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Review article

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Neurovascular interactions in the ageing heart

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Sections

Abstract

The global rise in life expectancy underscores the urgent need to extend healthspan and prevent age-related diseases. Cardiovascular disease is the leading cause of death worldwide, with ageing as a major non-modifiable risk factor. Ageing drives progressive vascular dysfunction and cardiac decline, including heart failure with preserved or reduced ejection fraction. Vascular cells are particularly vulnerable to ageing, resulting in structural and functional deterioration of the microvasculature and macrovasculature. Emerging evidence highlights that ageing also disrupts the neurovascular interface – an intricate axis between the nervous and vascular systems that governs cardiac function. Alterations to the neurovascular unit in the heart contribute to impaired autonomic regulation, increasing the risk of arrhythmias and heart failure. In this Review, we examine how neurovascular ageing shapes cardiac dysfunction and explore the therapeutic potential of targeting the cardiac neurovascular unit to mitigate cardiovascular ageing and promote resilience in ageing populations.

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Key points

- The nervous and vascular systems form closely interconnected interfaces that coordinate tissue homeostasis, neuroimmune communication and vascular integrity in both health and disease.
- Vascular ageing causes endothelial dysfunction, which affects neurovascular signalling, leading to reduced cardiac innervation and electrical instability; these changes can be reversed by senolytic therapies targeting senescent cells.
- The cardiac neurovascular unit mirrors mechanisms in the central nervous system, where nerves and blood vessels align and co-develop, regulated by neural activity and endothelial signals, to maintain cardiac function.
- Heart–brain communication mediated by neurovascular and neuronal pathways regulates cardiac autonomic control, linking central neurodegenerative processes to peripheral cardiac innervation and function.

Introduction

The global population is ageing at an unprecedented rate, and therefore improving healthspan and preventing age-related diseases are increasingly important. Cardiovascular disease (CVD) is the leading cause of death worldwide. Despite advances in the management of traditional risk factors, a substantial proportion of cardiovascular morbidity and mortality remains unaddressed[1]. Ageing is a major non-modifiable risk factor for CVD, highlighting the need to better understand the mechanisms underlying cardiovascular dysfunction in aged organisms.

Ageing is associated with a broad spectrum of vascular pathologies, such as atherosclerosis, aneurysms and valvular heart disease, as well as with progressive cardiac dysfunction such as heart failure with preserved or reduced ejection fraction. The ageing myocardium shows diastolic and systolic functional impairment, increased fibrosis and hypertrophy, and electrical remodelling that predisposes to arrhythmias[2]. These processes arise partly from intrinsic changes in cardiomyocytes but are also modulated by the cardiac autonomic nervous system (ANS).

Age-induced endothelial dysfunction and microvascular impairment contribute substantially to disease pathologies. Vascular cells are particularly susceptible to ageing, which induces structural and functional deterioration in arteries, veins and lymphatic vessels. As a result, nutrient and oxygen delivery is compromised, endothelial transport becomes inefficient, proteostasis declines, immune surveillance weakens, and the heart is deprived of key endothelium-derived 'angiocrine' factors[2]. The vasculature and nervous system are deeply interconnected through extensive, parallel networks, and their functional decline in ageing is interdependent. Although neurovascular ageing has been extensively characterized in the brain, a growing body of evidence suggests its crucial role in cardiac ageing. In this Review, we explore the neurovascular mechanisms that contribute to age-related cardiac dysfunction and discuss their implications for developing targeted interventions in ageing populations.

The cardiac neurovasculome

Interactions between the vasculature and the nervous system have been most extensively studied in the brain, where cerebral blood vessels have close developmental, structural and functional relationships with the central nervous system (CNS). The terms 'neurovascular units' and 'neurovasculome' have been introduced to describe the diverse neurovascular associations across various brain regions[3]. This neurovascular coupling enables precise regulation of oxygen and nutrient delivery to the brain and is essential for maintaining brain health; additionally, its disruption is implicated in cognitive impairment. These interactions are also present in the cardiovascular system and, in this section, we introduce the individual components of the cardiac neurovasculome – the cardiac vasculature and the ANS – and explore how these systems interconnect (Fig. 1), with a focus on neurovascular interactions in the heart.

The cardiac vasculature

The heart receives oxygenated blood through the coronary circulation, beginning with the left and right coronary arteries, which branch from the aorta just beyond the aortic valve. These arteries (the macrocirculation) run beneath the epicardium into the myocardium, branching into arterioles and an extensive capillary network (the microcirculation), which supply the entire heart with blood (Fig. 1). Capillaries deliver oxygen and nutrients while removing waste and drain into venules and coronary veins, culminating in the coronary sinus. Each cardiomyocyte is typically served by at least one capillary, reflecting the high metabolic demands of the heart[4].

Endothelial cells form the inner lining of all blood vessels and are highly abundant in the heart, outnumbering cardiomyocytes by three to one. In capillaries, endothelial cells regulate blood flow, inflammation and signalling[5–7]. Pericytes surround capillaries and modulate vessel diameter[8]. Perivascular macrophages help to maintain barrier integrity and regulate flow[9,10], whereas perivascular fibroblasts contribute to the structure and function of the extracellular matrix and to signalling interactions[11,12]. Vascular smooth muscle cells (VSMCs) encase arterioles and arteries, controlling tone and stability[13] (Fig. 1).

The cardiac ANS

The heart is a highly innervated organ that is connected to the CNS via afferent sensory fibres and efferent fibres of the peripheral nervous system. Together, these connections are referred to as the cardiac ANS (cANS). In general, the cANS acts as a relay station to process input from the brain and to maintain cardiac homeostasis[14]. Sensory fibres transmit information from the heart to higher levels of the nervous system, whereas efferent fibres transmit neuromotor impulses to the myocardium. The efferent fibres of the peripheral nervous system are divided into parasympathetic and sympathetic branches, which act antagonistically on heart function (Fig. 1). By interacting with cardiomyocytes via muscarine and adrenergic receptors, efferent nervous fibres regulate beating frequency (chronotropy), contractile amplitude (inotropy), conduction velocity (dromotropy) and cardiac relaxation (lusitropy).

The parasympathetic system originates from the vagus nerve, which projects to the heart and connects to cholinergic parasympathetic ganglia residing in atrial epicardial fat[15]. The mouse heart contains up to 30 ganglia, with an average of 90 neurons per ganglion[16]. The sympathetic system arises from the paired sympathetic chain ganglia on both sides of the vertebral column. The atria and ventricles of the heart are primarily innervated by long adrenergic fibres of the cervical chain ganglia (superior, middle and inferior cervical ganglia) and the upper thoracic chain ganglia (located from T1 to T4

