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Autonomic nervous system: anatomy, physiology, and relevance in anaesthesia and critical care medicine

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Key points

- The autonomic nervous system (ANS) regulates involuntary functions. Anaesthesia, surgery, and critical illness lead to a varied degree of physiological stress that alters the ANS.
- The organization of ANS is on the basis of the reflex arc and it has an afferent limb, efferent limb, and a central integrating system.
- Neurotransmitters and receptors are an integral part of the ANS.
- Autonomic neuropathy refers to damage to the autonomic nerves and diabetes mellitus is the most common cause.
- Autonomic neuropathy involves a number of organs and has serious clinical consequences in the perioperative period and during their management in the critical care unit.

The autonomic nervous system (ANS) is the part of the nervous system that regulates involuntary functions.[1] Examples are the heartbeat, the digestive functions of the intestines, control of respiration, and secretion by glands.

Basic anatomy and physiology

The organization of the ANS is on the basis of the reflex arc and it has an afferent limb, efferent limb, and a central integrating system.[1]

Afferent limb

The afferent limb transmits information from the periphery to the central nervous system (CNS). The receptors are present in the abdominal and thoracic viscera.[1] The transmissions from these receptors are conducted along neural pathways into the spinal cord via the dorsal root ganglion or to the brain stem via cranial nerves. Baroreceptors and chemoreceptors are examples of the afferent pathway. These are present in the aortic arch and carotid sinus. The sensory impulses from these receptors are transmitted via glossopharyngeal and vagus nerves to the brain stem.

Efferent limb

The efferent limb is made up of preganglionic and post-ganglionic fibres and an autonomic ganglion. The efferent limb is further subdivided based on its anatomic and physiological differences into sympathetic and parasympathetic components. A useful generalization is that the sympathetic system responds for 'flight-or-fight' and prepares the body for such a response by increasing the heart rate, arterial pressure, blood flow to the skeletal muscles, heart, and brain.[1] The parasympathetic system prepares the body for 'rest and digest' by depressing the central venous system and increasing the activity of the abdominal viscera.[1]

Central integration

Simple reflexes are completed within the organ system involved. More complex reflexes are regulated by higher autonomic centres present in the CNS, mainly the hypothalamus and the brain stem.[1]

Structure of the ANS

Preganglionic fibres of both the sympathetic and parasympathetic system are myelinated, whereas the post-ganglionic fibres are

