hypertension and as an early clinical consequence after cardiac transplantation. Common types of denervation include autonomic denervation (loss of sympathetic innervation and loss of parasympathetic innervation), muscle denervation due to nerve compression, and the use of axonal microsurgery, neurotomy, and nerve blocks.

1.2 Cardiac denervation

Sympathetic and parasympathetic fibers of the autonomic nervous system innervate the intact heart. Most sympathetic fibers originate in the stellate ganglion and innervate the heart via the right and left cardiac nerves [3]. The scope of cardiac autonomic regulation is extensive, and denervation can have a dramatic effect on the autonomic function of the heart. Cardiac denervation can lead to loss of neural input to the sinus node, loss of efferent and afferent neural signals from inside and outside the heart, loss of sensory input to the ventricles, loss of presynaptic neuronal uptake and hypersensitivity to catecholamines. Thus, cardiac denervation can cause consequent effects on myocardial contractility, heart rate, and nocturnal blood pressure [4]. Ziegler *et al.* [5] found that sympathetic denervation of the pineal gland is a possible cause of physiological sleep-wake cycle disruption and decreased melatonin levels in cardiac patients. The denervation has been localized by single-cell and RNA sequencing to the superior cervical ganglion, which responds to cardiac disease by accumulating inflammatory macrophages, fibrosis, and selective loss of pineal innervation neurons. Depletion of macrophages in the superior cervical ganglion prevents pineal gland disinhibition associated with cardiac disease and restores physiologic melatonin secretion. This study identifies denervation as one of the mechanisms underlying circadian rhythm disturbances in cardiac disease. It suggests that cardiac disease can affect organs distal to the anatomical site through spatial integration of subpopulations of organ-specific neurons in the sympathetic ganglia. In addition to its effects on cardiac disease, the role of the sympathetic ganglion as a relay station between organs warrants further exploration for other diseases.

1.3 RDN

The effects of RDN on the cardiovascular system are mediated by afferent and efferent nerves. Abundant afferent nerve projections in the renal pelvic wall to the paraventricular nucleus of the hypothalamus modulate sympathetic nerves to innervate the heart, kidneys, and small arteries, and efferent nerve activation induces renin secretion, regulates sodium absorption and renal vascular resistance, which in turn leads to increased blood pressure and fluid retention, which is disrupted with RDN [6]. In preclinical studies, a mouse model of RDN was made by wrapping bilateral renal arteries with 10% phenol for 15 min until the bilateral renal arteries turned white [7]. In clinical studies, RDN has been done by radiofrequency ablation and ultrasound, which reduces blood pressure by high-energy ablation of the renal artery lining, thereby inhibiting sympathetic nerves. Studies have shown that RDN has important effects on hypertension, atherosclerosis, arrhythmia, infarction, cardiac metabolism, cardiac circadian rhythm, and myocardial inflammatory response.

2. Denervation and CVD

2.1 Denervation and myocardial infarction / myocardial ischemia-reperfusion injury

Myocardial infarction is the most common cause of heart failure and a leading cause of mortality and morbidity worldwide. Transmural myocardial infarction not only leads to cardiomyocyte death, but also damages sympathetic nerve fibers passing through the infarcted area, resulting in local sympathetic denervation. Sympathetic nerves are more susceptible to ischemic injury than cardiomyocytes, and loss of sympathetic innervation is strongly associated with ventricular arrhythmias and sudden cardiac death. In an attempt to identify post-infarction myocardial loss of sympathetic innervation and potentially provide an alternative prognostic marker for the risk of sudden cardiac death, Kiss *et al.*[8] first demonstrated that cardiac loss of sympathetic innervation after myocardial infarction can be significantly improved by remote ischemic pre-adaptation, which may be associated with a significant reduction in the expression content of the chondroitin sulfate proteoglycan, a matrix component in the cardiac scar, and inflammation. Subsequently, Blake *et al.* [9] further found that loss of chondroitin sulfate proteoglycan sulfation in a mouse model delayed sympathetic reinnervation after cardiac ischemia-reperfusion. Li *et al.*[10] in 6-hydroxydopamine-induced cardiac loss of sympathetic innervation plays a vital role in attenuating myocardial ischemia-reperfusion injury through the lncRNA/CircRNA-SmRNA-mRNA network in the upper thoracic spinal cord. The effects of denervation on myocardial ischemia-reperfusion injury are also associated with inflammation. Wang *et al.* [11] found that RDN ameliorated oxidative stress, neurohormonal activation, adverse left ventricular remodeling, and intramyocardial inflammation in a large animal model with concomitant ischemia/reperfusion (I/R) injury. Huang *et al.* [12] found in a rabbit model of cardiomyopathy that RDN inhibited the renin-angiotensin-aldosterone system and inflammatory cytokine activity, thereby preventing cardiac remodeling. The specific mechanism by which denervation is involved in myocardial ischemia-reperfusion injury by modulating inflammatory pathways in the above findings may be that activation of the sympathetic nervous system promotes the recruitment and homing of inflammatory cells, especially neutrophils and macrophages.