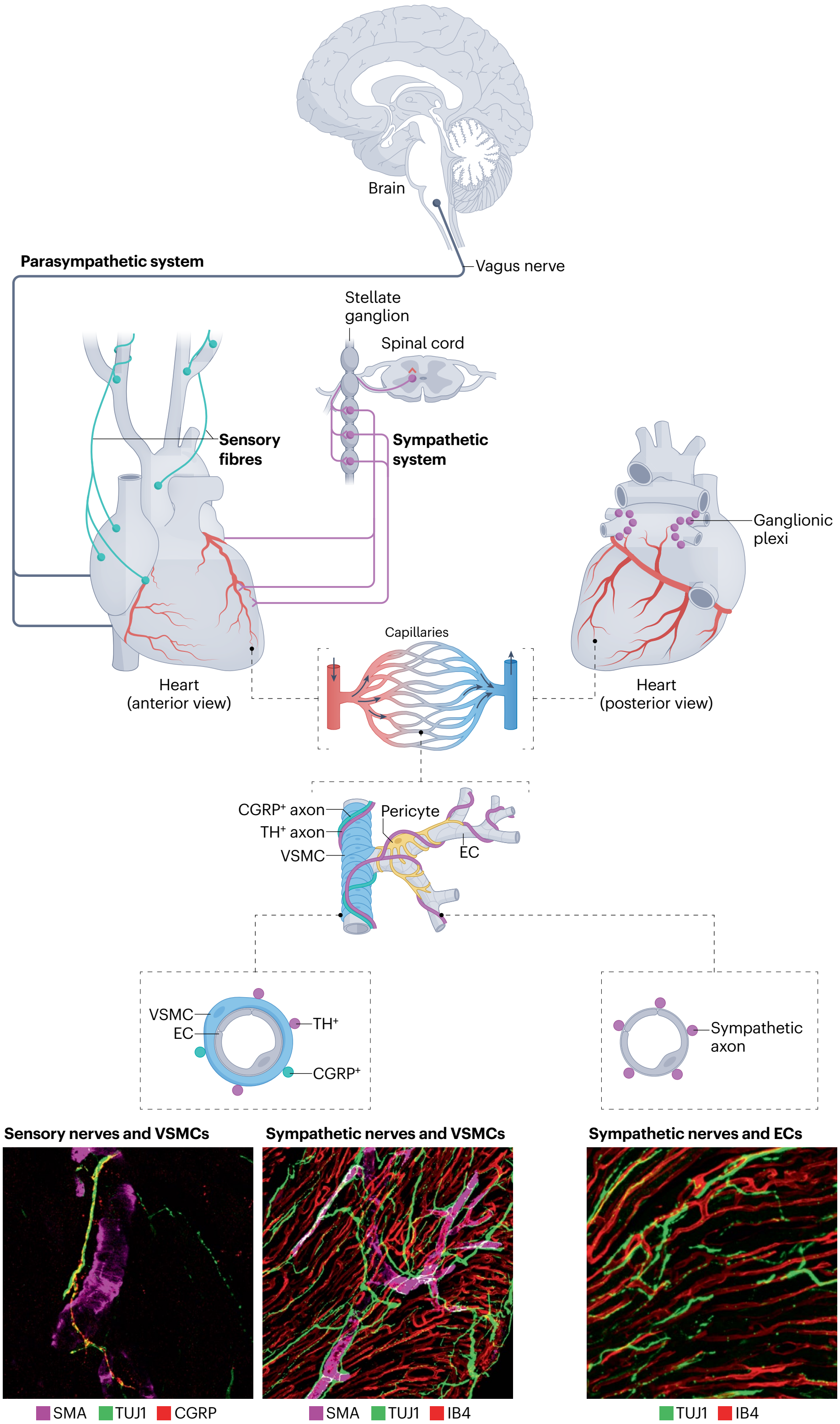

Fig. 1 | The cardiac neurovasculome. The cardiac neurovascular unit comprises the close structural and functional interactions between cardiac vascular cells and autonomic and sensory nerve fibres but is not well characterized in terms of cellular composition and dynamics. In the heart, sympathetic fibres (descending from the sympathetic chain ganglia, including the stellate ganglion) accompany arteries, arterioles and capillaries, whereas sensory fibres predominantly track along arteries, and parasympathetic fibres (descending from the vagus nerve) mainly innervate the atria and the base of the heart, with little innervation of the ventricular myocardium. Nerve fibres reach into the heart by following the blood vasculature; this co-alignment is referred to as the neurovascular unit. The histology images show neurovascular alignment in the hearts of young mice (aged 3 months). In the left-hand panel, arterioles are visualized with smooth muscle actin (SMA) staining (magenta), nerve fibres generally with tubulin-β3 chain (TUJ1) staining (green), and sensory nerves specifically with calcitonin gene-related peptide (CGRP) staining (red). In the centre and right-hand panels, endothelial cells (ECs) are visualized with isolectin B4 (IB4) staining (red). Whereas sympathetic nerve fibres co-align with both arteries and capillaries, sensory nerve fibres align only with arteries. TH, tyrosine hydroxylase; VSMC, vascular smooth muscle cell. Immunostaining images adapted with permission from ref. 20, AAAS.

or T5)[17] (Fig. 1). The inferior cervical ganglion and the first thoracic ganglion form the stellate ganglion, a prominent structure of the sympathetic chain at the level of the first rib. The sympathetic fibres from these ganglia converge with the parasympathetic ganglia and sensory ganglia in the cardiac plexus, which is located at the base of the heart[18].

The neurovascular unit in the heart

The neurovascular unit of the CNS is composed of vascular cells and axons that are intricately organized and separated by specialized glial cells known as astrocytes. These astrocytes function as crucial gatekeepers, mediating the transfer of nutrients from the bloodstream to neurons, while simultaneously acting as a selective barrier that filters neurotoxins. Through this dual role, astrocytes have a vital role in safeguarding neuronal health and maintaining CNS homeostasis[19]. The cardiac neurovascular unit represents a close interaction between vascular cells and nervous fibres but remains understudied compared with the brain, with substantially less known about its cellular composition and functional dynamics. In the heart, sympathetic fibres follow arteries, arterioles and capillaries, whereas sensory fibres follow only arteries. Parasympathetic fibres innervate the atria and cardiac base of mouse hearts but are not present in the ventricles[20].

Although the neurovascular unit of the CNS has been extensively studied[21], only a few studies have been conducted on neurovascular interactions during development and ageing in the heart (mainly in mice)[20,22–24]. During embryonic development, neurovascular interaction is a tightly coordinated process, in which coronary vessels have a pivotal role. Growth and branching of developing coronary veins provide anatomical scaffolding, allowing sympathetic fibres to project along the surface of the heart and to extend into the developing myocardium[22,24]. In mouse embryos at embryonic day (E) 13.5, VSMCs of coronary veins guide sympathetic fibres along the epicardial surface via the release of nerve growth factor (NGF). In parallel to vascular remodelling, VSMCs of distal veins release NGF at E15.5, whereas subepicardial coronary veins downregulate NGF expression to allow axons to reach into the heart. At E17.5, sympathetic fibres penetrate the myocardium, guided by NGF from arterial VSMCs, but venous VSMCs no longer express NGF[24]. This vessel-guided innervation allows temporospatial organization of cardiac nerve patterns. In addition to the close local anatomical interaction between nerves and vessels, the cardiac neurovascular unit provides feedback to the CNS. Sensory fibres innervate the large arteries, such as the aorta, and sense vascular tone to control blood pressure and flow[25].

Neurovascular mechanisms in ageing

Structural changes in the cardiac neurovasculome

Ageing exerts systemic effects on the vasculature, marked by endothelial dysfunction, arterial stiffening and extracellular matrix remodelling. These changes impair arterial compliance, elevate systolic blood pressure and increase pulse wave velocity, leading to left ventricular hypertrophy and diastolic dysfunction[2]. Vascular ageing also impairs baroreceptor function due to stiffening of the aortic arch and carotid sinus, reducing baroreflex sensitivity[26]. These changes result in orthostatic hypotension, increased blood pressure variability and heightened cardiovascular risk[26]. Importantly, vascular and haemodynamic ageing are closely linked to structural and functional brain alterations, including white matter damage and impaired neurovascular and autonomic regulation, which disrupt integrative cardiovascular control and crosstalk with other organs[27].

In the heart, a study published in 1994 showed that ageing leads to reduced capillary and arteriolar density, increased heterogeneity in capillary spacing, and the presence of enlarged arterioles with thickened walls in mice aged 23 months[28]. Subsequent immunohistochemical studies have confirmed and refined these observations by showing that capillary enlargement, correlated with a marked loss of pericytes, occurred in mice from the age of 18 months[29]. Capillary rarefaction is also seen with ageing[20,29] and, importantly, is not merely a consequence of endothelial cell dysfunction but is preceded by mural cell impairment (especially pericyte loss), which is pivotal to initiating vessel remodelling[29] (Fig. 2). Capillary dysfunction and rarefaction can directly contribute to impaired diastolic function, as reported in models of heart failure with preserved ejection fraction[30,31].

In addition to structural alterations, ageing induces changes in the cellular composition of the neurovasculature in the brain and the heart. Notably, in the heart, alterations in neural elements precede visible structural changes in the vasculature. In mice, axon density has been found to decline early in the ageing trajectory (16 months), before measurable reductions in capillary density are observed (>18 months)[20]. In the left ventricle, sympathetic denervation is particularly pronounced around arterioles and capillaries, especially in regions close to the endocardium, whereas the epicardial regions retain more intact nerve fibres[20]. Interestingly, the decrease in sympathetic fibres is evident only in the left ventricle, whereas the right ventricle shows no loss of innervation[20]. This imbalance of sympathetic fibres suggests that the vulnerability of cardiac neurovascular units to ageing is spatially heterogeneous.

Sensory fibres, which are exclusively detected in close proximity to arteries and arterioles, have been shown to be less abundant in aged versus young hearts[20]. Parasympathetic fibres are also scarcer in older versus younger hearts. However, these fibres are primarily found in the base of the heart and very rarely in the ventricles[20], raising the questions of whether they contribute to the ventricular neurovascular unit and whether the age-related reduction in these fibres is linked to vascular impairment.

Although animal models have provided valuable insights into age-related neurovascular changes, our understanding of these processes in the human heart remains limited due to the limited availability of healthy aged cardiac tissue. As a result, much of our knowledge relies on comparative histological data from animals[32], which reveal the complex, compartment-specific nature of neurovascular ageing. Studies in humans are needed to examine vascular and neural components together, given their probable joint role in preserving cardiac function and influencing age-related diseases such as heart failure with preserved ejection fraction.

Cell changes in the cardiac neurovascular unit

Beyond its systemic effects, vascular ageing alters the cardiac neurovascular unit, involving endothelial cells, mural cells (such as pericytes and VSMCs), fibroblasts, cardiomyocytes and immune cells, all of which interact with nerves. These age-related changes are associated with functional alterations across the neurovascular axis, impairing coordination between the vascular system and neural control of the heart. Over time, these changes compromise cardiac performance, increase vulnerability to arrhythmias and contribute to heart failure. In this section, we delineate the mechanisms and functional consequences of ageing on various cellular components of the neurovascular interface as well as the interaction with the ANS during ageing (Fig. 3). Experimental assessment of the cardiac neurovascular unit is associated with various technical challenges that are summarized in Box 1.

Endothelial cells. The endothelium has a crucial role in the cardiac neurovascular unit. Ageing is a major driver of endothelial dysfunction, which is characterized by reduced nitric oxide bioavailability and increased oxidative stress[26,33]. Ageing vessels exhibit chronic inflammation via nuclear factor-κB signalling, with upregulated expression