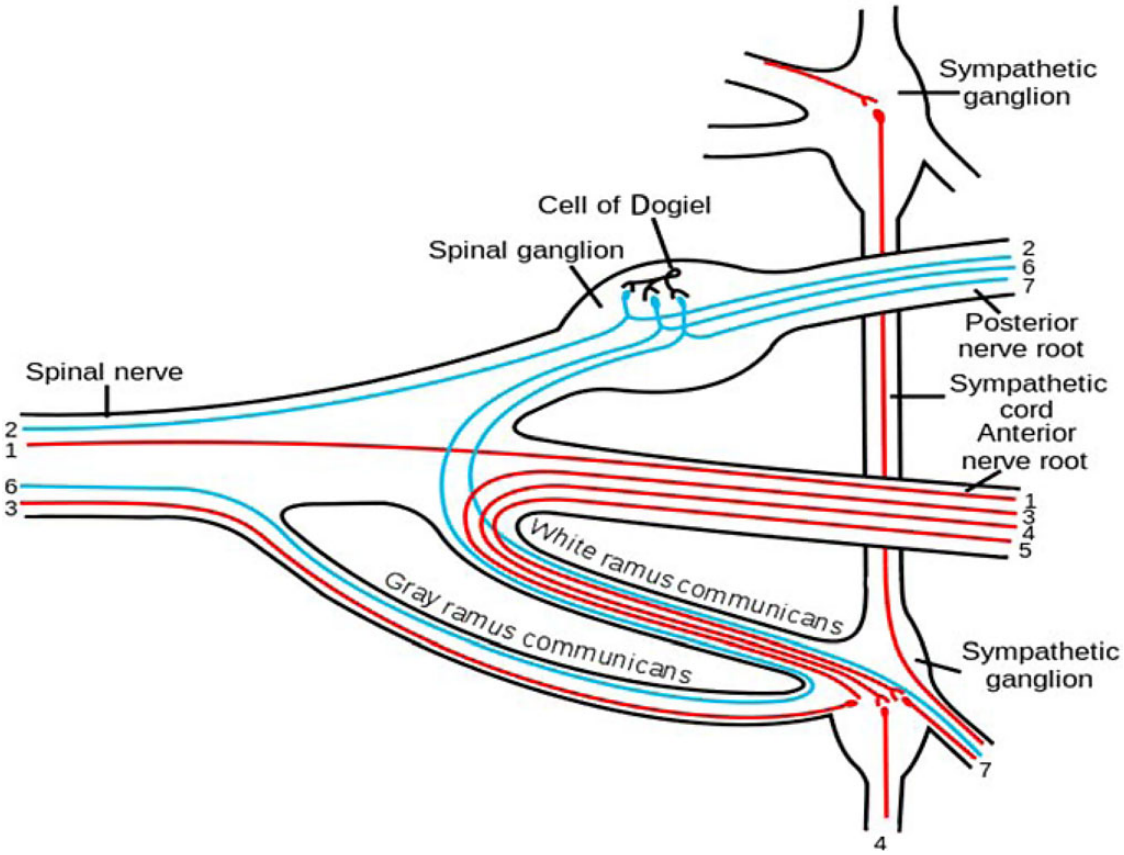

Fig 1 Sympathetic nervous system anatomy at the spinal cord level. 1, Somatic efferent; 2, somatic afferent; 3–5, sympathetic efferent; 6 and 7, sympathetic afferent. This image is from the 20th US edition of *Gray's Anatomy of the Human Body* and is in the public domain.

unmyelinated. Both the divisions of the ANS innervate most of the organs in the body, usually with opposing effects. The effects may also be parallel as seen in the salivary glands.

Sympathetic nervous system

Preganglionic fibres originate from cell bodies in the grey matter of the lateral horn of the spinal cord between the first thoracic segment down to the second or third lumbar segment (T1 to L2/3). The so-called 'thoraco-lumbar' outflow.[2] These preganglionic fibres synapse with the post-ganglionic neurones in the ganglia of the sympathetic chain (Fig. 1). The ganglia form the sympathetic chain arranged as two paravertebral chains. The post-ganglionic fibres leave the ganglia and join the spinal nerves or visceral nerves to innervate the target organs.[1]

The paravertebral sympathetic chain[2]

The paravertebral sympathetic chain is divided into four parts.

(i) *A cervical part*: consists of three ganglia (superior, middle, and inferior) supplying the head, neck, and thorax. The inferior cervical ganglion fuses with the first thoracic ganglion to form the stellate ganglion.
(ii) *A thoracic part*: consists of series of ganglia from each thoracic segment. T1–T5 branches supply the aortic, cardiac, and pulmonary plexus.
(iii) *Lumbar part*: situated in front of the lumbar vertebral column as the prevertebral ganglia. Branches from the lumbar part form the coeliac plexus.

Table 1 Neurotransmitters and receptors of the ANS

ANS efferent pathway	
Preganglionic cholinergic fibres	
Release acetylcholine	
Ganglia	
Acetylcholine nicotinic receptors	
Sympathetic nervous system	Parasympathetic nervous system
Post-ganglionic adrenergic fibres	Post-ganglionic cholinergic fibres
Release predominantly norepinephrine	Release acetylcholine
Release acetylcholine at sweat glands, piloerector muscles of the hairs, and few blood vessels	
Adrenergic receptors	Acetylcholine (Ach) receptors
α1, α2, β1, β2, β3	Muscarinic receptors
	Nicotinic receptors

(iv) *Pelvic part*: lies in front of the sacrum and consists of the sacral ganglia.

Parasympathetic nervous system

Preganglionic fibres arise from the CNS from both the cranial (from brain stem) and sacral nerves called 'craniosacral' outflow. Cranial parasympathetic fibres arise from brainstem motor nuclei of the 3rd, 7th, 9th, and 10th cranial nerves. Sacral outflow arises from the second, third, and fourth sacral segments of the spinal cord. Fibres emerge from ventral rami of nerves S2–4 and form the pelvic splanchnic nerves.