Studies have shown that the denervation of organs and tissues other than the heart can likewise be involved in the developmental process of CVD. Sun *et al.* [13] explored the effects of RDN on immune cell mobilization after myocardial I/R injury in mice, discovered a novel link between sympathetic nervous system activity and inflammatory response during myocardial I/R injury, and determined that RDN counteracts myocardial I/R injury by preserving splenic immune cell mobilization. RDN pre-emptively blockade of renal sympathetic efferent and afferent nerves inhibits myeloid cell recruitment and infiltration and attenuates the inflammatory response in myocardial I/R-injured mice. In examining the role of activation of the ventral extrastriate subnucleus of the ventral hypothalamus in a rat model of myocardial infarction and its underlying mechanisms, Liu *et al.* [14] found that activation of the ventral hypothalamus neurons augmented cardiac sympathetic nervous system activity through the paraventricular nucleus and superior cervical ganglion. This activation led to increased catecholamine levels, which subsequently modulated myosin function and triggered the release of anti-inflammatory factors, leading to poor cardiac prognosis. In contrast, denervation of the superior cervical ganglion effectively blocked sympathetic effects and improved cardiac prognosis.

2.2 Denervation and hypertension

Currently, the main treatment for renal hypertension is antihypertensive drugs, and due to poor adherence to medication and drug tolerance in some patients with refractory hypertension, catheter-based interventional therapy such as RDN, has become a new therapeutic measure. In the last decade, a number of studies have been conducted on the effectiveness and safety of RDN in lowering blood pressure. A single-blind, multicenter, sham-controlled, randomized clinical trial (the SYMPLICITY HTN-3 trial), which investigated the long-term outcomes of renal artery denervation in patients with single-electrode radiofrequency denervation, recruited 535 patients with recalcitrant hypertension at 88 centers in the United States. At 6-month follow-up, the RDN group met the primary safety endpoint but did not report an overall treatment benefit compared with the sham-operated group. However, after 36 months of follow-up the report not only demonstrated the safety of renal artery denervation at 36 months postoperatively, but also a greater decrease in blood pressure and better control of blood pressure from 12 to 36 months postoperatively in patients who received renal artery denervation compared with those who received sham control [15]. The large disparity in results obtained at 6- to 36-month follow-up may be attributable to the limitations imposed by the first-generation, single-stage ablation technique, which achieved effective circumferential denervation in only 6% of study subjects. Catheter-based RDN of the renal arteries has undergone significant technical and methodological improvements after the failed results of the SYMPLICITY-HTN 3 trial in 2014, and the SPYMPLICITY-HTN (SHAM) controlled randomized trial was conducted, which yielded promising results. The current 2023 European Society of hypertension (ESH) guidelines provide recommendations for catheter-based renal artery RDN for two main areas of application (1) patients with untreated hypertension, for whom renal artery denervation is a first-line treatment, and (2) patients with difficult-to-control or truly resistant hypertension [16]. When hypertension is combined with atrial fibrillation, RDN seems to be more effective in the treatment of hypertension. Zeijen *et al* [17] implemented radiofrequency RDN therapy in 20 patients suffering from hypertension combined with atrial fibrillation in an AFFORD study. They detected atrial fibrillation loads using implantable cardiac monitors and performed 24 h ambulatory blood pressure testing. After 3 years of follow-up, the application of RDN was found to reduce blood pressure in patients with hypertension and symptomatic atrial fibrillation, but no significant reduction in atrial fibrillation load was found at the 3-year follow-up.

Regarding how RDN reduces blood pressure and how RDN affects arterial function, it has been suggested that RDN affects vascular function by improving endothelial function, but Rommel *et al.* [18] noted that the effects of RDN appear to be independent of hemoglobin levels, which are thought to affect vascular function through endothelial mechanisms. Meanwhile, Kiuchi *et al.* [19] studied combined denervation of the renal and common hepatic arteries as a new approach to reduce cardiometabolic risk in a porcine model and assessed the feasibility and safety of the approach, and the animals included in the study were in good health during a 30- to 90-day follow-up period, with no stenosis or abnormalities of the vasculature and no significant changes in serum chemistry. Hyperactivation of the sympathetic nervous system is a crucial factor associated with cardiometabolic disorders [20].

2.3 Denervation and arrhythmia

In recent years, many studies have used denervation as an interventional therapy for arrhythmia treatment and evaluated its safety and efficacy. Vassallo *et al.* [21] applied high-power short-duration ablation combined with parasympathetic denervation to treat patients with atrial fibrillation and used the degree of increase in heart rate to determine the recurrence rate of atrial fibrillation. In the long-term follow-up, it was found that patients with a lower heart rate were prone to recurrence, while patients with a higher heart rate had a higher maintenance of sinus rhythm. Zheng *et al.* [22] found that after radiofrequency ablation of pulmonary artery denervation in dogs, the low-frequency component of heart rate variability, serum norepinephrine, and angiotensin II levels were significantly reduced, and the refractory period of the right ventricular outflow tract was shortened. The number of premature ventricular beats and the number and duration of tachycardia episodes in the right ventricular outflow tract induced by left stellate ganglion stimulation were found to be significantly reduced. Thus, pulmonary artery denervation ameliorates the shortening of the ventricular

effective response period and ventricular arrhythmias in the right ventricular outflow tract induced by left stellate ganglion stimulation through inhibition of cardiac sympathetic nerve activity. However, denervation can also increase the incidence of arrhythmias by affecting circadian rhythms. Prado *et al.* [23] found that loss of melatonin circadian rhythms after supra carotid ganglionectomy in rats rendered the heart susceptible to arrhythmias, predominantly ventricular tachycardia, which was due to conduction disturbances and repolarization changes.