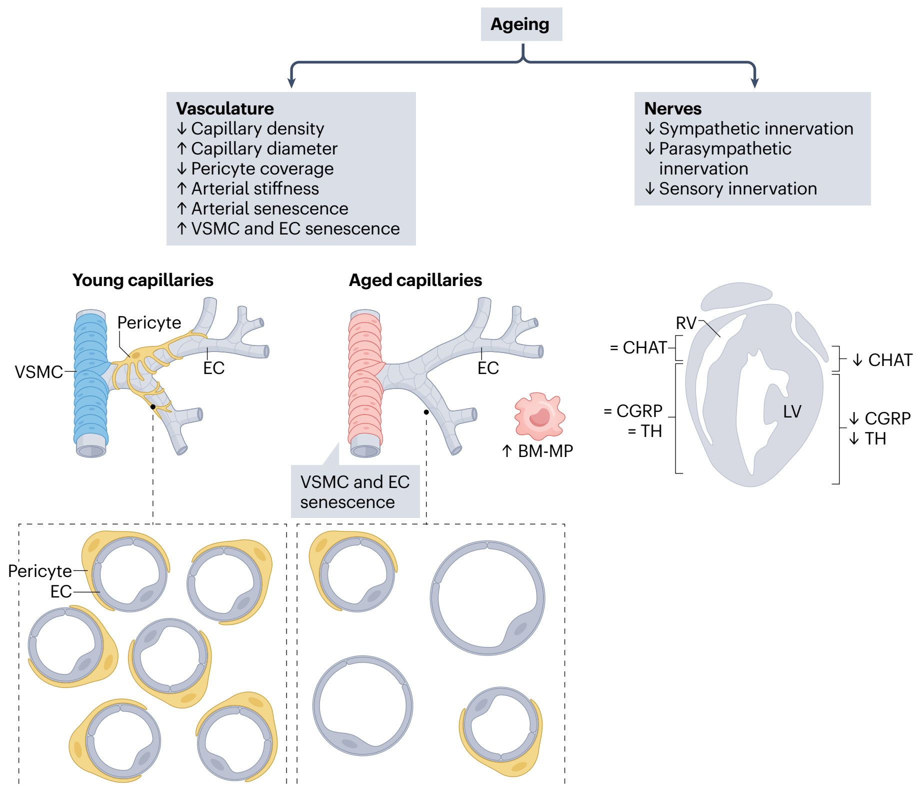

Fig. 2 | Age-related alterations in the cardiac neurovasculome. Cardiac ageing is associated with both vascular and neuronal changes. The ageing heart shows a decline in capillary density and pericyte coverage and an increase in capillary diameter. Bone marrow-derived macrophages (BM-MP) accumulate in the myocardium. Arteries become stiff, and senescence occurs in vascular smooth muscle cells (VSMCs) and endothelial cells (ECs). The nervous system shows alterations in the left ventricle (LV) but not in the right ventricle (RV). Towards the base of the heart, the density of choline acetyltransferase-positive ($CHAT^{+}$) parasympathetic fibres declines, whereas the density of calcitonin gene-related peptide-positive ($CGRP^{+}$) sensory fibres and tyrosine hydroxylase-positive (TH^{+}) sympathetic fibres declines throughout the entire LV.

of adhesion molecules such as intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion protein 1, pro-inflammatory cytokines and matrix metalloproteinases[26,34], which can lead to endothelial barrier dysfunction[35]. Senescent endothelial cells exacerbate vascular inflammation by altering ICAM1 clustering, which promotes leukocyte adhesion[36], and by the release of senescence-associated secretory phenotype (SASP) components. Single-cell analyses have uncovered a population of 'immune-modulatory endothelial cells' that can modulate age-associated vascular immune responses[37]. Notably, endothelial senescence emerges early, often preceding haematopoietic immunosenescence[38].

Pro-inflammatory conditions and transforming growth factor-β signalling can force the loss of endothelial cell identity and promote endothelial-to-mesenchymal transition. This process contributes to a reduction in vasoprotective effects associated with increased oxidative stress, collagen upregulation and loss of anti-inflammatory markers as well as dysregulated nuclear factor erythroid 2-related factor 2–serine/threonine-protein kinase mTOR signalling[39,40]. Although observed in vitro and in aged tissues, the causative role of endothelial-to-mesenchymal transition in vascular and cardiac ageing remains to be confirmed.

Endothelial cell ageing and senescence have a major effect on the innervation of the heart. In mice, the induction of endothelial cell senescence by transgenic expression of progerin was sufficient to cause left ventricular denervation[20]. In addition, senescent endothelial cells were shown to secrete repelling factors, such as semaphorins, whereas neuroprotective genes, such as *Vegfb*, were repressed in aged mouse hearts[20,23]. This imbalance in the abundance of neurotrophic factors contributes to axon repelling and left ventricular denervation in the ageing heart. In mice, mimicking the effects of ageing by overexpression of semaphorin 3A in endothelial cells was sufficient to induce denervation[20]. Functionally, cardiac denervation was associated with reduced heart rate variability (HRV) and increased susceptibility to ventricular tachyarrhythmia[20]. Treatment with the senolytic drugs dasatinib and quercetin reduced the expression of genes encoding neuro-repellent proteins and restored cardiac innervation, leading to improved HRV and reduced tachyarrhythmia[20]. In another study, cardiac innervation in aged mice was rescued by overexpression of *Vegfb*[23]. Together, these findings support a causal role for endothelial cellular senescence in disturbing neurovascular control.

Mural cells. VSMCs, which are present in the walls of arterioles and arteries, but to a lesser extent in veins, also influence the cardiac neurovascular unit. Interactions between VSMCs and nerve fibres have been observed during embryonic heart development[24]. However, these interactions have not yet been studied in the ageing heart. Notably, 'hotspots' of cellular senescence were primarily detected in VSMC-covered arterioles and arteries in the ageing heart[38], at locations where profound nervous denervation occurred[20]. This spatial co-localization suggests that VSMC ageing or senescence might contribute to impairment of the cardiac neurovascular unit. Additionally, neurovascular communication could be bidirectional. In rat femoral and tail arteries, sympathetic fibres promote VSMC differentiation, and pharmacological denervation impairs femoral artery development and VSMC maturation[41], raising the possibility of similar interactions in the heart. Given that both arteriole and axon densities decline in the ageing heart[20,28], it will be interesting to elucidate whether arteriole ageing drives denervation or vice versa.

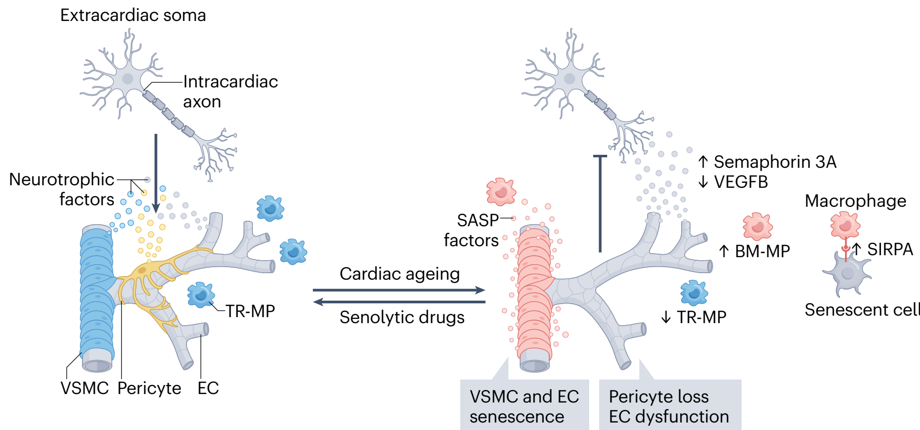

Fig. 3 | Ageing impairs the cardiac neurovascular unit. The cardiac neurovascular unit is fostered by paracrine interactions between nervous and vascular cells. The vasculature produces neurotrophic factors that stabilize cardiac innervation. During ageing, axon-repelling signals, such as semaphorin 3A, are increased, whereas the production of neuroprotective factors, such as vascular endothelial growth factor B (VEGFB), is reduced. In addition, senescence-associated secretory phenotype (SASP) factors are released by senescent vascular cells. These changes are associated with vascular dysfunction, shown by vascular smooth muscle cell (VSMC) senescence, loss of pericyte coverage, endothelial cell (EC) dysfunction and a switch in macrophage populations (from tissue-resident macrophages (TR-MP) to bone marrow-derived macrophages (BM-MP)), resulting in a decline in axon density in the ageing heart. Senescent cells have increased expression of 'do-not-eat-me signals', such as tyrosine-protein phosphatase non-receptor type substrate 1 (SIRPA), which prevent their clearance by phagocytosis. Eliminating cellular senescence using senolytic drugs restores the expression of neurotrophic factors and the presence of TR-MP populations, leading to increased innervation.

Other mural cells closely associated with capillaries, such as pericytes, have not been shown to directly maintain the ageing cardiac neurovascular unit. However, the number of pericytes decreases with age[29], and reduced pericyte coverage could contribute to age-related endothelial dysfunction, thereby impairing the neurovascular unit in the cardiac microvasculature. Given the proximity between pericytes and nerves, direct interaction between these two cell types might also be possible and needs further exploration.

Fibroblasts. Ageing profoundly activates fibroblasts, which are present not only in interstitial tissue but are especially enriched in the perivascular space of the ageing heart[29,38]. The main contribution of fibroblasts in ageing is the expression of collagens and extracellular matrix proteins, which augment the stiffness of cardiac tissue. In addition, fibroblasts interact with the vasculature, specifically with endothelial cells. Single-nucleus RNA-sequencing has identified an ageing-associated fibroblast cluster in the mouse heart expressing angiogenic factors such as plasminogen activator inhibitor 1 (PAI-1; encoded by *Serpine1*)[42]. PAI-1, a SASP component and senescence marker, impairs endothelial function, promotes inflammation and can induce senescence[42,43]. Therefore, fibroblast activation might drive endothelial senescence and indirectly contribute to cardiac denervation. In addition, fibroblasts might directly interact with axons in the heart and induce axon growth by releasing NGF[44,45], although this interaction has not been well studied.

Macrophages. Ageing is associated with major changes in macrophage populations. Cardiac-resident macrophage populations decline with age and are replenished by bone marrow-derived macrophages, which accumulate in the ageing heart, typically around the vascular niches. In other tissues, several lines of evidence suggest that macrophages can regulate the neurovascular axis. Perivascular macrophages, a specific class of tissue-resident macrophage, interact with sympathetic fibres and regulate local catecholamine levels via amine oxidase (flavin-containing) A (also known as monoamine oxidase A), influencing adipose tissue metabolism[46,47]. In brown fat, these macrophages control innervation and thermogenesis, and their absence leads to reduced nerve density[48]. In the gut, perivascular macrophages are associated with neurons and support neuronal development[49–51]. Interactions between nerves and macrophages have also been studied in the context of myocardial infarction. In female rats after ovariectomy, macrophages were suggested to drive sympathetic hyperinnervation after myocardial infarction by releasing NGF[52]. Depletion of macrophages prevented hyperinnervation and reduced the arrhythmic burden in the infarcted heart[52]. However, other studies have highlighted a distinct role for tissue-resident macrophages in maintaining electrical conduction, whereas the recruitment of circulating monocytes has been linked to the development of atrial fibrillation[53]. Therefore, further research is required to determine the relevance of macrophage populations – and how they alter innervation and electrical conduction – in various regions of the heart. Overall, these data suggest crucial interactions between macrophages and the neurovasculature, which might be relevant in the ageing heart.

