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Autonomic dysfunction in older people

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Summary

The autonomic nervous system comprises the sympathetic, parasympathetic and enteric nervous systems and plays an integral role in homeostasis. This includes cardiovascular and temperature control, glucose metabolism, gastrointestinal and reproductive function and increasing evidence to support its involvement in the inflammatory response to infection and cancer. Ageing is associated with autonomic dysfunction, and many clinical syndromes associated with older adults are due to inadequate autonomic responses to physiological stressors. The aim of this review is to explore the relationship between autonomic dysfunction and ageing illustrated with examples of maladaptive autonomic responses in a variety of different clinical syndromes including an exploration of autonomic cellular changes. Appropriate investigation and management strategies are outlined, recognizing the fine balance needed to improve symptoms without creating further medical complications.

Key words: autonomic nervous system, elderly, dysfunction, failure, geriatrics.

Introduction

The autonomic nervous system (ANS) is a component of the peripheral nervous system whose principle function is to maintain homeostasis. Langley first conceived the term in the early 20th century, describing the absence of sensory nerve cell bodies in autonomic ganglia.[1] It has motor and sensory pathways that convey and relay neurons to every organ in the body. Autonomic dysfunction produces a complex array of clinical problems including cardiovascular dysregulation resulting in inappropriate blood pressure and heart rate responses to physiological stressors, erectile dysfunction, and thermoregulatory and sweating problems producing an inability to adapt to environmental thermal extremes.[2–4]

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Search methods

Search methods involved Medline using the key words: autonomic dysfunction, autonomic failure, geriatrics and older people. Subsection searches used the words autonomic dysfunction, diabetes mellitus, neuronal cellular changes, alpha synuclein, toll-like receptors, paraneoplastic syndrome, autonomic function tests, orthostatic hypotension, neurocardiogenic syncope, carotid sinus hypersensitivity, erectile dysfunction, gastrointestinal dysfunction and thermoregulation.

Anatomy and physiology

The ANS consists of sensory neurons arising from both the primary viscera and the cranial sensory ganglia from nerves VII, IX and X, which then project to second-order neurons in the nucleus solitarius of the medulla oblongata. These monitor and regulate carbon dioxide arterial tension, blood glucose and pH.[5–7] They have afferents to the chemoreceptor trigger zone stimulating vomiting from noxious substances. Motor neurons comprise the sympathetic, parasympathetic and enteric nervous systems. Sympathetic ganglia lie within the prevertebral and para-aortic chains close to the spinal cord,[8] and neuronal stimulation produces a 'fight or flight' response, diverting blood flow away from the gastrointestinal tract and skin towards skeletal muscle and lung.[8] This increases oxygen exchange, cardiac chronotropy and inotropy and subsequently cardiac output, and results in pupillary dilatation.[9] The parasympathetic nervous system dilates the splanchnic circulation, aiding digestion.[10] It causes bronchoconstriction in the lungs when oxygen demands falls, produces pupillary constriction in

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the eye during accommodation, stimulates salivary gland secretion in the mouth, and controls erectile function in the genitalia.[11–13]

Autonomic failure and ageing

Several studies have demonstrated deteriorating autonomic function with increasing age. Collins *et al*. examined three physiological tests of autonomic function in 29 young adults and 64 healthy older patients (age range 66–86 years).[14] These included heart rate response to standing, changes in hand blood flow in response to differing thermal conditions, and the cardiovascular effects of lower body negative pressure. Heart rate response to standing increased by 20 beats/min in younger patients compared with only 10–15 beats/min in the older group. Interestingly, younger patients with diabetic neuropathy showed a similar response to the older age group.[15] The effects of changes in body temperature including shivering and sweating on hand blood flow were measured using volume plethysmography. One-third of older volunteers had higher than expected blood flow in colder temperatures, showing a diminished ability to vasoconstrict. Patients with abnormal blood flow responses had higher rates of autonomic dysfunction elsewhere. Forty-three per cent of those with abnormal vasomotor responses to cooling and 10% of those with normal responses were found to have a postural drop in systolic blood pressure of greater than 20 mmHg. Lower body negative pressure produces an increase in heart rate, fall in blood pressure, falls in central and peripheral blood flow and a decrease in cardiac output. Ten young adults and ten healthy older patients underwent lower body negative pressure (–10 to –50 mmHg) testing. Blood pressure fell earlier in the older group, but heart rate increased significantly in the younger group. Younger subjects showed a much greater reduction in peripheral blood flow as measured by a photo electric pulsimeter measured at the thumb, suggesting a greater ability to redirect blood flow in response to negative pressure. These tests demonstrate reduced cardiovascular responses to physiological stressors in older people and are partially replicated in younger patients with diabetic peripheral neuropathy, suggesting similar mechanisms of loss of autonomic control in both groups.