2.4 Denervation and heart failure

Many studies have suggested that denervation may be involved in treating heart failure, improving cardiac function, and slowing cardiac remodeling. Rommel *et al.* [18] found that the application of RDN to patients with heart failure with ejection fraction-preserved partially reversed the abnormalities of arterial function, observing reductions in BP and BP variability. The possible mechanism may be that the RDN intervention disrupts afferent and efferent sympathetic fibers along the renal arteries sympathetic fibers, thereby decreasing sympathetic tone. Pushpakumar *et al.* [24] found in a mouse model of heart failure that RDN contributes to the maintenance of ejection fraction by maintaining eNOS levels and endocardial endothelial function during heart failure, and that RDN intervention helps to decrease the activity of the renal sympathetic afferent-hypothalamic-renal sympathetic efferent neural circuitry system, which may contribute to the improvement of left cardiac function in patients prone to heart failure and cardiac death. Li *et al.* [25] found that RDN improved cardiac function in dogs with post-infarction heart failure in a Beagle model of post-infarction heart failure.RDN reduced levels of cytokines and other pro-inflammatory factors in myocardial tissue and the hypothalamus, which may affect cytokine-induced CNS excitability in heart failure, and subsequently sympathetic activity. Polhemus *et al.* [26] described an improved post-infarction cellular therapy alternative by combining treatment with pericardium-derived cells (CDCs) with RDN for the first time, and showed that CDCs improved early systolic function. In contrast, RDN maintained late function and prevented cardiac remodeling. The left ventricular ejection fraction was maintained at higher levels when both treatments were given concurrently than with either CDCs or RDN alone, and that combining these strategies may have a role in the treatment of post-infarction injury to attenuate cardiac remodeling and heart failure progression. Polhemus *et al.*[27] found in a rat model of spontaneous hypertensive heart failure that receiving bilateral radiofrequency RDN treatment resulted in reduced left ventricular fibrosis and improved vascular function compared with controls, suggesting that radiofrequency RDN treatment significantly improves responsiveness to endothelium-dependent and nonendothelium-independent vasodilators and vascular compliance in severe heart failure, increasing circulating natriuretic peptide levels and improving left ventricular function in heart failure. Krim [28] found that autonomic modulation in heart failure patients with reduced ejection fraction appears to be safe in the short term, but long-term safety and efficacy are unproven.

2.5 Denervation and atherosclerosis

Atherosclerosis is a disease of the arterial vasculature characterized by the narrowing of the arterial lumen due to the accumulation of subendothelial lipids. Ischemic cardiac disease and stroke secondary to atherosclerosis are the two leading causes of death worldwide [29]. Arteries are innervated by nerves, especially the sympathetic nervous system, which is important in forming atherosclerosis. Sympathetic nerves innervate large arteries and small precapillary arterioles, and the integration of the efferent activity of the sympathetic nervous system with the vasculature occurs in the medulla oblongata of the brainstem, where the hypothalamus and cerebral cortex regulate its activity. The atherosclerotic cardiovascular disease manifests in the renal arteries as renal artery stenosis. Several studies have found that RDN inhibits atherosclerotic progression. Elevated blood pressure induces a proinflammatory response and promotes vascular remodeling and the progression of atherosclerosis and end-organ damage [30]. A small clinical study applied RDN treatment to patients with refractory hypertension and found that RDN had no adverse effects on renal artery structure at follow-up after 12 months and that control of blood pressure and improvement of vascular endothelial function after RDN may even inhibit the progression of atherosclerosis in the renal arteries [31]. Li *et al.* [32] performed RDN treatment in high-fat-fed ApoE knockout mice and found that RDN inhibited renal arterial progression by decreasing mitochondrial monoamine oxidase A activity, maintaining mitochondrial homeostasis, and reducing ROS accumulation and NF-κB activation, thereby decreasing the expression of atherogenic and proinflammatory molecules in endothelial cells. The possible mechanism is that the action of RDN on mitochondrial monoamine oxidase A disrupts the positive feedback regulation between mitochondrial dysfunction and inflammation, thereby inhibiting the alteration of the atherosclerotic phenotype of endothelial cells and the development of atherosclerosis. Chen *et al.* [33] found that in ApoE knockout mice, RDN inhibited the increase of atherosclerotic plaque size and ameliorated inflammation in the plaques, reduced the accumulation of circulating neutrophils and monocytes, and the production of splenic neutrophils. Monocytes and splenic sympathetic nerve activity suggest that RDN could treat atherosclerosis as a potential anti-inflammatory treatment by limiting the production of splenic immune cells. Some studies have found that the effects of RDN on atherosclerosis may not be related to hypertension. Wang *et al.* [34] found that RDN attenuated the progression of atherosclerosis in the mice compared with the sham-operated group when RDN treatment of ApoE-deficient mice, which may be related to reduced aldosterone levels, monocyte chemotactic protein-

1, and markers of oxidative stress.