ANS regulation. Beyond structural denervation, ageing disrupts ANS regulation of both the vasculature and the heart. Sympathetic and parasympathetic control becomes less effective due to alterations at both the neural and receptor levels. In the vasculature, adrenergic responsiveness diminishes with age. Older adults have blunted vasoconstrictive responses to intra-arterial noradrenaline, reflecting reduced α-adrenergic receptor sensitivity and impaired downstream signalling[54].

In aged mice (20–22 months), functional ultrasonography of the brain revealed impairment of the neurovascular unit, reducing the functional hyperaemia response that is a hallmark of neurovascular coupling in the brain[55]. These data suggest that dysfunctional neurovascular coupling in the ageing or diseased heart might result in impaired stimulus-evoked blood flow. This hypothesis is particularly interesting because sympathetic regression can be observed before capillary decline occurs.

Ageing also affects autonomic control of cardiomyocytes by altering β-adrenergic receptor (βAR) signalling in these cells through a series of molecular and biochemical mechanisms, including reduced βAR affinity for agonists, decreased G protein and adenylate cyclase activity, and impaired protein kinase A-mediated phosphorylation[56,57]. These changes diminish the contractile response to sympathetic stimulation. In aged rat hearts (24 months), βAR activation did not significantly increase calcium influx and cytosolic calcium transients, leading to reduced cardiac contractility and decreased cardiac reserve[58]. Ageing also impairs noradrenaline storage at sympathetic nerve terminals due to reduced vesicular monoamine transporter activity[59]. This situation results in elevated extracellular noradrenaline levels and decreased βAR responsiveness. Paradoxically, although noradrenaline availability increases, the reduced receptor sensitivity and signalling efficacy impair cardiac function and contribute to arrhythmias and decreased contractility. Taken together, these findings indicate that age-related impairment of the neurovascular unit in the heart drives an uneven patterning of cardiac innervation, which could promote autonomic imbalance and, therefore, increase susceptibility to cardiac arrhythmia with ageing.

The heart–brain axis in ageing

Studying the cardiac neurovascular unit underscores the idea that the heart functions as an integrated part of a complex, systemic network rather than in isolation. The heart receives signals via efferent autonomic fibres and sends feedback through afferent fibres, forming a dynamic bidirectional network known as the heart–brain axis (Fig. 4). This axis reflects the complex interaction between the cardiovascular system and the CNS, mediated through neural, immunological and humoral pathways. This understanding raises fundamental questions. Does ageing simply exert systemic effects on the neurovascular interface across various organs with parallel, but independent, outcomes? Or are age-related pathologies of the heart and brain intrinsically connected, such that dysfunction in one system precipitates or exacerbates dysfunction in the other?

CVD and cerebrovascular diseases share several common risk factors, such as ageing, hypertension and metabolic disturbances, suggesting the possibility of co-development without direct interdependence. However, accumulating evidence supports the view that these two systems are tightly linked. Disruption in one can profoundly affect the function of the other, indicating a deeper level of interconnection. Inhibition of cholinergic nerve function in the ANS has been shown to impair cardiac recovery after myocardial infarction in neonatal mice and zebrafish[60,61]. Likewise, stroke, induced by an acute ischaemic injury in the brain, can lead to impairment of the cardiovascular system[62]. Indeed, electrocardiographic alterations and elevated biomarkers of cardiac injury are commonly seen after brain injury[62,63]. In addition, brain stress, particularly from acute emotional or physical events, can trigger a surge of catecholamines that overstimulate cardiac βARs, leading to transient myocardial stunning and Takotsubo cardiomyopathy[64].

In the context of ageing, neurodegenerative disorders offer another example of how the brain can affect cardiac function. Conditions such as Alzheimer disease and Parkinson disease can be accompanied by cardiac alterations and autonomic dysfunction, including orthostatic hypotension[65,66]. Structural and functional changes in the heart have also been observed in patients with Alzheimer disease[67], although the exact molecular mechanisms remain unclear. However, these findings might also be explained by the accumulation of amyloid-β proteins in the vasculature and myocardium (as well as the brain), potentially contributing to cardiovascular pathology.

The heart can also influence brain function through autonomic and inflammatory pathways. The ANS, particularly its sympathetic and parasympathetic branches, has a key role in regulating this two-way communication. Variations in heart rate and rhythm can activate specific brain regions, such as the insular cortex, which in turn influence behaviour and mood, including depression[68]. Dysregulation of the ANS is frequently observed in both CVD and neurodegenerative conditions, pointing to a shared vulnerability. However, an elegant study using a mouse model with a non-invasive optogenetic pacemaker provided direct evidence of a causal link between heart and brain function by demonstrating that optically evoked tachycardia increases anxiety-like behaviour[69].

This bidirectional relationship can create a self-reinforcing feedback loop. For example, CVD can promote neurodegeneration through haemodynamic disturbances, impaired cerebral perfusion and systemic inflammation[70]. Simultaneously, degeneration of brain regions that regulate autonomic outflow, such as the amygdala, brainstem, hypothalamus and insular cortex, can impair cardiac control[71,72]. Compromise of this central autonomic network leads to an

Box 1 | Studying the cardiac neurovascular unit in vivo

Assessing the cardiac neurovascular unit in vivo remains a substantial challenge. In addition to conventional immunofluorescence imaging, neuroscientists have developed a comprehensive toolkit for imaging the cerebral neurovasculome in living small animals. For example, polymeric cranial windows can be implanted into the skull, enabling longitudinal monitoring of the brain's vascular bed and associated nerve fibres. Imaging techniques, such as functional ultrasonography, super-resolution ultrasound localization microscopy and confocal optical imaging, are commonly used for this purpose[55,130].

By contrast, intravital imaging of the cardiac neurovasculome is limited. Although implantation of cardiac windows is possible, the surgical procedure is more complex than for cranial windows, and the beating of the heart complicates continuous live imaging. As a consequence, cardiac windows can be maintained only for a few days and cannot be used for monitoring long-term treatments[131,132]. This limitation can be addressed by using functional positron emission tomography or scintigraphy. Notably, ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy can be used clinically in humans to measure catecholamine uptake in the heart, serving as a surrogate marker for nerve density[133]. ^{123}I-MIBG is a synthetic tracer that is taken up by nerve endings[134,135]. Therefore, increased ^{123}I-MIBG uptake can indicate greater innervation or heightened sympathetic activity. However, this technically demanding method requires expertise in nuclear medicine, a lengthy approval process and offers limited cellular resolution, highlighting the need for improved imaging platforms to visualize the cardiac neurovasculome in vivo.

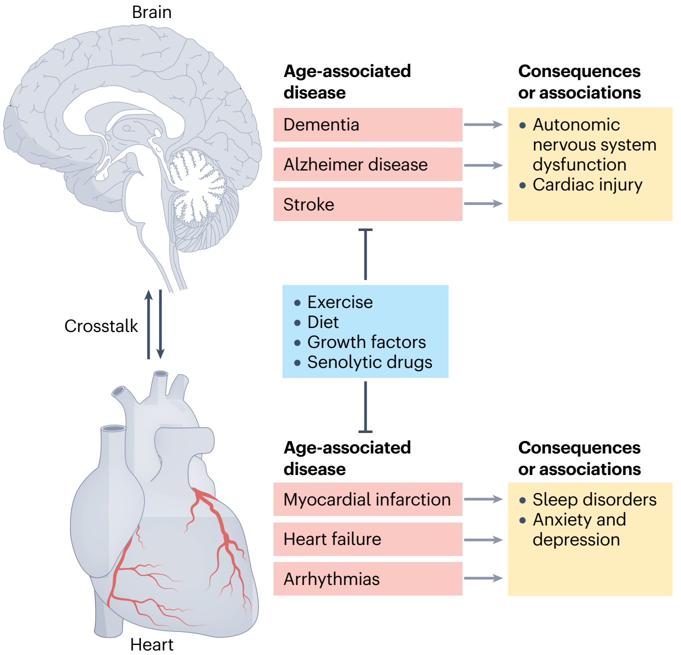

Fig. 4 | The ageing heart–brain axis. Ageing is a major risk factor for both cardiovascular diseases and neurodegenerative diseases. Interactions between the heart and brain are inextricably linked and, therefore, pathological changes in one organ can cause dysfunction in the other. For example, heart failure can impair the pineal gland in the brain, leading to sleep disorders, and cardiac arrhythmias can result in anxiety and depression. Similarly, disorders of the central nervous system can impair the autonomic nervous system, affecting heart rate variability. Exercise, diet or treatment with growth factors, such as vascular endothelial growth factor B, or senolytic drugs can ameliorate these age-related deteriorations.

imbalance favouring sympathetic overactivity. The resulting chronic release of catecholamines, such as noradrenaline, promotes arrhythmias, myocardial apoptosis and fibrosis, which in turn worsen heart function[73,74]. Reduced parasympathetic (vagal) tone further amplifies this imbalance[75]. Additionally, neurodegenerative changes can activate neurohumoral systems, including the renin–angiotensin axis and vasopressin pathways, increasing vascular tension and exacerbating dysfunction in both the heart and brain[76]. Electrical remodelling of cardiac tissue can also occur in response to altered brain activity, increasing the risk of arrhythmias and sudden cardiac death[77].