Autonomic failure and diabetes mellitus

The prevalence of autonomic related conditions such as type 2 diabetes mellitus and neurogenic orthostatic hypotension increases with age. It has been estimated that 18–20% of people over 65 have type 2 diabetes in the USA, and 20–25% have impaired glucose tolerance, a condition associated with a twofold increase in macrovascular complications.[16,17] Distal sensorimotor neuropathy commonly presents as an autonomic neuropathy. Cardiac involvement produces an increased resting heart rate when the vagus nerve is affected. If sympathetic and parasympathetic fibres are involved, the heart rate becomes less able to increase in response to physiological demands.[18] Orthostatic hypotension occurs due to arteriolar efferent sympathetic denervation, producing reduced vasoconstriction in the major blood vessels on standing.[19] Autonomic dysfunction can cause sudden death in diabetes via a number of postulated mechanisms. These include absent or altered perception of myocardial ischaemia, inadequate haemodynamic responses to physiological stressors, cardiac arrhythmias due to QT interval lengthening, and alterations in regional myocardial function following changes in innervations[20–23] predisposing to ischaemia and arrhythmia.

Autonomic cellular changes and ageing

Autonomic ganglia do not change in number with ageing. However, ageing is associated with dendritic alterations, changes in synapse function and neuroaxonal dystrophy (NAD). NAD produces dramatic axonal swellings and neurofilamentous and tubulovesicular deposits as a result of impaired axonal regeneration. Normal synaptic turnover is exaggerated, producing excess swelling and sprout formation.

The relationship between ageing and peripheral nervous system ganglia is largely unknown, although several hypotheses have been proposed. These include oxidative stress in nerve terminals resulting in lipid peroxidation, alterations in membrane structure and function, and mitochondrial dysfunction. Neurotrophic substances become deficient, depleting end organ innervation. Exogenous neurotrophic growth factor was found to increase sympathetic innervation in older patients, suggesting that growth factor deficiency

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may be detrimental to neuronal function. Conversely, neurotrophic excess causes dendritic and neuronal swelling and axonal sprouts contributing to neuroaxonal dystrophy, which have been found in the senile plaques of Alzheimer's disease.[24,25] Excessive neurofilament glycosylation and phosphorylation occurs in ageing and diabetes, and results in their accumulation in axonal terminals.[26] These cellular processes diminish synaptic transmission, reduce end organ innervation, and the overall functionality of the autonomic nervous system.

Alpha synucleinopathies and autonomic dysfunction

Alpha synuclein (AS) is an inclusion protein found in patients with several neurodegenerative conditions including Lewy body dementia, Parkinson's disease and multiple system atrophy.[27,28] Alpha synuclein is deposited in neurons and glial cells in both the central nervous system and the spinal cord, and in key areas involved in the control of autonomic function. Basal ganglia AS deposition in the thalamus has been demonstrated in patients with Parkinson's disease[29] and failure of AS protein degradation occurs in oligodendrocytes in multiple system atrophy.[29] In 102 cases of multiple system atrophy, Yoshida *et al.* found glial and neuronal cytoplasmic inclusions and positive alpha synuclein immunostaining in the pontine nuclei, putamen, substantia nigra, locus coeruleus, inferior olivary nucleus and the intermediolateral column of the thoracic spinal cord.[30] The intermediolateral column is a key area of autonomic control which is damaged in multiple system atrophy.[31]

Can early AS protein deposition predict later onset of neurodegenerative disease? Surgical specimens from 100 patients (age range 44–84 years) undergoing resection of an abdominopelvic organ were examined by anti-AS immunoassaying.[32] Nine per cent of patients had positive immunostaining for antibodies against AS. At 16 months, none of the subjects had clinical features of Parkinson's disease, dementia or autonomic failure. However, when asked to perform a Valsalva manoeuvre, the AS-positive group showed a longer blood pressure recovery time. Cardiac metaiodobenzylguanide uptake was reduced in the AS group and striatal muscle ^{123}I-ioflupane was low in one AS-positive subject. At 30 months, these lower cardiac and striatal uptake values reflect similar findings in patients with higher UKPDS III scores. This suggests that AS aggregates in the peripheral autonomic nervous system may pre-date the onset of a number of neurodegenerative disorders.

The autonomic nervous system, response to infection and toll-like receptors

Dendritic cells and macrophages process antigens and act as antigen-presenting cells in response to systemic infection. The innate immune response is activated, involving the interaction between microbe molecules and surface receptors on antigen-presenting cells. These molecules are collectively known as pathogen-associated molecular patterns (PAMP) and the set of receptors with which they interact are known as pattern recognition receptors (PRR). PRRs can be subdivided into signalling and endocytic receptors and secreted proteins. The main signalling receptor is the toll-like receptor (TLR) of which there are thought to be 10–15 different types in most mammalian species.[33] In septic shock, damaged and dying tissues release intracellular proteins or mediators known as 'alarmins', which stimulate TLR as a crucial part of the initial stages of the inflammatory response. The TLR-4 receptor responds to the lipopolysaccharide component of the cell wall of gram-negative bacteria, forming a complex with CD14 and MD2.[34] There is considerable interaction between TLR-4 and the complement system. The complement anaphylatoxin C5a, which is released early in sepsis, has been found to negatively regulate TLR4-mediated responses correlating with lower levels of complement activation products.[35] Lymphoid tissue is richly innervated by the autonomic nervous system, and cytokines produced peripherally can stimulate the induction of brain cytokines in macrophages and microglial cells through central toll receptors. These brain-produced cytokines act on cortical tissue to produce the central factors associated with infection, namely fever (IL-6), neuroendocrine activation and sickness behaviour. Munford and Tracey have suggested that severe sepsis is a neuroendocrine disorder.[36]

The parasympathetic nervous system plays a key neuromodulatory role in the systemic response to infection. Activation of α_7 acetylcholine

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nicotinic receptors by vagal nerve or direct agonist stimulation decreases intracellular cytokine synthesis in macrophages, dampening down the inflammatory response to sepsis. Inflammation is thus under neuronal control by the autonomic nervous system, which can reflexively modulate the inflammatory response by inhibiting the production of pro-inflammatory cytokines.