However, several studies have found that RDN can increase the risk of atherosclerosis. Chen *et al.* [35] induced arterial pressure reflex dysfunction promoting the development of atherosclerosis by upstream loss of sinus aortic innervation in Apoe knockout mice decreased the expression of VAChT and α7nAChR and significantly increased the level of oxidative stress and inflammation. Su *et al.*[36] found that RDN resulted in the intima of vascular smooth muscle cells significantly thickened and significantly promoted endothelin B receptor production, significantly inhibited the expression of AMPK/Akt/eNOS signaling pathway proteins, decreased NO production, and increased the expression of endothelin system proteins, such as endothelin-1, endothelin-converting enzyme 1, endothelin A receptor, and ETBR, up-regulated the expression of NOX2 and 4-HNE proteins, and enhanced NF-κB activation, which resulted in aggravation of the endothelial endocrine function of minor endothelial endocrine dysfunction, intimal thickening, and increased risk of atherosclerosis in porcine renal arteries. Wang *et al.* [37] RDN significantly increased the level of matrix metalloproteinase-2 expression in angiotensin II-injected hypertensive ApoE-deficient mice, promoting atherosclerosis formation.

3. Denervation and cardiac transplantation

Cardiac transplantation is the most effective treatment for end-stage heart failure. A series of physiologic changes occur over a period after cardiac transplantation, including hemodynamic changes, changes in cardiac rhythm, and changes in responses to exercise. Cardiac transplantation results in axonal transection of the postganglionic nerve innervating the heart, and axonal degeneration occurs within a few days after transplantation, resulting in complete depletion of the cardiac norepinephrine reserve, the disappearance of nerve endings in the transplanted tissue, and complete loss of cardiac innervation [38]. The heart is usually in a state of complete denervation for 6 to 12 months after cardiac transplantation, and recovery of cardiac reinnervation is usually found in the second year after transplantation [38]. Autonomic denervation of the transplanted heart results in many changes, such as increased resting heart rate, decreased heart rate variability, abnormal time-varying responses to exercise, and excessive bradycardic responses following adenosine administration [39]. Cardiac denervation and subsequent loss of sympathetic and parasympathetic regulation are responsible for various physiologic changes in the cardiovascular system and limit exercise tolerance in patients. Restoration of cardiac innervation improves exercise capacity and quality of life, but the reinnervation process is only partially restored even several years after cardiac transplantation [40]. Clinical findings suggest an elevated resting heart rate of 90-110 beats/min due to loss of parasympathetic innervation of the donor heart after transplantation, representing the inherent depolarization rate of the sinus node [39]. Under a graded exercise test, heart rate after cardiac transplantation usually does not increase or has a delayed increase for the first few minutes, followed by a gradual increase due to loss of sympathetic innervation of the sympathetic nervous system, with a peak slightly below normal (averaging about 150 beats/min) [41]. A study reported that a patient who underwent sequential heart and kidney transplantation and suffered from refractory hypertension was treated with autologous renal artery RDN after a combination of six antihypertensive medications failed to work and experienced a significant decrease in systolic and diastolic blood pressure, suggesting that RDN can be an effective complementary treatment for lowering blood pressure in patients who have undergone heart and kidney transplantation, and can reduce cardiovascular risk[42].

In summary, denervation plays an important role in CVDs such as myocardial infarction, hypertension, arrhythmia, atherosclerosis, and heart failure. However, it is currently understudied in other CVDs such as diabetic cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, and myocarditis, which are of significant research interest. Denervation is clinically crucial in various CVDs, both as a therapeutic tool and as a clinical manifestation after cardiac transplantation. Currently, the hottest study is the intervention of RDN in refractory hypertension. However, the mechanism of other types of denervation in various CVDs is still unclear, especially the effect of RDN on atherosclerosis is controversial and deserves further exploration. The role of denervation may become a potential research direction in myocardial ischemia-reperfusion injury, circadian rhythm of clock genes, and cardiac transplantation.

Conflict of interest None

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失神经支配在心血管疾病中的研究进展

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摘要：失神经支配与心肌梗死、心肌缺血再灌注损伤、高血压、心律失常、心力衰竭、动脉粥样硬化以及心室重塑等多种心血管疾病密切相关。失神经支配在心脏移植早期影响患者的静息心率和对运动的反应性。因此，本文就失神经支配在心血管疾病领域的研究进展进行综述，阐述失神经支配在治疗心血管疾病中的作用机制，以期为心血管疾病治疗提供新的补充治疗手段。

关键词：失神经支配；心血管疾病；肾脏失神经支配；心脏移植；高血压
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Research progress on denervation in cardiovascular diseases

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Abstract: Denervation is closely related to many cardiovascular diseases, such as myocardial infarction, myocardial ischemia-reperfusion injury, hypertension, arrhythmia, heart failure, atherosclerosis and ventricular remodeling. Denervation affects the patient's resting heart rate and responsiveness to exercise in the early stages of heart transplantation. Therefore, this article reviews the research progress of denervation in the field of cardiovascular diseases and elaborates on the mechanism of denervation in the treatment of cardiovascular disease, intending to provide new complementary treatment methods for the treatment of cardiovascular diseases.