Beyond neural circuits, studies have uncovered other modes of heart-to-brain communication. For example, heart failure has been associated with macrophage infiltration and fibrosis of the superior cervical ganglion, an important sympathetic relay for the heart. Fibrosis leads to denervation of the superior cervical ganglion, which in turn affects the pineal gland, the brain structure that produces melatonin[78]. Given that the superior cervical ganglion provides crucial sympathetic input to the pineal gland, its dysfunction results in reduced melatonin synthesis and sleep disturbances. Intriguingly, experiments in mice have shown that depleting macrophages after aortic constriction can restore innervation of the superior cervical ganglion and normalize function of the pineal gland[78], suggesting a potential therapeutic approach. This pathway could have implications for ageing because melatonin production naturally declines with age[79]. Ageing is also associated with pineal gland dysfunction, which disrupts circadian rhythms and contributes to disturbances in metabolism and sleep[80]. Exogenous melatonin supplementation has been shown to prevent pineal dysfunction and delay various age-associated changes in animal models[79]. These findings suggest that the decrease in melatonin level might not only be a marker of ageing but could also have a causative role in age-related physiological decline. A vicious cycle ensues, in which ageing reduces melatonin production, and the resulting deficiency in melatonin accelerates the ageing processes.

Restoring neurovascular function in ageing

In this section, we turn to a central question: can interventions targeting dysregulated structure and function in the cardiac neurovascular unit and the heart–brain axis promote healthy ageing of the cardiovascular and nervous systems and mitigate age-related cardiovascular risk?

Direct interventions in the heart

Given that the vasculature, particularly endothelial cells, constitutes a vital component of the cardiac neurovascular unit, strategies aimed at preserving vascular function might help to maintain the functional integrity of this unit during ageing. Such interventions could include well-established endothelium-protective strategies such as increasing nitric oxide signalling or counteracting oxidative stress. However, therapeutic interventions that directly target the nitric oxide pathway to improve endothelial cell function have so far been unsuccessful[81,82], and only indirect approaches, such as exercise or lipid lowering by statins, have demonstrated clinical benefit[83,84]. The effects of available cardiovascular drugs on the ageing cardiac neurovascular unit warrant further investigation.

The clearance of senescent cells can help to eliminate SASP components, which contribute to the 'inflammageing' process. Senolytic drugs have been shown to restore innervation, improve HRV and prevent age-associated arrhythmias in mice[20]. Various senolytic and senomorphic agents have yielded promising results in experimental studies, showing improvements in the neurovascular unit of the brain as well as cognitive and physical function and lifespan in aged mice[85–88], prompting the initiation of the first clinical trials of senolytics for age-related diseases[89–91]. However, further studies are needed to establish the safety and efficacy of this approach[91]. Importantly, eliminating widely distributed senescent cells is likely to have off-target, systemic effects. Nevertheless, given the substantial contribution of cardiovascular health to longevity and its influence on brain function, assessments of HRV and cardiac function should be included in future clinical trials of senolytic drugs, even when the primary focus is on neurodegenerative diseases.

Growth factors, such as members of the vascular endothelial growth factor (VEGF) family, might also offer therapeutic benefits. For instance, restoring *Vegfb* expression in the ageing mouse heart was shown to increase innervation and improve several hallmarks of cardiac ageing[23]. However, VEGFB also promoted cardiomyocyte hypertrophy, probably through direct effects on cardiomyocytes[23]. Although hypertrophy was not associated with impaired cardiac function, this outcome must be considered when evaluating VEGFB therapy. In mice, VEGFA therapy has also shown promising preservation of organ homeostasis with ageing as well as increased life expectancy[92]. However, its effect on the ageing heart and the cardiac neurovascular unit has not been explored. Neurotrophic factor BDNF (also known as brain-derived neurotrophic factor) has been shown to promote nerve growth and support cardiac regeneration in mice[93], although its role in cardiac ageing remains unclear. In addition, glial cell line-derived neurotrophic factor (GDNF) and neurotrophin 3 have also been shown to increase cardiac innervation during embryonic development[94,95]. In injured rat hearts, GDNF treatment improved cardiac innervation and increased cardiomyocyte contractility[96]. Reelin, a neurotrophic factor studied in models of Alzheimer disease[97], has been reported to have cardioprotective effects[98]. However, its role in cardiac innervation remains unclear. Levels of another neurotrophic factor, insulin-like growth factor 1 (IGF1), were shown to be decreased in aged mouse brains, which was associated with reduced brain capillary density[99]. Inducing IGF1 production has protective effects on the cerebral vasculature and restores brain capillary density[99,100]. Although the role of IGF1 in the neurovascular unit of the heart is unclear, it is known to induce adaptive cardiac hypertrophy[101,102], raising concerns about the use of this growth factor as a long-term therapeutic approach.

Directly targeting axon-guidance molecules, such as semaphorin 3A, is another strategy to modulate the cardiac neurovascular unit. Overexpression of semaphorin 3A in mice reduces cardiac innervation and decreases HRV[20]. Similarly, depletion of microRNA-143 (miR-143) and miR-145, which derepress semaphorin 3A, also reduces innervation and HRV[20]. However, whether blocking semaphorin 3A via miR-145 or other approaches could be used therapeutically to restore the cardiac neurovascular unit remains to be determined. Importantly, targeting such guidance cues must be approached with caution because they could affect other neuronal populations and often have a role in immune regulation.

Together, these findings show that several strategies can be used to directly restore neurovascular function in the heart, but whether they also counteract cardiovascular ageing remains unclear. Whether sympathetic nerve loss in ageing is adaptive, and how restoring innervation affects long-term heart health, also remains to be determined. Of note, cardiac reinnervation needs to be well balanced because heterogeneous (patchy) reinnervation or cardiac hyperinnervation can induce severe arrhythmias[103,104]. Therefore, strategies aimed at restoring or protecting the cardiac neurovascular unit, rather than merely increasing innervation, will be necessary.

Systemic approaches

In addition to directly targeting the cardiac neurovascular unit, various systemic interventions could help to break the vicious cycle of heart–brain dysfunction. These strategies include lifestyle modifications, such as exercise, sleep optimization and dietary interventions, as well as anti-inflammatory therapies and neuromodulation[105].

Regular exercise undeniably confers cardiovascular benefits[106]. Specifically, exercise positively modulates ANS balance and increases HRV in older adults[107,108]. Exercise also increases VEGFA expression and improves endothelial cell function in aged rodent hearts[109,110]. However, the effects of exercise on the ageing cardiac neurovascular unit have not been reported.

As discussed in the section on the heart–brain axis, ageing disrupts circadian rhythms through diminished activity of the suprachiasmatic nucleus, leading to a decline in melatonin production and bidirectional heart–brain dysfunction. Behavioural changes to restore healthy sleep patterns could help to mitigate this cycle by reducing inflammation and improving neurocardiac communication. Notably, senolytic treatment restored the day–night cycle of HRV in aged mice[20], supporting a link between cellular senescence and circadian rhythmicity.

The effect of metabolic syndromes on cardiac innervation is well established and is particularly evident in patients with diabetic cardiomyopathy[111]. Diabetes mellitus reduces the expression of NGF, which is crucial for cardiac sensory innervation[112], and leads to a reduction in NAD^+ level. In the CNS, age-associated NAD^+ depletion has been shown to lead to neurovascular unit dysfunction, which was associated with vascular cognitive impairment. Increasing NAD^+ levels via nicotinamide riboside or nicotinamide mononucleotide supplementation restored pathways associated with mitochondrial rejuvenation and activated anti-inflammatory and anti-apoptotic genes to improve neurovascular function in mice[113,114] as well as vascular and cognitive function in older patients (aged ≥55 years) with peripheral artery disease[113,114]. Although the role of NAD^+ on cardiac innervation has not been studied, impaired cardiac NAD^+ biosynthesis is known to lead to dilated cardiomyopathy[115]. These findings suggest that interventions targeting metabolism might not only mitigate cardiometabolic complications but also preserve the function of the cardiac neurovascular unit and contribute to healthy ageing.

Caloric restriction, which has been shown to promote longevity in rodent and primate models, also exerts effects on the brain and could influence age-related changes in the cardiac neurovascular unit[116–118]. In rats, caloric restriction prevents the age-related decline in βAR density, maintains baroreceptor reflex sensitivity, and shifts autonomic balance towards increased parasympathetic tone and reduced sympathetic tone[116,119]. Diet also shapes the gut microbiota, which can also have systemic effects. Changes in the composition of the microbiota affect the bioavailability of metabolites and lead to the formation of a 'permissive' microbial environment that promotes inflammation[120,121]. These alterations can lead to vascular dysfunction, including cavernous angioma in the CNS[120,121]. Remarkably, transplantation of faecal microbiota from young mice has been shown to reverse age-associated alterations in brain metabolism and microglial activation in older animals[122], and early-stage clinical trials of this approach suggest cognitive and behavioural improvements in older adults[123], a finding that warrants further investigation.

Targeting neuro-immuno-senescence circuits could offer additional strategies to disrupt the self-perpetuating inflammatory cycles that contribute to age-related diseases. Epidemiological studies have demonstrated that the long-term use of non-steroidal anti-inflammatory drugs is associated with a reduced risk of neurodegenerative disorders[124]. However, clinical trials have generally not supported the therapeutic efficacy of non-steroidal anti-inflammatory drugs or other general anti-inflammatory agents in this context[125]. Therefore, targeted approaches are needed, and precision anti-inflammatory strategies, senolytics or selective inhibition of specific SASP components might hold potential. For instance, inhibition of IL-1β in the CANTOS trial[125] showed protective effects in patients with coronary artery disease. Building on this finding, anti-inflammatory therapies are being evaluated in patients with established CVD in several ongoing clinical studies[126]. These trials will potentially pave the way for interventions that mitigate cardiovascular ageing. Autonomic function could be used as a surrogate marker in these studies to identify the therapeutic effects on the neurovascular interface.