Catecholamines are released early by the sympathetic nervous system in response to systemic sepsis. Leucocytes are also an abundant source, and themselves have catecholamine receptors suggesting autocrine and paracrine effects. α- and β-receptor stimulation results in alterations in lymphocyte trafficking, changes in vascular perfusion and cell proliferation and apoptosis. Pro-inflammatory cytokine release by macrophages and neutrophils is also tightly regulated by α-adrenergic receptors.

Toll-like receptors have been found in murine intestine and human ileum as well as in dorsal root ganglia with TLR-3, -7 and -4 the predominant receptor subtypes.[37] This suggests a local enteric neural network, which may activate in response to local bacterial and viral invasion through closely regulated cytokine production utilizing both the autonomic nervous system and toll-like receptor mechanisms.

Autonomic dysfunction has been demonstrated to contribute to multiple organ failure in septic shock. Loss of cholinergic inflammatory inhibition, reduced catecholamine sensitivity in providing cardiovascular stability and reduced macrophage and Europhile-mediated cytokine release could be potential explanations. Heart rate variability as a marker of autonomic dysfunction has been shown to be an independent predictor of 28- and 60-day mortality in critically ill patients with multiple organ dysfunction.[38]

Autonomic receptor downregulation in response to inflammation

There is increasing evidence to support autonomic receptor downregulation in response to inflammation. Young healthy volunteers were injected with a bolus of lipopolysaccharide endotoxin, and muscle sympathetic nerve activity, heart rate and blood pressure were observed and compared with placebo. Muscle sympathetic nerve burst activity was suppressed, whilst heart rate increased and blood pressure was unchanged following endotoxin injection. This suggests a blunting of postsynaptic receptor and uncoupling of baroreceptor activity in humans in septic shock.[39] Rat models in which colitis was pharmacologically induced resulted in diminished enteric smooth muscle activity related to β-adrenoreceptor downregulation and may well explain the diarrhoea associated with inflammatory bowel disease.[40]

Autonomic dysfunction and paraneoplastic syndromes

Guichard and Vignon first used the term 'paraneoplastic' in 1949 in a patient with metastatic uterine cancer.[41] The commonest paraneoplastic syndromes associated with autonomic dysfunction include small cell lung cancer,[42] tumours of the breast and ovary, and lymphoma.[43] Dysautonomias with a well-recognized paraneoplastic association include paraneoplastic autoimmune autonomic gangliopathy (AAG), paraneoplastic sensory neuropathy, paraneoplastic encephalomyeloneuropathy, and the Lambert-Eaton myaesthenic syndrome. Common clinical features include orthostatic hypotension, impaired gastrointestinal motility, lack of heart rate changes with respiration, bladder dysfunction, impotence, abnormal sweating, and dry eyes and mouth. Autonomic symptoms may arise prior to the diagnosis of malignancy, and during and after treatment, with orthostatic hypotension, constipation and pseudo-obstruction being the commonest presentations.[44] The clinical course is subacute but usually rapidly progressive, with many patients immobile within a few weeks.[45]

Autoimmune antibodies produced by the tumour can attack parts of the autonomic nervous system with lymphocytic infiltrates a histological finding in anti-Hu encephalomyeloneuropathy and in autonomic postganglionic and myenteric neurons with antineuronal antibodies. Antibodies associated with paraneoplastic autonomic dysfunction include Hu, CV2, Yo and voltage-gated calcium channels.

Investigations include identification of the tumour and its anatomical location through imaging such as CT, MRI and PET scanning. Tissue diagnosis can be made through biopsy and cellular washings for cytology. CSF analysis may

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also detect malignant cells, and often shows an inflammatory pleocytosis and raised total protein. Blood tests include serum profiles for antineuronal autoantibodies.

Treatment of the underlying cancer occasionally improves autonomic dysfunction, but in the majority of cases there is little response. Therapeutic options include immunotherapy via intravenous immunoglobulin, steroids, plasma exchange and cyclophosphamide, although results have generally been disappointing. Early aggressive immunotherapy may benefit some patients with anti-Hu paraneoplastic sensory neuropathy.[46]

Clinical investigation

Ewing and Clarke developed five tests to assess diabetic autonomic neuropathy, which can be performed with simple equipment over 20 min.[47] These include a heart rate response to a Valsalva manoeuvre, heart rate variability during deep breathing, blood pressure response to sustained handgrip, immediate heart rate response to standing, and blood pressure response to standing.

During the Valsalva maneoeuvre, expiration against a closed glottis usually produces a fall in blood pressure and rise in heart rate. Following release, the blood pressure usually rises producing an increase above the resting value and the heart rate slows. In patients with autonomic failure, blood pressure falls slowly during expiration and returns to normal but with no overshoot in blood pressure or change in heart rate.