Keywords: Denervation; Cardiovascular diseases; Renal denervation; Heart transplantation; Hypertension
Fund program: National Natural Science Foundation of China (82172160, 82100894)

心血管疾病(cardiovascular diseases, CVD)是全球死亡和致残的重要因素，也是造成世界疾病负担的主要原因。数据显示，多数国家在持续数十年内 CVD 负担均呈上升趋势[1]。CVD 的防治方式主要包

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括预防危险因素、减轻患者临床症状和改善患者生活质量为目标的药物和手术治疗。近年来随着射频和超声技术的不断发展,通过介入治疗实现的失神经支配作为一种新型补充治疗手段在许多 CVD 中显示出积极的治疗效果。近年来肾脏失神经支配(renal denervation, RDN)在肾性高血压治疗中的有效性得到验证,但失神经支配作为治疗方式在其他 CVD 中的有效性和安全性尚待研究。此外心肌病终末期患者通常需要寻求心脏移植治疗,心脏移植的实施必然伴随着失神经支配的发生,尽管后期移植心脏会出现再神经支配,但在移植后前期失神经支配对移植心脏产生的影响和其发生机制也有待研究。

1　失神经支配

1.1　失神经支配概述　失神经支配又可称为去神经支配,是由损伤、疾病或者外科手术引起。首先,失神经支配可能是神经损伤的结果。根据 Seddon 的分类,神经损伤的三种主要类型有神经失用、轴索断裂和神经断裂[2]。其次,失神经支配可能由某些疾病造成。脊髓灰质炎后综合征患者持续经历失神经支配与再神经支配的过程,运动单元的增加在一定范围内代偿失神经支配,失代偿后会出现肌肉萎缩并发肌肉力量的丧失。最后,失神经支配与外科手术有关。失神经支配应用于去肾交感神经术治疗高血压和作为心脏移植后早期临床后果。常见的失神经支配有失自主神经支配(失交感神经支配和失副交感神经支配)、神经挤压所致肌肉失神经支配以及应用轴索显微外科术、神经根切断术和神经阻滞等。

1.2　心脏失神经支配　完整的心脏由自主神经系统的交感神经和副交感神经纤维支配。大多数交感神经纤维起源于星状神经节并通过左右心脏神经支配心脏[3]。心脏自主神经调节的范围十分广泛,一旦出现失神经支配,将对心脏的自主调节功能产生巨大的影响。心脏失神经支配可导致窦房结的神经输入消失、心脏内外的传出和传入神经信号丢失、心室感觉输入丧失,还可导致突触前神经元摄取机制的丧失和对儿茶酚胺的超敏感性,最终对心肌收缩力、心率、夜间血压等产生影响[4]。Ziegler 等[5]研究发现松果体的交感神经失神经是心脏病患者可能伴随着生理性睡眠-觉醒周期紊乱与下降的褪黑素水平出现的根本原因,经过单细胞和 RNA 测序等手段将此失神经定位到颈上神经节,该神经节对心脏病的反应是炎症巨噬细胞的积聚、纤维化和松果体神经支配神经元的选择性丧失。耗竭颈上神经节中的巨噬细胞可阻止与心脏病相关的松果体失神经支配,并恢复生理性褪黑素分泌。这项研究证实失神经支配是心脏病昼夜节律紊乱的机制之一,并提示心脏病可通过交感神经节中器官特异性神经元亚群的空间整合,影响解剖学部位远端的器官。除了对心脏病的影响外,交感神经节作为器官之间的中继站的作用值得对其他疾病实体进行进一步探索。

1.3　RDN　RDN 对心血管系统的影响由传入神经和传出神经介导。在肾盂壁上丰富的传入神经投射到下丘脑室旁核调节交感神经以支配心脏、肾脏和小动脉,传出神经激活诱导肾素分泌、调节钠吸收和肾血管阻力,进而导致血压升高和液体潴留,这一切随着 RDN 而中断[6]。临床前研究采取 10%苯酚包裹双侧肾动脉 15 min 至双侧肾动脉变白制作小鼠 RDN 模型[7]。在临床研究中,RDN 的方法有射频消融、超声等,通过高能消融肾动脉内膜,从而抑制交感神经而降低血压。研究表明,RDN 对高血压、动脉粥样硬化、心律失常、心梗、心脏代谢、心脏病昼夜节律和心肌炎症反应有重要影响。