Table 2 ANS effects on various organs of the body

Organ	Sympathetic response	Parasympathetic response
Eyes	Dilatation (α1)	Constriction
Heart	Increase heart rate (β1, β2)	Decrease heart rate
	Increase contractility (β1, β2)	Decrease contractility
	Increase conduction velocity	Decrease conduction velocity
Arterioles	Vasoconstriction (α)	Vasodilatation
	Vasodilatation (β)	
Systemic veins	Vasoconstriction (α)	
	Vasodilatation (β)	
Lungs	Bronchodilatation (β2)	Bronchoconstriction
Kidney	Increase renin secretion (β1)	
Gut	Decrease peristalsis and tone	Increase peristalsis and tone
	Contraction of sphincter (α)	Relaxation of sphincter
Liver	Glycogenolysis (α1, β2)	Slight glycogen synthesis
	Lipolysis	
Bladder	Detrusor relaxation (β2)	Detrusor contraction
	Sphincter contraction (α1)	Sphincter relaxation
Uterus	Contraction in pregnancy (α1)	
	Relaxation of pregnant and non-pregnant uterus (β2)	
Basal metabolism	Increased	
Adipose tissue	Lipolysis (α1, β1, β3)	
Salivary glands	Thick, viscous secretion (α1)	Profuse, watery secretion

The physiology of the ANS

Neurotransmitters and receptors are integral to the automatic functioning of the ANS (Tables 1 and 2). Receptors mediate actions of the neurotransmitters involved in the ANS by activation of a second messenger, or by a change in ion channel permeability.

Pathophysiology

Autonomic neuropathies

Autonomic neuropathy refers to damage to the autonomic nerves. They are a group of disorders affecting the autonomic neurones, either sympathetic or parasympathetic, or both (Fig. 2). In developed countries, diabetes is the most common cause of autonomic neuropathy.[3]

Aetiology and pathogenesis

The pathophysiology of autonomic neuropathies is variable and depends upon the medical condition or the complication that lead to it. Exact mechanism of damage to the ANS is still unclear. Poor blood sugar control may be an important contributing factor in many of the proposed mechanisms[4] (Table 3).

Anaesthetic management of a patient with autonomic neuropathy

Preoperative assessment

Autonomic neuropathy involves a number of organ systems and has serious clinical consequences during the perioperative period. Anaesthetists therefore must be aware of the clinical conditions that are associated with autonomic neuropathy (Table 4). It is vital to look for evidence of dysfunction (Table 5) in order to anticipate and possibly prevent perioperative complications.[5]

Cardiac autonomic neuropathy (CAN) is a clinically significant and life-threatening complication of diabetic autonomic neuropathy. Significant intraoperative haemodynamic instability and major cardiac events can occur. Poor glycaemic control and duration of diabetes are mainly responsible for the severity and it is also known to exist in patients with advanced diabetic complications like retinopathy and nephropathy.[4] Resting tachycardia is a feature of diabetic neuropathy and a heart rate between 90 and 130 beats min^{-1} is a feature of cardiac autonomic dysfunction.[4] This occurs due to sympathetic over-activity as parasympathetic dysfunction occurs first.[4]

The loss of afferent nerve fibres in the ischaemic areas of the heart may be responsible for the 'defective anginal warning' in diabetic patients with autonomic neuropathy. Not only can acute myocardial infarction occur without symptoms, but chronic painless ischaemia is also common.[5] Even in the absence of any cardiac disease, autonomic neuropathy may be associated with LV systolic and diastolic abnormalities.

Prolonged QTc on ECG is seen in patients with CAN. These patients are more at risk of developing perioperative cardiac complications like painless myocardial ischaemia, arrhythmias such as torsades de pointes, and sudden death.[3,4] Altered cardiac sympathetic innervation (imbalance in the right and left stellate ganglion activity) is suggested to be the reason for the prolongation of the QTc interval.[4,6]

Exercise tolerance is impaired in patients with autonomic dysfunction because the compensatory responses of heart rate and arterial pressure are decreased in response to exercise. Poor exercise tolerance would warrant further evaluation of the cardiopulmonary function and assessment of the ANS.[4]

Orthostatic hypotension may be present in patients with diabetic autonomic neuropathy due to damage to the efferent sympathetic fibres. Sympathetic dysfunction leads to a decrease in norepinephrine release and reduced vasoconstriction causing hypotension during postural changes.[4] Any history of fainting, dizziness, visual impairment, and syncope in these patients should be actively sought and would be suggestive of orthostatic hypotension due to autonomic neuropathy.