Finally, neuromodulation presents a promising avenue to restore neurovascular and autonomic function[105]. Advances in techniques, such as vagus nerve stimulation[127] and targeted neuroelectrical modulation[128], have resulted in the potential to modulate inflammatory pathways and improve clinical outcomes in age-related diseases. As our understanding of neuroimmune interactions deepens, integrating neuromodulatory approaches with molecular therapies could lead to the development of novel strategies to combat chronic inflammation and promote healthy ageing.

Glossary

Cardiac neurovascular unit
A microscale concept describing the intimate structural and functional association between neurons, vascular cells (endothelial cells, pericytes and vascular smooth muscle cells) and the extracellular matrix at a given microvascular segment (arteriole, capillary or venule) in the heart.

Cardiac neurovasculome
A macroscale systems concept denoting the totality of all neurovascular units, including all vascular and nervous structures, in the heart.

Conclusions

A substantial body of evidence highlights the importance of the cardiac neurovascular interface in the context of cardiovascular and neurological diseases. In addition, studies have shown that interventions targeting the cardiac neurovascular unit can provide protection against CVD and promote healthy ageing. However, direct evidence remains limited because many of the observed therapeutic effects are likely to arise from the complex interaction between cardiac tissue and the nervous system. Further in-depth research is needed to elucidate how these strategies influence autonomic balance and neurovascular interactions during ageing, particularly concerning the roles of afferent and sensory nerves in vascular units and the regulatory influence of specific brain regions.

Several questions remain about the mechanisms regulating functional crosstalk between endothelial cells, pericytes, VSMCs, fibroblasts, cardiomyocytes, immune cells and nerve cells in the ageing heart. The effects of nerve-derived factors in this cellular environment are also understudied. Moreover, the distinct innervation patterns in the various chambers and regions of the heart warrant further investigation. Notably, the left ventricle and right ventricle show differential responses to adrenergic stimulation[129], and the right side of the heart undergoes structural, functional and electrical changes over time, contributing substantially to overall cardiac ageing. These changes are often closely associated with pulmonary diseases (usually associated with right heart failure), the incidence of which also increases with age.

An important area for future exploration is whether therapies targeting cardiac neurovascular ageing might also confer benefits for cerebrovascular ageing, and vice versa. This bidirectional potential could be especially relevant in conditions such as vascular cognitive impairment and dementia, in which comorbid cardiac dysfunction is frequently observed. Addressing shared neurovascular ageing mechanisms across organ systems might therefore offer a synergistic therapeutic strategy. Overall, advancing our understanding of neurocardiac interactions is crucial for developing targeted therapies aimed at preserving heart function in ageing populations.

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References

1. The Global Cardiovascular Risk Consortium. Global effect of modifiable risk factors on cardiovascular disease and mortality. *N. Engl. J. Med.* **389**, 1273–1285 (2023).
2. Liberale, L. et al. Roadmap for alleviating the manifestations of ageing in the cardiovascular system. *Nat. Rev. Cardiol.* **22**, 577–605 (2025).
3. Iadecola, C. et al. The neurovasculome: key roles in brain health and cognitive impairment: a scientific statement from the American Heart Association/American Stroke Association. *Stroke* **54**, e251–e271 (2023).
4. Anversa, P., Olivetti, G., Melissari, M. & Loud, A. V. Stereological measurement of cellular and subcellular hypertrophy and hyperplasia in the papillary muscle of adult rat. *J. Mol. Cell Cardiol.* **12**, 781–795 (1980).
5. Wagner, J. U. G. & Dimmeler, S. The endothelial niche in heart failure: from development to regeneration. *Eur. Heart J.* **42**, 4277–4279 (2021).
6. Wagner, J. U. G. & Dimmeler, S. Cellular cross-talks in the diseased and aging heart. *J. Mol. Cell Cardiol.* **138**, 136–146 (2020).
7. Bassat, E. et al. The extracellular matrix protein agrin promotes heart regeneration in mice. *Nature* **547**, 179–184 (2017).
8. Dalkara, T., Østergaard, L., Heusch, G. & Attwell, D. Pericytes in the brain and heart: functional roles and response to ischaemia and reperfusion. *Cardiovasc. Res.* **120**, 2336–2348 (2024).
9. Vågesjö, E. et al. Perivascular macrophages regulate blood flow following tissue damage. *Circ. Res.* **128**, 1694–1707 (2021).
10. He, H. et al. Perivascular macrophages limit permeability. *Arterioscler. Thromb. Vasc. Biol.* **36**, 2203–2212 (2016).
11. Farbehi, N. et al. Single-cell expression profiling reveals dynamic flux of cardiac stromal, vascular and immune cells in health and injury. *eLife* **8**, e43882 (2019).
12. Litviňuková, M. et al. Cells of the adult human heart. *Nature* **588**, 466–472 (2020).
13. Majesky, M. W. Vascular smooth muscle cells. *Arterioscler. Thromb. Vasc. Biol.* **36**, e82–e86 (2016).
14. Valenza, G., Matić, Z. & Catrambone, V. The brain–heart axis: integrative cooperation of neural, mechanical and biochemical pathways. *Nat. Rev. Cardiol.* **22**, 537–550 (2025).
15. Pauza, D. H., Skripka, V., Pauziene, N. & Stropus, R. Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. *Anat. Rec.* **259**, 353–382 (2000).
16. Rysevaite, K. et al. Immunohistochemical characterization of the intrinsic cardiac neural plexus in whole-mount mouse heart preparations. *Heart Rhythm.* **8**, 731–738 (2011).
17. Vincentz, J. W., Rubart, M. & Firulli, A. B. Ontogeny of cardiac sympathetic innervation and its implications for cardiac disease. *Pediatric Cardiol.* **33**, 923–928 (2012).
18. Kawashima, T. The autonomic nervous system of the human heart with special reference to its origin, course, and peripheral distribution. *Anat. Embryol.* **209**, 425–438 (2005).
19. Wu, D. et al. The blood–brain barrier: structure, regulation and drug delivery. *Signal. Transduct. Target. Ther.* **8**, 217 (2023).
20. Wagner, J. U. G. et al. Aging impairs the neurovascular interface in the heart. *Science* **381**, 897–906 (2023).
21. Schaeffer, S. & Iadecola, C. Revisiting the neurovascular unit. *Nat. Neurosci.* **24**, 1198–1209 (2021).
22. Manousiouthakis, E., Mendez, M., Garner, M. C., Exertier, P. & Makita, T. Venous endothelin guides sympathetic innervation of the developing mouse heart. *Nat. Commun.* **5**, 3918 (2014).
23. Manickam, N. et al. Beneficial effects of vascular endothelial growth factor B gene transfer in the aged heart. *Cardiovasc. Res.* **121**, 1594–1608 (2025).
24. Nam, J. et al. Coronary veins determine the pattern of sympathetic innervation in the developing heart. *Development* **140**, 1475–1485 (2013).
25. Ketch, T., Biaggioni, I., Robertson, R. & Robertson, D. Four faces of baroreflex failure. *Circulation* **105**, 2518–2523 (2002).
26. Lakatta, E. G. & Levy, D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises. *Circulation* **107**, 139–146 (2003).
27. Song, R. et al. Associations between cardiovascular risk, structural brain changes, and cognitive decline. *J. Am. Coll. Cardiol.* **75**, 2525–2534 (2020).
28. Rakusan, K. & Nagai, J. Morphometry of arterioles and capillaries in hearts of senescent mice. *Cardiovasc. Res.* **28**, 969–972 (1994).
29. Tamiato, A. et al. Age-dependent RGS5 loss in pericytes induces cardiac dysfunction and fibrosis. *Circ. Res.* **134**, 1240–1255 (2024).
30. Grootaert, M. O. J. et al. Mural cell dysfunction contributes to diastolic heart failure by promoting endothelial dysfunction and vessel remodelling. *Cardiovasc. Diabetol.* **24**, 62 (2025).
31. Simmonds, S. J. et al. Pericyte loss initiates microvascular dysfunction in the development of diastolic dysfunction. *Eur. Heart J. Open* **4**, oead129 (2024).
32. Gates, P. E., Strain, W. D. & Shore, A. C. Human endothelial function and microvascular ageing. *Exp. Physiol.* **94**, 311–316 (2009).
33. Vasa, M., Breitschopf, K., Zeiher, A. M. & Dimmeler, S. Nitric oxide activates telomerase and delays endothelial cell senescence. *Circ. Res.* **87**, 540–542 (2000).
34. Li, Z., Froehlich, J., Galis, Z. S. & Lakatta, E. G. Increased expression of matrix metalloproteinase-2 in the thickened intima of aged rats. *Hypertension* **33**, 116–123 (1999).
35. Ungvari, Z. et al. Endothelial dysfunction and angiogenesis impairment in the ageing vasculature. *Nat. Rev. Cardiol.* **15**, 555–565 (2018).
36. Zhou, X., Perez, F., Han, K. & Jurivich, D. A. Clonal senescence alters endothelial ICAM-1 function. *Mech. Ageing Dev.* **127**, 779–785 (2006).
37. Liu, Z. et al. Insights gained from single-cell RNA analysis of murine endothelial cells in aging hearts. *Heliyon* **9**, e18324 (2023).
38. Rodriguez Morales, D. et al. Vascular niches are the primary hotspots for aging within the multicellular architecture of cardiac tissue. *Circ. Res.* **137**, 1353–1367 (2025).
39. Hall, I. F., Kishta, F., Xu, Y., Baker, A. H. & Kovacic, J. C. Endothelial to mesenchymal transition: at the axis of cardiovascular health and disease. *Cardiovasc. Res.* **120**, 223–236 (2024).
40. Kovacic, J. C. et al. Endothelial to mesenchymal transition in cardiovascular disease: JACC state-of-the-art review. *J. Am. Coll. Cardiol.* **73**, 190–209 (2019).