2　失神经支配与 CVD

2.1　失神经支配与心肌梗死/心肌缺血再灌注损伤　心肌梗死是心力衰竭(心衰)最常见的原因,也是世界范围内死亡的主要原因。跨壁心肌梗死不仅导致心肌细胞死亡,还会损害经过梗死区的交感神经纤维,导致局部交感神经失神经支配。交感神经比心肌细胞更容易受到缺血性损伤,失交感神经支配与室性心律失常和突发性心脏病紧密相关。为了识别心梗后心肌失交感神经支配,并为心源性猝死的风险提供替代预后的可能标志,Kiss 等[8]首次证明了心肌梗死后的心脏失交感神经支配可由远程缺血预适应显著改善,这可能与心脏瘢痕中的基质成分硫酸软骨素蛋白多糖表达和炎症因子的显著减少有关。随后 Blake 等[9]进一步发现在小鼠模型中的硫酸软骨素蛋白多糖硫酸化缺失可使心脏缺血再灌注后的交感神经再支配延迟。Li 等[10]在 6-羟基多巴胺诱导的心失交感神经通过上胸段脊髓中的 lncRNA/circRNAs-miRNA-mRNA 网络对减轻心肌缺血再灌注损伤发挥了重要作用。失神经支配对心肌缺血再灌注损伤的影响也与炎症相关。Wang 等[11]研究发现在伴有心肌梗死/心肌缺血再灌注损伤的大型动物模型中,RDN 可以改善氧化应激、神经激素激活、不良的左心室重塑和心肌内炎症。Huang 等[12]在心肌病兔模型中发现 RDN 可以抑制肾素-血管紧张素-醛固酮系统

和炎症细胞因子的活性，从而预防心脏重塑。上述研究结果中失神经支配通过调控炎症通路进而参与心肌缺血再灌注损伤的的具体机制可能是交感神经系统的激活促进了炎症细胞的募集和归巢，尤其是中性粒细胞和巨噬细胞。

研究显示，除心脏外的器官组织失神经支配同样可参与 CVD 的发展进程。Sun 等[13]探讨了 RDN 对小鼠心肌缺血再灌注损伤后免疫细胞动员的影响，发现了心肌缺血再灌注损伤时交感神经系统活性与炎症反应之间的新联系，并确定 RDN 是通过保留脾脏免疫细胞动员来对抗心肌缺血再灌注伤害。RDN 预先阻断肾交感传出和传入神经可抑制骨髓细胞的募集和浸润，减轻心肌缺血再灌注损伤小鼠的炎症反应。Liu 等[14]在研究腹内侧下丘脑的腹外侧亚核激活在心肌梗死大鼠模型中的作用及其潜在机制中发现，腹内侧下丘脑神经元的激活通过室旁核和颈上神经节增强了心脏交感神经系统的活性。这种激活导致儿茶酚胺水平升高，随后调节肌球蛋白功能并触发抗炎因子的释放，导致心脏预后变差，而颈上神经节失神经支配可有效阻断交感神经的作用，改善心脏预后。

2.2　失神经支配与高血压　目前肾性高血压的主要治疗手段为服用抗高血压药物。由于患者服用药物的依从性不佳以及有些顽固性高血压患者对药物耐受等，基于导管的 RDN 介入治疗成为新的治疗措施。近十年不少研究围绕 RDN 的降压有效性、安全性进行临床试验。一项单盲、多中心、假对照、随机临床试验（SYMPLICITY HTN-3 试验）研究单电极射频 RDN 治疗的长期结果，该试验在美国 88 个中心招募了 535 例顽固性高血压患者，6 个月随访后，与假手术组相比，RDN 组虽然达到主要安全终点，但未报告总体治疗益处；但经过 36 个月的随访后，报告不仅证明了 RDN 术后 36 个月的安全性，而且术后 12～36 个月，与接受假对照的患者相比，接受 RDN 的患者血压下降幅度更大，血压控制更好[15]。6～36 个月随访得出的结果有较大差距，这可能归因于受第一代单级消融技术的限制，只有 6%的受试者实现了有效的环向失神经支配。基于导管的肾动脉 RDN 在 2014 年 SYMPLICITY-HTN 3 试验结果失败后，经过技术和方法的改进，开展了重要的假手术对照随机试验 SPYRAC HTN-ON MED，取得了理想的结果。目前 2023 年欧洲高血压学会高血压管理指南为基于导管的肾动脉 RDN 提供了建议，主要应用于两个领域：（1）仍未治疗的高血压患者，RDN 是一种一线治疗方法；（2）难以控制或真正具有抵抗力的高血压患者[16]。当高血压合并心房颤动（房颤）时，RDN 似乎对高血压的治疗效果更好。Zeijen 等[17]在一项 AFFORD 研究中对 20 例患有高血压合并房颤的患者实施射频 RDN 治疗，使用植入式心脏监测仪检测房颤负荷并进行 24 h 动态血压检测，经过 3 年的随访发现，在高血压和症状性房颤患者中，应用 RDN 降低了血压，但 3 年随访未发现有显著减轻房颤负荷。

关于 RDN 如何降低血压以及 RDN 如何影响动脉功能，有学者认为 RDN 通过改善内皮功能影响血管功能。但 Rommel 等[18]指出 RDN 的作用似乎不受血红蛋白水平的影响，而血红蛋白水平被认为通过内皮机制影响血管功能。同时，Kiuchi 等[19]研究在猪模型上将肾动脉和肝总动脉联合失神经作为降低心脏代谢风险的新方法，并评估该方法的可行性和安全性，纳入研究的动物在 30～90 d 的随访期间健康状况良好，未发现血管有狭窄或异常，血清化学成分无明显变化。交感神经系统的过度激活已被证明是心脏代谢紊乱的关键因素[20]。