Gastroparesis leading to delayed gastric emptying and increased risk of acid reflux and aspiration is an important concern for the anaesthetist even in fasted patients. The presence

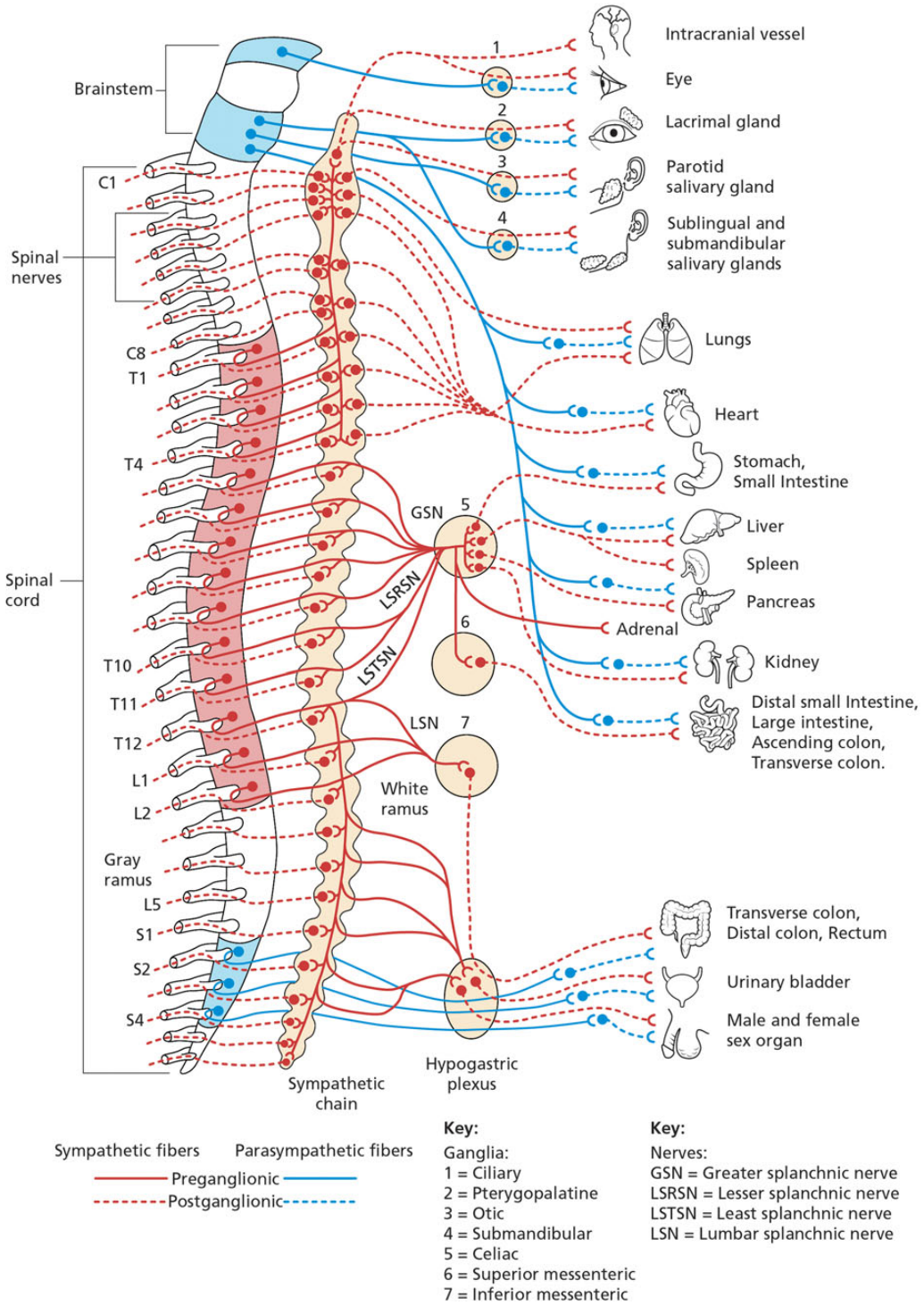

Fig 2 ANS overall anatomy. Parasympathetic pathways represented by blue and the sympathetic pathways in red. The interrupted red lines indicate post-ganglionic rami to the cranial and spinal nerves. This image is from the 20th US edition of *Gray's Anatomy of the Human Body* and is in the public domain.