Deep breathing causes heart rate variability in normal subjects and this is dependent on an intact parasympathetic nerve supply. Patients with autonomic failure have a reduction in and sometimes a complete absence of heart rate variation. Subjects sit quietly taking 6 breaths per minute and the maximum and minimum R–R intervals during each breathing cycle are measured. One study suggested that this is the most reliable test in patients with diabetes compared with heart rate on standing, the Valsalva manoeuvre and metronomic breathing tests.[48]

Standing produces heart rate increases peaking at the 15th beat, followed by slowing which peaks at the 30th beat.[49] This effect can be abolished in normal subjects by intravenous atropine but not propranalol, suggesting mediation via the vagus nerve.[50] Diabetic patients with autonomic neuropathy show only a gradual or no increase in heart rate after standing.[51] Blood pressure falls on standing, and in patients with severe sympathetic neuropathy, standing blood pressure remains lower than that when sitting.

Sustained handgrip produces a rise in blood pressure related to a heart rate-dependent increase in cardiac output with no change in systemic vascular resistance.[52] Blood pressure rises in autonomic failure are attenuated.

Vasoconstrictor tests include isometric exercise where a sustained handgrip is held for several minutes,[53] cold immersion of the hand in ice cold water and mental arithmetic, which stimulate sympathetic outflow producing a rise in blood pressure and heart rate. In autonomic failure, these cardiovascular responses to vasoconstrictor stimuli are blunted.[54]

Sympathetic cholinergic response

1. Thermoregulatory sweat test. Body temperature is raised by using heat blankets or hot water vessels, and the patient's skin is covered in quinizarine or Ponceau red, which turns purple on exposure to moisture. Autonomic failure resulting in reduced sweating at higher ambient temperatures attenuates this response.[55]

2. Sudomotor axon reflex test. The test has three parts and measures resting skin temperature, resting sweat output, and stimulated sweat output. Measurements are typically taken on arms, legs or both. A small plastic cup is placed on the skin and the temperature and amounts of sweat under the skin are measured. To stimulate sweat pilocarpine is delivered intradermally to a sweat gland, but the patient will only feel warmth. Changes in temperature and sweat output are recorded and analysis detects local reflex dysfunction.[56]

3. Sympathetic skin response. Electrical activity on the hand or foot increases with increasing sweat gland activity and this is recorded in response to a variety of stimuli including sound, touch and nerve stimulation, e.g. median nerve. Cholinergic dysfunction (e.g. primary autonomic failure) produces no response, but those with adrenergic failure (e.g. multisystem atrophy) may see some response.

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Clinical consequences of autonomic failure

Orthostatic hypotension

Orthostatic hypotension is defined as a fall of 20 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure within 3 min of standing, or during a 60 deg head-up tilt.[57] It affects 30% of those >75 years, and up to 50% of the frail elderly living in nursing homes.[58] 500–1000 ml of blood normally pool in the lower limbs on standing, and this results in reduced cardiac filling sensed by the baroreceptors located in the aortic arch and carotid arteries.[59] This produces a reflex activation of the sympathetic nervous system, increasing heart rate through β-receptor stimulation and peripheral vasoconstriction to maintain blood pressure and cardiac output. As humans age, in addition to loss of α_1-mediated vasoconstriction and decreased baroreceptor sensitivity, parasympathetic activity decreases resulting in a withdrawal of vagal tone.[60] Reduced levels of renin, angiotension, and aldosterone, and an elevation of natriuretic peptide prevent salt and water conservation in the volume-depleted older patient. Increased vascular resistance results in impaired diastolic cardiac filling, stiffened ventricles, a reduction in stroke volume and a decrease in preload. Symptoms may include dizziness, light-headedness, blackouts, nausea, paracervical, lower back and chest pain. Disturbed speech, visual changes, falls, confusion and impaired cognition are often seen.[61] Patients are at significant risk of falls, fractures, transient ischaemic attack, and myocardial infarction.[62–65] Recurrent orthostatic hypotension and hypoperfusion have been associated with the development of vascular dementia.[66]

Initial evaluation should include a full history and examination. A clear history is essential in determining an accurate account of symptoms and their temporal relationship to a change in posture. Where there is loss of consciousness, establishing a witness account can distinguish syncope from other causes such as seizures. A review of current medications may reveal a culprit such as a potent antihypertensive drug. A thorough examination identifies not only the presence of postural hypotension, but may also detect peripheral neuropathy due to diabetes, peripheral vascular disease and evidence of ischaemic heart disease. The blood pressure and heart rate should be measured once the patient has been supine for 5 min, then after 1 min and 3 min of standing.