2.3　失神经支配与心律失常　近年来许多研究将失神经支配作为一种介入治疗手段用于治疗心律失常，并对其安全性和有效性进行评估。Vassallo 等[21]应用高功率短时程消融术联合副交感失神经支配治疗房颤患者，并且以心率增加的程度来判断房颤复发率，在长期随访中发现心率增加较低的患者容易复发，而心率增加较高的患者窦性心律维持率较高。Zheng 等[22]研究发现对犬采取射频消融肺动脉失神经后心率变异性低频成分、血清去甲肾上腺素和血管紧张素Ⅱ水平显著降低，并且减轻左侧星状神经节刺激引起的收缩压升高，右心室流出道心室有效不应期缩短，发现右心室流出道室性早搏次数以及左侧星状神经节刺激引起的右心室流出道心动过速发作次数和持续时间显著减少，因此肺动脉失神经支配通过抑制心交感神经活动，改善了左侧星状神经节刺激引起的右心室流出道心室有效不应期缩短和室性心律失常。然而失神经支配也可通过影响昼夜节律从而增加心律失常的发生率。Prado 等[23]发现大鼠颈上神经节切除术后褪黑激素昼夜节律的丧失易导致心律失常，主要是室性心动过速，这是由于传导障碍和复极变化所致。

2.4　失神经支配与心衰　许多研究表明，失神经支配可能参与治疗心衰并改善心功能，减缓心脏重塑。Rommel 等[18]发现在射血分数保留型心衰患者中应用 RDN 可以部分逆转动脉功能的异常，观察到血压

和血压变异性的降低，可能机制是 RDN 干预会破坏肾动脉沿线的传入和传出交感纤维，从而降低交感神经张力。Pushpakumar 等[24]在小鼠心衰模型中发现 RDN 通过在心衰期间保持内皮型一氧化氮合酶（eNOS）水平和心内膜内皮功能以维持射血分数，RDN 干预有助于降低肾交感传入神经-下丘脑-肾交感传出神经回路系统的活性，这可能有助于改善易发生心衰和心脏病死亡患者的左心功能。Li 等[25]在犬心梗后心衰模型中发现 RDN 可以改善心梗后心衰犬的心功能，降低心肌组织和下丘脑中细胞因子和其他促炎因子的水平，可能影响细胞因子诱导的心衰中枢神经兴奋，随后影响交感神经活动。Polhemus 等[26]介绍了一种改善心梗后细胞治疗的替代方法，首次将心包膜衍生细胞（CDCs）治疗与 RDN 结合，结果表明，CDCs 改善早期收缩功能，而 RDN 维持晚期功能和防止心脏重塑，当同时给予两种治疗时，左室射血分数维持在比单独使用 CDCs 或 RDN 更高的水平，结合这些策略可能在治疗梗死后损伤以减轻心脏重塑和心衰进展方面具有治疗潜力。Polhemus 等[27]在自发性高血压心衰大鼠模型中发现，与对照组相比，接受双侧射频 RDN 治疗后左心室纤维化程度减少，血管功能改善，说明射频 RDN 治疗能显著改善对内皮依赖性和非内皮依赖性血管舒张剂的反应性和在严重心衰下的血管顺应性，提高循环中钠尿肽水平，改善心衰下的左心室功能。Krim[28]发现自主神经调控在射血分数降低的心衰患者的治疗在短期内似乎是安全的，但长期安全性和有效性未得到验证。

2.5　失神经支配与动脉粥样硬化　动脉粥样硬化是一种动脉血管疾病，其特征是内皮下脂质积聚导致的动脉管腔变窄。动脉粥样硬化继发的缺血性心脏病和脑卒中是全球死亡的两个主要原因[29]。动脉受神经支配，尤其是交感神经系统对动脉粥样硬化的形成十分重要。大动脉和毛细血管前小动脉由交感神经支配，交感神经系统的传出活动与血管的整合发生在脑干的延髓，其活动受下丘脑和大脑皮层的调节。动脉粥样硬化性心血管疾病在肾动脉的表现为肾动脉狭窄。一些研究发现 RDN 可抑制动脉粥样硬化进展。血压升高会诱导促炎反应，并促进血管重塑以及动脉粥样硬化和末端器官损伤的进展[30]。一项小型临床研究对顽固性高血压患者应用 RDN 治疗，在 12 个月后的随访中发现 RDN 对肾动脉结构没有不良影响，而且 RDN 后血压的控制和血管内皮功能的改善甚至可能抑制肾动脉粥样硬化的进展[31]。Li 等[32]在高脂饲养的载脂蛋白 E（ApoE）敲除小鼠进行 RDN 治疗，发现 RDN 通过降低线粒体单胺氧化酶 A 的活性，维持线粒体稳态，减少活性氧（ROS）积累和核因子（NF）-κB 激活，从而减少内皮细胞中致动脉粥样硬化和促炎分子的表达。其可能机制是 RDN 对线粒体单胺氧化酶 A 的作用破坏了线粒体功能障碍和炎症之间的正反馈调节，从而抑制内皮细胞动脉粥样硬化表型的改变和动脉粥样硬化的发展。Chen 等[33]发现在 ApoE 敲除小鼠中 RDN 可抑制动脉粥样硬化斑块大小的增加并改善斑块中的炎症，减少了循环中性粒细胞和单核细胞的积累，降低了脾脏中性粒细胞和单核细胞的产生和比例及脾脏交感神经活性，表明 RDN 可通过限制脾脏免疫细胞的产生来治疗动脉粥样硬化作为一种潜在抗炎治疗措施。有研究发现 RDN 对动脉粥样硬化的影响可能与高血压无关。Wang 等[34]对 ApoE 缺陷但血压正常小鼠行 RDN 治疗发现，与假手术组相比，RDN 可缓解小鼠的动脉粥样硬化进展，可能与降低的醛固酮水平、单核细胞趋化蛋白-1 和氧化应激标志物有关。