of cardiovascular autonomic dysfunction is in no way evidence of the presence of gastroparesis.[3] If acid reflux is present, it is prudent to prescribe these patients with H2 receptor antagonists like ranitidine and prokinetics like metoclopramide as premedication.

Recent studies have shown the presence of obstructive sleep apnoea (OSA) in diabetic patients with autonomic neuropathy.[7] Impaired vagal input to inspiratory phasic dilator muscles has been suggested as the mechanism for the sleep apnoea.[6,7]

Assessment of ANS

Methods for the evaluation of cardiovascular autonomic reflexes were described by Ewing and Clarke.[8] These methods were

Table 3 Mechanisms of nerve damage in diabetic autonomic neuropathy[4]

Vascular endothelial damage
Caused by increased oxygen free radicals and intracellular hyperglycaemia
Degeneration of nerve fibres due to hyperglycaemia
Hyperglycaemia causes destruction of nerve growth factors
Autoimmune-mediated nerve damage
Occurs due to changes in the immune system due to the disease process

Table 4 Causes of autonomic neuropathy

Inherited
Amyloidosis
Porphyria
Fabry disease
Hereditary sensory autonomic neuropathy
Acquired
Diabetes mellitus
Uraemic neuropathy, chronic liver diseases
Nutritional deficiency: vitamin B12
Toxic/drug induced: alcohol, amiadarone, chemotherapeutic agents
Infections: human immunodeficiency virus, leprosy, botulism, diphtheria, Lyme disease, Chagas disease, tetanus
Autoimmune: Guillain–Barré, Sjogren, rheumatoid arthritis, systemic lupus erythematosis, Lambert–Eaton myasthenic syndrome
Neoplasia: paraneoplastic syndromes, brain tumours

described by them for the assessment of diabetic autonomic neuropathy. The simplicity and effectiveness of these methods have led to its use in the evaluation of patients with non-diabetic causes of autonomic dysfunction as well (Table 6).[3]

Power spectral analysis

New methods using analysis of biomedical signal variability to assess autonomic function have been developed and are gaining popularity. Heart rate (R–R interval) or arterial pressure variability is analysed using power spectral analysis.[6] Power spectral analysis consists of breaking down variability into its component sinusoidal waves by means of fast Fourier transformation. Information derived from applying Fourier transformation on biomedical signal variability is indirectly used to assess ANS activity.[6]

Intraoperative considerations

Monitoring should be consistent with the standards of the Association of Anaesthetists of Great Britain and Ireland. Additional monitoring would depend on the cause of autonomic neuropathy, comorbidities present, and the nature of surgery.

Induction and intubation responses

During induction of anaesthesia and intubation of the trachea, increased cardiovascular instability and abnormal cardiovascular responses have been described with diabetic autonomic neuropathy.[9]

Table 5 Clinical features of autonomic neuropathy

Cardiovascular
Postural hypotension
Resting tachycardia
Fixed heart rate
Gastrointestinal
Dysphagia (oesophageal atony)
Gastroparesis causing nausea and vomiting, abdominal fullness
Constipation
Nocturnal diarrhoea
Genitourinary
Atonic bladder causing urinary incontinence, recurrent infection, urgency, retention
Sexual
Erectile dysfunction, retrograde ejaculation
Sudomotor
Anhidrosis
Gustatory sweating
Nocturnal sweats
Vasomotor
Dependent oedema due to loss of vasomotor tone and increased vascular permeability
Cold feet due to loss of skin vasomotor responses
Pupillary
Decreased pupil size
Absent or delayed light reflexes

The pressor response to tracheal intubation and extubation is reduced with less tachycardia and hypertension when compared with patients with no autonomic neuropathy.[3,4] The defective cardiac autonomic fibres lead to loss of compensatory mechanisms like increasing heart rate and vasoconstriction. The decrease in arterial pressure and heart rate is more significant and exaggerated in these patients due to these reasons and hence an increased need for vasopressor support post-induction of anaesthesia.[4]

Although the risk of hypotension appears to be significantly higher with induction agents like thiopental and propofol, there is no evidence available to suggest any one single induction agent is superior in this patient group.