Investigations should include a 12-lead electrocardiogram, which may show evidence of sinus tachycardia, reduced R–R variability, a prolonged QTc interval and changes consistent with pre-existing ischaemic heart disease, all of which potentially signify underlying autonomic dysfunction. Blood tests including a full blood count, urea, electrolytes and fasting blood glucose should be performed, as should liver function tests and a bone profile to potentially detect alcoholic or malignancy-related neuropathy. Neuroimaging should be considered if an underlying neurological abnormality or cerebrovascular disease is suspected. Further clinical investigation may include the Ewing and Clarke protocol to evaluate cardiovascular autonomic function in more detail.[47]

Management consists of pharmacological and non-pharmacological interventions, and patient education. Non-pharmacological interventions include compression stockings, adequate fluid intake, slow and supported changes in posture, and a liberal salt intake to achieve a 24 h urinary volume of 1.5–2 litres, which may attenuate orthostatic hypotension in sympathetic dysfunction. Head-up tilt at night, and reducing the quantity of meals and alcohol may be helpful in susceptible patients. In older patients prone to muscular deconditioning, exercise regimes involving aerobic exercise have led to a significant reduction in reported symptoms.[67,68] Pharmacological interventions include mineralocorticoid therapy with fludrocortisone,[70] and vasopressors such as midodrine, an α-agonist with selective α-activity.[69–72] Reducing or stopping relevant medications, such as antihypertensives, antidepressants and neuroleptics is a simple measure that can have a dramatic effect on orthostatic hypotension. Paradoxically, some orthostatic changes have been found to improve with time following commencing antihypertensive therapy, and these drugs should be used at the lowest dose possible and titrated upwards but preventing large changes in blood pressure following postural change.[73] Other potential agents of benefit include prostaglandin inhibitors such as indomethacin, erythropoietin in those with coexistent anaemia, caffeine, and octreotide.[74–76]

Supine hypertension and postural hypotension

Supine hypertension can occur in up to 50% of patients with orthostatic hypotension.[77] Autonomic failure results in lability of blood pressure

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as demonstrated by profound hypotension on standing in the heat and on exercise, but a marked pressor effect on water drinking.[78,79] Proposed mechanisms for supine hypertension include baroreflex dysfunction, high blood volume with low blood pressure due to plasma redistribution in primary autonomic failure, and hypersensitive postsynaptic adrenoreceptors with an increase in resting sympathetic tone.[80–82] Treatment options include prevention by avoiding vasopressor agents in the early evening and sleeping with elevation of the head of the bed. Vasodilators such as glyceryltrinitrate can help when supine blood pressures remain elevated. Pyridostigmine may improve postural hypotension without causing a rise in lying blood pressure.[83]

Cerebral autoregulation changes with ageing and autonomic dysfunction

Cerebral autoregulation is the maintenance of stable perfusion to the brain despite variations in systemic blood pressure. In healthy patients without autonomic dysfunction, mean arterial pressure ranges of 50–150 mmHg produce an insignificant change in cerebral perfusion with increasing systemic pressure producing cerebral arteriolar dilatation and lower pressures resulting in vasoconstriction.[84] Postulated control mechanisms include a myogenic theory in which vascular smooth muscle tone is altered in response to changes in mean arterial pressure, a metabolic mechanism in which vasoactive substances regulate cerebral blood flow to maintain autoregulation, and neurogenic control where perivascular nerve fibres influence cerebral arteriolar constriction and dilatation.

In autonomic failure and ageing, cerebral autoregulation appears to be preserved despite loss of baroreceptor sensitivity. Dynamic cerebral blood flow as measured by transcranial doppler imaging and beat-to-beat arterial blood pressure measured at the radial artery suggested little effect on cerebral autoregulation with increasing age.[85] There was no reduction in cerebral blood flow despite a fall in middle cerebral artery velocity measured by transcranial doppler in patients with pure autonomic failure and multiple system atrophy undergoing tilt-table testing.[86] In orthostatic hypotension, the autoregulation range is expanded at both upper and lower limits so that cerebral perfusion remains relatively constant when the patient is supine and in response to standing, and may explain why many patients are asymptomatic.[87]

Neurocardiogenic syncope

Neurocardiogenic syncope is characterized by a sudden failure of the autonomic nervous system to maintain blood pressure and heart rate leading to insufficient cerebral perfusion pressure. It has an unknown trigger, but the afferent arc synapses with the brainstem cardioinhibitory and vasodepressor centres causing vasodepressive hypotension and heart rate slowing or asystole resulting in loss of consciousness. It can therefore be subdivided into a vasodepressor, cardioinhibitory response with and without asystole, or a mixed response.[88] Three phases may exist, including a prodrome, loss of consciousness and post-syncope episode.[89] Prodromal symptoms include palpitations, nausea, sweating, light-headedness, blurred vision, paraesthesiae and pallor.[90] An identifiable precipitant is common, and in older people is mostly attributable to vasodilator medication or prolonged standing. Normally, prolonged standing leads to the pooling of blood in the lower extremities, and the subsequent arterial hypotension is sensed in the carotid bodies. Afferent fibres trigger a reflex increase in heart rate and contractility. Pressure receptors located in the infero-posterior wall of the left ventricle may respond to a variety of stimuli including arterial hypotension, stretch, chemical substances and drugs that produce an increase in parasympathetic and decrease in sympathetic activity.[91] The resultant heart rate slowing, vasodilatation and hypotension is known as the Bezold-Jarisch reflex and is a possible physiological explanation for neurocardiogenic syncope.[92] Loss of consciousness is usually brief, lasting 30 s to 5 min, and some patients develop myoclonic or tonic-clonic jerks mimicking epileptic attacks. Recovery is rapid, although a small proportion of patients may experience distressing symptoms for a number of hours.