然而，一些研究发现 RDN 可提高动脉粥样硬化的风险。Chen 等[35]在 ApoE 敲除小鼠中行失窦主动脉神经支配诱导动脉压力反射功能障碍促进动脉粥样硬化的发展，同时降低囊泡乙酰胆碱转运体（VAChT）和 α7 烟碱型乙酰胆碱受体（α7nAChRs）的表达，并显著增加氧化应激和炎症水平。Su 等[36]发现 RDN 导致血管平滑肌细胞内膜明显增厚，并显著促进内皮素 B 受体的产生，显著抑制 AMPK/Akt/eNOS 信号通路蛋白的表达，降低 NO 的产生，并增加内皮素-1、内皮素转换酶 1、内皮素 A 受体和内皮素 B 受体等内皮素系统蛋白的表达，上调 NADPH 氧化酶 2（NOX2）和 4-羟基壬烯酸（4-HNE）修饰蛋白的表达，增强 NF-κB 的活化，结果加重小型猪肾动脉内皮分泌功能障碍，内膜增厚，并增加了动脉粥样硬化的风险。Wang 等[37]发现 RDN 显著增加了血管紧张素Ⅱ注射的高血压 ApoE 缺陷小鼠的基质金属蛋白酶-2 表达水平，促进动脉粥样硬化形成。

3　失神经支配与心脏移植

心脏移植是治疗终末期心脏功能衰竭最有效的方法。心脏移植后的一定时间内会发生一系列的生理变化，包括血流动力学变化、心脏节律变化以及对运动的反应性变化等。心脏移植导致支配心脏的节后神经轴突横断，移植后几天内发生轴突变性，导致心脏去甲肾上腺素储备完全耗尽，移植组织中神经末梢消失，心脏完全失神经支配[38]。一般在心脏移植

后的 6~12 个月内，心脏处于完全失神经支配的状态，而心脏再神经支配的恢复通常在移植后第 2 年发生[38]。移植心脏的自主失神经支配导致许多变化，例如静息心率增加、心率变异性降低以及腺苷给药后的过度心动过缓反应[39]。心脏失神经支配和随后交感神经和副交感神经调节的丧失是心血管系统各种生理变化的原因，也限制了患者运动耐受性。心脏神经支配的恢复可以提高运动能力和生活质量，但即使在心脏移植后几年，神经再支配过程也只是部分恢复[40]。临床研究结果提示，由于移植后供体心脏的副交感神经支配丧失，静息时的心率升高为 90~110 次/min，代表了窦房结固有的去极化速率[39]。在分级运动试验下，心脏移植后心率通常在最初几分钟内不会增加或延迟增加，随后由于交感神经系统失神经支配，心率逐渐增加，峰值略低于正常值（平均约 150 次/min）[41]。一项研究报告了 1 例先后接受心脏和肾脏移植并患上难治性高血压的患者，在复合使用六种降压药无效后应用了自体肾动脉 RDN 治疗，收缩压和舒张压显著下降，说明 RDN 可成为接受心肾移植患者降压的有效补充治疗方式，可以降低心血管风险[42]。

综上所述，失神经支配在心肌梗死、高血压、心律失常、动脉粥样硬化和心衰等 CVD 中发挥重要作用，但目前在其他 CVD 如糖尿病心肌病、扩张型心肌病、肥厚型心肌病和心肌炎中的研究较少，具有重要的研究意义。失神经支配在各种 CVD 中不论是作为一种治疗手段还是心脏移植后的临床表现都具有重要的临床价值。目前研究最热的为 RDN 对难治性高血压的介入治疗，但是其他类型的失神经支配对于各种 CVD 的作用机制还尚不清楚，尤其 RDN 对动脉粥样硬化的影响目前也存在争议，值得进一步探索。失神经支配在心肌缺血再灌注损伤中的作用、在时钟基因昼夜节律中的作用以及在心脏移植中的作用可能成为潜在的研究方向。

利益冲突　无

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