41. Damon, D. H. Sympathetic innervation promotes vascular smooth muscle differentiation. *Am. J. Physiol. Heart Circ. Physiol.* **288**, H2785–H2791 (2005).
42. Vidal, R. et al. Transcriptional heterogeneity of fibroblasts is a hallmark of the aging heart. *JCI Insight* **4**, e131092 (2019).
43. Kortlever, R. M., Higgins, P. J. & Bernards, R. Plasminogen activator inhibitor-1 is a critical downstream target of p53 in the induction of replicative senescence. *Nat. Cell Biol.* **8**, 877–884 (2006).
44. Hasan, W. et al. Sympathetic hyperinnervation and inflammatory cell NGF synthesis following myocardial infarction in rats. *Brain Res.* **1124**, 142–154 (2006).
45. Mias, C. et al. Cardiac fibroblasts regulate sympathetic nerve sprouting and neurocardiac synapse stability. *PLoS ONE* **8**, e79068 (2013).
46. Camell, C. D. et al. Inflammasome-driven catecholamine catabolism in macrophages blunts lipolysis during ageing. *Nature* **550**, 119–123 (2017).
47. Pirzgalska, R. M. et al. Sympathetic neuron–associated macrophages contribute to obesity by importing and metabolizing norepinephrine. *Nat. Med.* **23**, 1309–1318 (2017).
48. Wolf, Y. et al. Brown-adipose-tissue macrophages control tissue innervation and homeostatic energy expenditure. *Nat. Immunol.* **18**, 665–674 (2017).
49. Moura Silva, H. et al. c-MAF-dependent perivascular macrophages regulate diet-induced metabolic syndrome. *Sci. Immunol.* **6**, eabg7506 (2021).
50. Viola, M. F. et al. Dedicated macrophages organize and maintain the enteric nervous system. *Nature* **618**, 818–826 (2023).
51. Matheis, F. et al. Adrenergic signaling in muscularis macrophages limits infection-induced neuronal loss. *Cell* **180**, 64–78.e16 (2020).
52. Wernli, G., Hasan, W., Bhattacherjee, A., van Rooijen, N. & Smith, P. G. Macrophage depletion suppresses sympathetic hyperinnervation following myocardial infarction. *Basic Res. Cardiol.* **104**, 681–693 (2009).
53. Hulsmans, M. et al. Macrophages facilitate electrical conduction in the heart. *Cell* **169**, 510–522.e20 (2017).
54. Elliott, H. L., Sumner, D. J., McLean, K. & Reid, J. L. Effect of age on the responsiveness of vascular α-adrenoceptors in man. *J. Cardiovasc. Pharmacol.* **4**, 388–392 (1982).
55. Pinckard, J. et al. Functional ultrasound as a quantitative approach for measuring functional hyperemia in aging models. *Neuroimage* **316**, 121313 (2025).
56. Bristow, M. R. et al. Decreased catecholamine sensitivity and β-adrenergic-receptor density in failing human hearts. *N. Engl. J. Med.* **307**, 205–211 (1982).
57. Lakatta, E. G. & Sollott, S. J. Perspectives on mammalian cardiovascular aging: humans to molecules. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **132**, 699–721 (2002).
58. Xiao, R. P., Spurgeon, H. A., O'Connor, F. & Lakatta, E. G. Age-associated changes in beta-adrenergic modulation on rat cardiac excitation-contraction coupling. *J. Clin. Invest.* **94**, 2051–2059 (1994).
59. Perez, S. D. et al. Chronically lowering sympathetic activity protects sympathetic nerves in spleens from aging F344 rats. *J. Neuroimmunol.* **247**, 38–51 (2012).
60. Mahmoud, A. I. et al. Nerves regulate cardiomyocyte proliferation and heart regeneration. *Dev. Cell* **34**, 387–399 (2015).
61. White, I. A., Gordon, J., Balkan, W. & Hare, J. M. Sympathetic reinnervation is required for mammalian cardiac regeneration. *Circ. Res.* **117**, 990–994 (2015).
62. Tahsili-Fahadan, P. & Geocadin, R. G. Heart–brain axis. *Circ. Res.* **120**, 559–572 (2017).
63. Nolte, C. H. et al. Type 1 myocardial infarction in patients with acute ischemic stroke. *JAMA Neurol.* **81**, 703–711 (2024).
64. Singh, T. et al. Takotsubo syndrome: pathophysiology, emerging concepts, and clinical implications. *Circulation* **145**, 1002–1019 (2022).
65. Kwaśniak-Butowska, M. et al. Cardiovascular dysautonomia and cognition in Parkinson's disease — a possible relationship. *Neurol. Neurochir. Pol.* **55**, 525–535 (2021).
66. Allan, L. M. et al. Autonomic dysfunction in dementia. *J. Neurol. Neurosurg. Psychiatry* **78**, 671 (2007).
67. Sanna, G. D. et al. Cardiac abnormalities in Alzheimer disease: clinical relevance beyond pathophysiological rationale and instrumental findings? *JACC Heart Fail.* **7**, 121–128 (2019).
68. Guendelman, S., Kaltwasser, L., Bayer, M., Gallese, V. & Dziobek, I. Brain mechanisms underlying the modulation of heart rate variability when accepting and reappraising emotions. *Sci. Rep.* **14**, 18756 (2024).
69. Hsueh, B. et al. Cardiogenic control of affective behavioural state. *Nature* **615**, 292–299 (2023).
70. Huang, L.-Y. et al. Associations of cardiovascular risk factors and lifestyle behaviors with neurodegenerative disease: a Mendelian randomization study. *Transl. Psychiatry* **13**, 267 (2023).
71. Dampney, R. A. L. Central neural control of the cardiovascular system: current perspectives. *Adv. Physiol. Educ.* **40**, 283–296 (2016).
72. Ruiz Vargas, E., Sörös, P., Shoemaker, J. K. & Hachinski, V. Human cerebral circuitry related to cardiac control: a neuroimaging meta-analysis. *Ann. Neurol.* **79**, 709–716 (2016).
73. Karim, S., Chahal, A., Khanji, M. Y., Petersen, S. E. & Somers, V. K. Autonomic cardiovascular control in health and disease. *Compr. Physiol.* **13**, 4493–4511 (2023).
74. Harrison, N. A., Cooper, E., Voon, V., Miles, K. & Critchley, H. D. Central autonomic network mediates cardiovascular responses to acute inflammation: relevance to increased cardiovascular risk in depression? *Brain Behav. Immun.* **31**, 189–196 (2013).
75. Dyavanapalli, J. Novel approaches to restore parasympathetic activity to the heart in cardiorespiratory diseases. *Am. J. Physiol. Heart Circ. Physiol.* **319**, H1153–H1161 (2020).
76. Liu, J. et al. Heart–brain interaction in cardiogenic dementia: pathophysiology and therapeutic potential. *Front. Cardiovasc. Med.* **11**, 1304864 (2024).
77. Zhang, D. et al. Correlation of ventricular arrhythmogenesis with neuronal remodeling of cardiac postganglionic parasympathetic neurons in the late stage of heart failure after myocardial infarction. *Front. Neurosci.* **11**, 252 (2017).
78. Ziegler, K. A. et al. Immune-mediated denervation of the pineal gland underlies sleep disturbance in cardiac disease. *Science* **381**, 285–290 (2023).
79. Martín Giménez, V. M. et al. Melatonin as an anti-aging therapy for age-related cardiovascular and neurodegenerative diseases. *Front. Aging Neurosci.* **14**, 888292 (2022).
80. Reiter, R. J., Rosales-Corral, S. & Sharma, R. Circadian disruption, melatonin rhythm perturbations and their contributions to chaotic physiology. *Adv. Med. Sci.* **65**, 394–402 (2020).
81. Li, H. et al. Pharmacological targeting of endothelial nitric oxide synthase dysfunction and nitric oxide replacement therapy. *Free Radic. Biol. Med.* **237**, 455–472 (2025).
82. Yu, J. et al. Endothelial nitric oxide synthase is critical for ischemic remodeling, mural cell recruitment, and blood flow reserve. *Proc. Natl Acad. Sci. USA* **102**, 10999–11004 (2005).
83. Daiber, A. et al. New therapeutic implications of endothelial nitric oxide synthase (eNOS) function/dysfunction in cardiovascular disease. *Int. J. Mol. Sci.* **20**, 187 (2019).
84. Gao, J., Pan, X., Li, G., Chatterjee, E. & Xiao, J. Physical exercise protects against endothelial dysfunction in cardiovascular and metabolic diseases. *J. Cardiovasc. Transl. Res.* **15**, 604–620 (2022).
85. Dookun, E., Passos, J. F., Arthur, H. M. & Richardson, G. D. Therapeutic potential of senolytics in cardiovascular disease. *Cardiovasc. Drugs Ther.* **36**, 187–196 (2022).
86. Xu, M. et al. Senolytics improve physical function and increase lifespan in old age. *Nat. Med.* **24**, 1246–1256 (2018).
87. Csik, B. et al. Senescent endothelial cells in cerebral microcirculation are key drivers of age-related blood–brain barrier disruption, microvascular rarefaction, and neurovascular coupling impairment in mice. *Aging Cell* **24**, e70048 (2025).
88. Tarantini, S. et al. Treatment with the BCL-2/BCL-xL inhibitor senolytic drug ABT263/Navitoclax improves functional hyperemia in aged mice. *Geroscience* **43**, 2427–2440 (2021).
89. Aratani, S. & Nakanishi, M. Recent advances in senolysis for age-related diseases. *Physiology* **38**, 205–216 (2023).
90. Gonzales, M. M. et al. Senolytic therapy in mild Alzheimer's disease: a phase 1 feasibility trial. *Nat. Med.* **29**, 2481–2488 (2023).
91. Wissler Gerdes, E. O., Misra, A., Netto, J. M. E., Tchkonia, T. & Kirkland, J. L. Strategies for late phase preclinical and early clinical trials of senolytics. *Mech. Ageing Dev.* **200**, 111591 (2021).
92. Grunewald, M. et al. Counteracting age-related VEGF signaling insufficiency promotes healthy aging and extends life span. *Science* **373**, eabc8479 (2025).
93. Pius-Sadowska, E. & Machaliński, B. BDNF — a key player in cardiovascular system. *J. Mol. Cell Cardiol.* **110**, 54–60 (2017).
94. Story, G. M. et al. Inactivation of one copy of the mouse neurotrophin-3 gene induces cardiac sympathetic deficits. *Physiol. Genomics* **2**, 129–136 (2000).
95. Miwa, K. et al. Glial cell line-derived neurotrophic factor (GDNF) enhances sympathetic neurite growth in rat hearts at early developmental stages. *Biomed. Res.* **31**, 353–361 (2010).
96. Miwa, K. et al. Axon guidance of sympathetic neurons to cardiomyocytes by glial cell line-derived neurotrophic factor (GDNF). *PLoS ONE* **8**, e65202 (2013).
97. Rossi, D. et al. Reelin reverts biochemical, physiological and cognitive alterations in mouse models of tauopathy. *Prog. Neurobiol.* **186**, 101743 (2020).
98. Liu, X. et al. Lymphoangiocrine signals promote cardiac growth and repair. *Nature* **588**, 705–711 (2020).
99. Sonntag, W. E. et al. The effects of growth hormone and IGF-1 deficiency on cerebrovascular and brain ageing. *J. Anat.* **197**, 575–585 (2000).
100. Xu, X. et al. IGF-1 Provides protective role in arteriosclerotic cerebral small vessel disease. *Hypertension* **82**, 1137–1150 (2025).
101. Zaman, R. et al. Selective loss of resident macrophage-derived insulin-like growth factor-1 abolishes adaptive cardiac growth to stress. *Immunity* **54**, 2057–2071.e6 (2021).
102. Perrotta, S. et al. A heart-brain-spleen axis controls cardiac remodeling to hypertensive stress. *Immunity* **58**, 648–665.e7 (2025).
103. Cao, J.-M. et al. Relationship between regional cardiac hyperinnervation and ventricular arrhythmia. *Circulation* **101**, 1960–1969 (2000).
104. Dajani, A. H. J. et al. Heterogeneous cardiac sympathetic innervation gradients promote arrhythmogenesis in murine dilated cardiomyopathy. *JCI Insight* **8**, e157956 (2023).
105. Ziegler, K. A. et al. Neural mechanisms in cardiovascular health and disease. *Circ. Res.* **136**, 1233–1261 (2025).
106. Hawley, J. A., Hargreaves, M., Joyner, M. J. & Zierath, J. R. Integrative biology of exercise. *Cell* **159**, 738–749 (2014).
107. Wichi, R. B., De Angelis, K., Jones, L. & Irigoyen, M. C. A brief review of chronic exercise intervention to prevent autonomic nervous system changes during the aging process. *Clinics* **64**, 253–258 (2009).
108. Roh, J., Rhee, J., Chaudhari, V. & Rosenzweig, A. The role of exercise in cardiac aging. *Circ. Res.* **118**, 279–295 (2016).
109. Iemitsu, M., Maeda, S., Jesmin, S., Otsuki, T. & Miyauchi, T. Exercise training improves aging-induced downregulation of VEGF angiogenic signaling cascade in hearts. *Am. J. Physiol. Heart Circ. Physiol.* **291**, H1290–H1298 (2006).
110. Lerchenmüller, C. et al. Restoration of cardiomyogenesis in aged mouse hearts by voluntary exercise. *Circulation* **146**, 412–426 (2022).
111. Fukuda, K., Kanazawa, H., Aizawa, Y., Ardell, J. L. & Shivkumar, K. Cardiac innervation and sudden cardiac death. *Circ. Res.* **116**, 2005–2019 (2015).