Investigations include 24-h and 7-day Holter monitoring for those with an abnormal ECG, postural blood pressure measurements, and tilt-table testing. Indications for tilt testing include following a single episode for those in a high risk setting, syncope associated with exercise,

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Table 1. *Outcomes following head-up tilt*

Response type	Description
Type 1	'Mixed response' – heart rate rises on tilting but falls during syncope, ventricular rate is 40 for less than 10 s, with or without asystole for 3 s. Blood pressure rises initially but falls as heart rate falls
Type 2a	'Cardioinhibitory' – heart rate rises on head-up tilt but falls during syncopal event, with a ventricular rate of 40 or less occurring for more than 20 s or asystole occurring for more than 3 s. Blood pressure rises initially but falls as heart rate falls
Type 2b	'Cardioinhibitory–inhibitory' – heart rate rises on tilting but falls during syncope, ventricular rate less than 40 bpm for more than 20 s or asystole for more than 3 s. Blood pressure rises initially but falls to hypotensive levels
Type 3	'Pure vasodepressor' – heart rate rises progressively as the patient adopts a head-up position and does not fall by more than 20 bpm, whereas blood pressure falls, causing syncope during the tilt

and for further evaluation of recurrent syncope in patients in whom a cause has yet to be identified.[93] Contraindications include severe ventricular outflow obstruction, severe mitral stenosis, syncope in the setting of critical proximal coronary artery disease, and cerebrovascular disease. Tilt testing in selected older patients can produce a reasonable yield.[94] In 176 patients aged over 65 referred for tilting due to unexplained syncope, 49 patients over 65 and 10 patients over 80 had a positive tilt test.[95]

Treatment of neurocardiogenic syncope involves avoidance of precipitants. A vasodepressor response can be attenuated by isometric manoeuvres such as leg crossing or intense handgrip, patient education, and manoeuvres to avert syncope when presyncopal symptoms arise.[96,97] Dietary measures such as increased salt intake and oral supplements may be helpful.[98,99] Beta-blockers suppress autonomic activity and blood pressure variability, and although there is much anecdotal and short term data to suggest a benefit, there is little longer term controlled data providing an evidence base to support their use.[100] Other agents of potential benefit include mineralocorticoids that promote salt and water retention, midodrine, and in refractory cases selective serotonin inhibitors such as paroxetine.[101–103] Patients with a predominant cardioinhibitory or mixed response should be considered for dual chamber permanent pacemaker insertion.[104]

Carotid sinus hypersensitivity

Carotid sinus hypersensitivity is defined as a ventricular pause lasting longer than 3 s and a drop of 50 mmHg in systolic blood pressure following 5–10 s of carotid sinus massage.[105] It was present in 39% of 272 asymptomatic older subjects, and an equally high prevalence has been suggested in patients with Alzheimer's and Lewy body dementia.[106] In a consecutive series of older patients with carotid sinus hypersensitivity who required pacemaker insertion, over 30% had presented to hospital with unexplained falls prior to pacing. Significant injuries occurred within this group, with 25% having fallen and sustained a fractured neck of femur prior to presentation.[107] Interestingly, amongst those with carotid hypersentivity, there is no increased risk of death compared with unexplained syncope in a population matched for age and sex.

Three subtypes of carotid sinus syndrome exist,[105] and include:

(1) cardioinhibitory, or when carotid sinus massage produces 3 s or more of asystole with symptom reproduction;
(2) a vasodepressor response, or where carotid sinus massage produces a drop in systolic blood pressure of 50 mmHg or more with symptoms;
(3) a mixed response where the criteria for both vasodepressor and cardioinhibitory responses are met.

Carotid sinus massage should be considered in elderly patients who present with syncope, presyncope or unexplained falls and in whom history, examination and investigation have not identified an underlying cause.[93] Contraindications include myocardial infarction, transient ischaemic attack or stroke, and a history of ventricular fibrillation or ventricular tachycardia. The right carotid should be massaged first for 5–10 s,

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followed by the left carotid after 1–2 min if no response. There should be continuous cardiac and blood pressure monitoring, and it should be performed in both supine and upright positions. It is positive if it induces syncope during or straight after massage, produces asystole of >3 s, or a fall in systolic blood pressure of 50 mmHg or more. Neurological complications of carotid sinus massage vary between 0.07 and 0.14%.[108]

Treatment is not necessary in asymptomatic patients. Carotid sinus massage producing more than 3 s of asystole is a mandatory criterion for pacemaker insertion, whereas recurrent syncope without provocative events but a hypersensitive cardioinhibitory response is a strong indication for pacing.[109] Drugs such as beta-blockers, calcium channel blockers and methyldopa can affect atrioventricular node function, and stopping them may improve carotid hypersensitivity in up to 50%. Management of the vasodepressor response is more challenging. Fludrocortisone can help but causes many unwanted adverse effects in older patients.[110]

Erectile dysfunction

Erectile dysfunction is defined as an inability to achieve and sustain an erection sufficient to permit satisfactory sexual intercourse.[111] Some 5–20% of men have moderate to severe dysfunction. The greatest risk factor is age. The Massachusetts Male Ageing Study showed that the incidence of erectile dysfunction increases with every decade of life.[112] These were 12.4 per 1000 man years aged 40–49, 29.8 between 50 and 59 years and 46.4 between 60 and 69 years.