112. Ieda, M. et al. Nerve growth factor is critical for cardiac sensory innervation and rescues neuropathy in diabetic hearts. *Circulation* **114**, 2351–2363 (2006).
113. Kiss, T. et al. Nicotinamide mononucleotide (NMN) supplementation promotes neurovascular rejuvenation in aged mice: transcriptional footprint of SIRT1 activation, mitochondrial protection, anti-inflammatory, and anti-apoptotic effects. *Geroscience* **42**, 527–546 (2020).
114. Szarvas, Z. et al. Effects of NAD^+ supplementation with oral nicotinamide riboside on vascular health and cognitive function in older adults with peripheral artery disease: results from a pilot 4-week open-label clinical trial. *J. Pharmacol. Exp. Ther.* **392**, 103607 (2025).
115. Dierickx, P. et al. Circadian REV-ERBs repress E4bp4 to activate NAMPT-dependent NAD^+ biosynthesis and sustain cardiac function. *Nat. Cardiovascular Res.* **1**, 45–58 (2022).
116. Weiss, E. P. & Fontana, L. Caloric restriction: powerful protection for the aging heart and vasculature. *Am. J. Physiol. Heart Circ. Physiol.* **301**, H1205–H1219 (2011).
117. Anderson, R. M., Shanmuganayagam, D. & Weindruch, R. Caloric restriction and aging: studies in mice and monkeys. *Toxicol. Pathol.* **3**, 47–51 (2009).
118. Barzilai, N., Banerjee, S., Hawkins, M., Chen, W. & Rossetti, L. Caloric restriction reverses hepatic insulin resistance in aging rats by decreasing visceral fat. *J. Clin. Invest.* **101**, 1353–1361 (1998).
119. Crandall, D. L., Lai, F. M., Huggins, F. J., Tanikella, T. K. & Cervoni, P. Effect of caloric restriction on cardiac reactivity and beta-adrenoceptor concentration. *Am. J. Physiol. Heart Circ. Physiol.* **244**, H444–H448 (1983).
120. Loh, J. S. et al. Microbiota–gut–brain axis and its therapeutic applications in neurodegenerative diseases. *Signal. Transduct. Target. Ther.* **9**, 37 (2024).
121. Polster, S. P. et al. Permissive microbiome characterizes human subjects with a neurovascular disease cavernous angioma. *Nat. Commun.* **11**, 2659 (2020).
122. Lin, L. et al. The brain-protective mechanism of fecal microbiota transplantation from young donor mice in the natural aging process via exosome, gut microbiota, and metabolomics analyses. *Pharmacol. Res.* **207**, 107323 (2024).
123. Kim, C.-S. et al. Probiotic supplementation improves cognitive function and mood with changes in gut microbiota in community-dwelling older adults: a randomized, double-blind, placebo-controlled, multicenter trial. *J. Gerontol. A Biol. Sci. Med. Sci.* **76**, 32–40 (2021).
124. Zhang, C., Wang, Y., Wang, D., Zhang, J. & Zhang, F. NSAID exposure and risk of Alzheimer's disease: an updated meta-analysis from cohort studies. *Front. Aging Neurosci.* **10**, 83 (2018).
125. Everett, B. M. et al. Inhibition of Interleukin-1β and reduction in atherothrombotic cardiovascular events in the CANTOS trial. *J. Am. Coll. Cardiol.* **76**, 1660–1670 (2020).
126. Finocchiaro, S. et al. Anti-inflammatory pharmacotherapy in patients with cardiovascular disease. *Eur. Heart J. Cardiovasc. Pharmacother.* **19**, pvaf058 (2025).
127. Koopman, F. A. et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *Proc. Natl Acad. Sci. USA* **113**, 8284–8289 (2016).
128. Tynan, A., Brines, M. & Chavan, S. S. Control of inflammation using non-invasive neuromodulation: past, present and promise. *Int. Immunol.* **34**, 119–128 (2022).
129. Zandstra, T. E. et al. Asymmetry and heterogeneity: part and parcel in cardiac autonomic innervation and function. *Front. Physiol.* **12**, 665298 (2021).
130. Nyúl-Tóth, Á. et al. Novel intravital approaches to quantify deep vascular structure and perfusion in the aging mouse brain using ultrasound localization microscopy (ULM). *J. Cereb. Blood Flow Metab.* **44**, 1378–1396 (2024).
131. Vinegoni, C., Aguirre, A. D., Lee, S. & Weissleder, R. Imaging the beating heart in the mouse using intravital microscopy techniques. *Nat. Protoc.* **10**, 1802–1819 (2015).
132. Ahn, S., Yoon, J. & Kim, P. Intravital imaging of cardiac tissue utilizing tissue-stabilized heart window chamber in live animal model. *Eur. Heart J. Imaging Methods Pract.* **12**, qyae062 (2024).
133. Borrelli, C., Bengel, F. M. & Gimelli, A. Integrated catecholamine imaging in heart and lung across different cardiopulmonary disorders: a systems-based pilot analysis. *Int. J. Cardiol.* **390**, 131208 (2023).
134. Mitsui, J. et al. Pathology of the sympathetic nervous system corresponding to the decreased cardiac uptake in ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy in a patient with Parkinson disease. *J. Neurol. Sci.* **243**, 101–104 (2006).
135. Orimo, S., Yogo, M., Nakamura, T., Suzuki, M. & Watanabe, H. ^{123}I-meta-iodobenzylguanidine (MIBG) cardiac scintigraphy in α-synucleinopathies. *Ageing Res. Rev.* **30**, 122–133 (2016).

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