Diabetes mellitus, smoking, hypertension and hyperlipidaemia are strongly associated, and there is a correlation between coronary artery and cerebrovascular disease when erectile dysfunction is present.[113]

Validated psychosexual questionnaires as well as detailed clinical examination focusing on penile structure, the presence of prostatic disease, signs of hypogonadism and cardiovascular and neurological status are key in making the diagnosis.[114] Routine investigations should include a fasting glucose and testosterone level.

Management includes psychosexual therapy for those with a psychological cause, hormonal replacement for those deficient in testosterone, treatment of prostatic disease, mechanical devices such as vacuum constriction and penile implants, and pharmacological agents such as sildenafil, tadafil and vardenafil. Second- and third-line therapeutic options include aloprostadil which may be administered by intracavernous injection, prostaglandin E1 which can be given intraurethrally, and sublingual apomorphine.

Sildenafil,[115] a phosphodiesterase type 5 inhibitor which is a smooth muscle dilator improving penile blood flow, and other drugs from the same class have significantly improved sexual function and outcomes in older men.

Gastrointestinal dysfunction

Dysphagia may result from reduced salivary gland function and also lower oesophageal dysfunction related to autonomic innervations of the lower two-thirds of the oesophagus. Gastric motility is reduced with age, as is the perception of gastric distension, and this is related to progressive autonomic nerve dysfunction. These features are found in diabetic gastroparesis in which there is abdominal distension and vomiting. Large intestinal motility also diminishes, and constipation is a common clinical problem. There are a reduced number of myenteric plexus neurones and reduced large bowel transit time is found in both primary autonomic failure and Parkinson's disease, in which there is a reduction in myenteric plexus neurones with Lewy body accumulations.[116] Diarrhoea can result from overflow in which constipation and faecal impaction result in loose motions and from changes in bowel flora and motility in diabetes mellitus.

Thermoregulation

Attenuated responses to thermal stress have been well documented in older patients. Nearly fifteen thousand people lost their lives in France in 2003 due to exceptionally high temperatures, the vast majority of whom were in the older age group.[117] Autonomic failure can produce sudomotor dysfunction, resulting in hypo- or anhidrosis, gustatory sweating, hypo- and hyperthermia and heat stress.[118]

Hyperthermia occurs when thermoregulatory cooling mechanisms are overwhelmed by excessive metabolic production of heat, excessive environmental heat, or inadequate heat dissipation.[119] Heat loss during periods of high temperatures

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Table 2. *Major syndromes encountered in autonomic failure*

Syndrome	Diagnosis	Management
Orthostatic hypotension	A fall of 20 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure within 3 min of standing or during a 60 deg head-up tilt	• *Pharmacological interventions* • *Dose reduction or medication cessation* Antihypertensives, neuroleptics, antidepressants • *Vasopressors* Fludrocortisone, midodrine • *Experimental* Prostaglandin inhibitors, erythropoietin, caffeine, octreotide • *Non-pharmacological interventions* • *Mechanical compression* Compression hosiery • *Diet* High salt intake • *Patient education* Slow and supported changes in posture, head-up tilt at night • *Exercise regimes in selected patients*
Neurocardiogenic syncope	*History* – especially medication and precipitants	• *Education* Avoidance of triggers, recognition of presyncopal symptoms and self help manoeuvres to avert syncope, eg isometric exercise
	Examination – assess for significant cardiac disease, and consider other causes of syncope, eg carotid sinus hypersensitivity or othostatic hypotension	• *Salt intake* Increase salt and fluid intake
	Investigations – 24-h and 7-day Holter monitoring, tilt table testing	• *Tilt training* Increasing length of periods of enforced upright posture on tilt table • *Pharmacological agents with potential benefit* Beta-blockers Midodrine Fludrocortisone Selective serotonin reuptake inhibitors
Carotid sinus hypersensitivity (CSH)	A ventricular pause lasting greater than 3 s and a drop of 50 mmHg in systolic blood pressure following 5–10 s of carotid sinus massage defines CSH	Asymptomatic patients require no intervention • *Pacemaker insertion* Patients in whom carotid sinus massage produces greater than 3 s of asystole and those who experience recurrent syncope without provocation but a hypersensitive cardioinhibitory response • *Pharmacological intervention* Stopping or reducing dose of beta-blockers, calcium channel antagonists and methyldopa improves AV nodal function Fludrocortisone may be of benefit in those with a vasodepressor response.
Erectile dysfunction	*History* Validated psychosexual questionnaire	• *Pharmacological interventions*
	*Examinatio*n Targeted clinical examination	Phosphodiesterase type 5 inhibitors, eg sildenafil, intracavernosal aloprostanil, intraurethral prostaglandin E1, sublingual apomorphine
	Investigations Fasting glucose and testosterone levels	• *Psychosexual therapy* • *Hormonal replacement*
	Specialist investigations refer to a sexual health specialist or urologist	• *Mechanical devices* eg vacuum constriction and penile implants

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Table 2. *(continued)*

Syndrome	Diagnosis	Management
Gastrointestinal dysfunction	Lack of salivation	• Artificial saliva
	Dysphagia	• Achalasia – dilatation, botulinum toxin, surgery
	Vomiting	• Oropharyngeal dysphagia – food type, consistency, artificial nutrition
	Abdominal distenstion	• Gastroparesis – prokinetic agents, eg metoclopramide, domperidone, erythromycin
	Constipation	• Constipation – laxatives and enemas, increased dietary fibre
	Diarrhoea	• Diarrhoea – treatment of constipation in overflow, opiates, octreotide, antibiotics in bacterial overgrowth
Thermoregulatory failure	Hypothermia – core temperature $< 35^{\circ}C$	*Hypothermia*
	Hyperthermia – core temperature $> 37.5–38.3^{\circ}C$	1 *Active External Rewarming* through immersion, radiant heat, forced air and electric or plumbed heating blankets 2 *Active Core Rewarming* through warmed intravenous fluids, bladder irrigation, warmed humidified oxygen, peritoneal lavage, closed pleural irrigation 3 *Extracorporeal Rewarming* In cardiac arrest, continuation of cardiopulmonary resuscitation *Hyperthermia* 1 *Active External Cooling:* colder environment, remove clothes, use of bedside fan, tepid sponges, ice pack application, hypothermic mattresses, immersion in ice water 2 *Active Core Cooling:* cold intravenous or intraperitoneal fluids, enemas with cold water, extracorporeal cooling 3 *Pharmacologial interventions* Antipyretics such as acetaminophen *Public Health Strategies* Patient advice and education during weather extremes

occurs through diversion of cardiac output with increases in skin blood flow and a reduction in splanchnic and renal blood flow, and sweat evaporation.[120] These are the principle mechanisms through which homeostatic cooling occurs. Kenney *et al*. found lower cardiac outputs and heart rates in older men exercising in warm environments compared with younger subjects.[121] Skin blood flow at a given temperature during passive and active heat stress was considerably less in older patients, suggesting less ability to lose heat through cutaneous vasodilatation than in younger patients.[122] This lack of vasodilatory response can be explained partially by an imbalance between noradrenaline and nitric oxide, producing an increase in vascular smooth muscle tone. Cardiac output diversion from the core to the periphery and heat dissipation is therefore more difficult to achieve in older patients during periods of heat stress.

Hypothermia is defined as an unintentional decline in core temperature below $35^{\circ}C$ where co-ordinated physiological responses to retain heat by minimizing conduction, convection, radiation,

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evaporation and respiration begin to fail.[123] In the USA in 2001, hypothermia was thought to have caused up to 600 deaths, whereas between 1982 and 1997 in England and Wales, there was an average of 491 deaths per year.[124,125] When exposed to cold temperatures, thermoreceptors in the skin, spinal cord and brain transmit impulses to the hypothalamus which produce cutaneous vasoconstriction, heat generation by shivering of skeletal muscle and other processes such as increased metabolism in brown adipose tissue. Cold perception is critical in preventing hypothermia, and thermoreceptor sensitivity is significantly reduced in older patients.[126] Shivering is reduced due to reduced skeletal muscle bulk, and onset of shivering is delayed compared with younger subjects.[127] Reduced skeletal muscle enzyme activity in aerobic metabolism has also been postulated as a mechanism for reduced shivering. Cutaneous blood vessels show a reduced ability to vasoconstrict coupled with an overall reduction in skin blood flow, producing cold stress in the older patient. Collins *et al*. measured changes in hand blood flow response to the cold in 43 older males over a period of 8 years. The proportion in whom there was no cold-induced reduction in blood flow was 14% at baseline, increasing to 32% after 4 years, with a higher percentage still at 8 years.[128] Blood flow has been shown to decrease in both young and old subjects in response to the cold, but it increases again to pre-cooling levels in the later group after 1 min. This suggests that older subjects are unable to maintain sustained vasoconstriction.[129]

Thermoregulatory dysfunction increases with age, but factors such as physical fitness, socioeconomic status, co-existent disease states and prior environmental acclimatization play an important role. Tight environmental temperature control with adequate heating in the winter months and cooling methods in the summer, as well as adequate social and financial support are vital in preventing thermal stress in the older patient.

Conclusions

The ageing autonomic nervous system produces complex physiological changes that manifest in a number of clinical syndromes, some of which can be very difficult to treat. Cardiovascular disease and diabetes mellitus directly damage autonomic nerve fibres and are particularly prevalent in older people. Orthostatic hypotension due to reduced baroreceptor sensitivity and reduced vasoconstriction is a significant cause of falls, morbidity and mortality in the elderly. Early identification of risk factors in middle age, careful diagnosis, treatment of vascular disease and diabetes, and potential future interventions to treat neurodegenerative processes may delay or prevent the onset and reduce the severity of autonomic-related disorders. In established autonomic failure, better patient information, education and understanding to avoid changes in posture, heat extremes and situational circumstances precipitating events such as neurocardiogenic syncope are key to successful long-term management. Clinical judgement is required to achieve a fine balance in supporting aberrant autonomic function in response to physiological stress without creating further medical complications.

Conflicts of interest

The authors declared no conflicts of interest.

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