Intraoperative cardiovascular instability

Significant hypotension may develop in patients with orthostatic hypotension in response to changes in position. Volatile anaesthetic agents can cause exaggerated hypotension because of the loss of compensatory mechanisms. The institution of positive pressure ventilation may profoundly decrease cardiac output and worsen the hypotension. There is evidence to suggest an increased requirement of intraoperative vasopressor support in these patients.[3,4]

Close monitoring is vital due to the possibility of these significant cardiac complications. Invasive arterial and central venous pressure monitoring is hence advisable in these patients. Detection and rapid treatment of silent ischaemia and myocardial infarction may be assisted through CM5 lead ECG configuration.

Other important factors

There is an association between cardiovascular autonomic neuropathy and severe intraoperative hypothermia.[10] Temperature should be monitored and normothermia maintained with the use of warming devices. Maintenance of anaesthesia may be

Table 6 Non-invasive tests for assessing the ANS[3,6,8]

	Normal	Borderline	Abnormal
Tests reflecting parasympathetic function			
Heart rate response to valsalva manoeuvre (valsalva ratio)	>1.21	1.11–1.20	<1.10
The valsalva ratio is the ratio of the longest R–R interval (slowest heart rate) to the shortest R–R interval (fastest heart rate)			
Heart rate (R–R interval) variation during deep breathing (max–min heart rate)	>15 beats min^{-1}	11–14 beats min^{-1}	<10 beats min^{-1}
The subject takes six deep breaths in 1 min and heart rate is recorded. The maximum and minimum heart rate during each cycle is measured. The mean difference (maximum heart rate–minimum heart rate) is the average of the differences in the heart rates for all six breaths			
Immediate heart rate response to standing (30:15 ratio)	>1.04	1.01–1.03	<1.00
The 30:15 ratio is the ratio of the longest R–R interval (around 30th beat) to the shortest R–R interval (around 15th beat)			
Tests reflecting sympathetic function			
Arterial pressure response to standing (decrease in systolic arterial pressure)	<10 mm Hg	11–29 mm Hg	>30 mm Hg
Postural decrease in arterial pressure is the difference between the systolic arterial pressure in the supine and systolic arterial pressure in the standing position			
Arterial pressure response to sustained handgrip (increase in diastolic arterial pressure)	>16 mm Hg	11–15 mm Hg	<10 mm Hg
Subject maintains handgrip of 30% of the maximum handgrip for up to 5 min or for as long as possible. The mean of the three diastolic readings before the testing is subtracted from the highest diastolic pressure during the handgrip			

complicated by the absence of autonomic 'signs' of depth of anaesthesia. Monitors of depth of anaesthesia provide dual advantage of reducing risk of awareness and excessive anaesthetic depth.

Central neuraxial block

Significant hypotension may be seen while establishing central neuraxial block due to sympathetic block in the presence of autonomic neuropathy. Central neuraxial anaesthesia may carry greater risks as profound hypotension may have deleterious consequences if they are associated with coronary artery, cerebrovascular, or renovascular disease.

Postoperative

Supplemental oxygen should be provided as these patients may have chronic silent ischaemia and are also prone to myocardial infarction without symptoms. If symptoms of OSA are present, they might need high dependency unit (HDU) care for the provision of non-invasive ventilation. If the patient is considered haemodynamically unstable, admission to intensive care or HDU should be arranged and invasive haemodynamic monitoring continued. Emerging issues from anaesthesia (e.g. pain, bleeding) should be identified and managed effectively to reduce the likelihood of increased cardiovascular instability and abnormal cardiovascular responses.

ANS dysfunction relevant to critical care

Autonomic changes in spinal cord injury

Spinal shock describes the initial phase of neurological dysfunction, consisting of loss of reflexes and autonomic control below the level of spinal cord injury. 'Spinal shock is a neurological, not a cardiovascular condition'.[11] This leads to flaccid paralysis, areflexia, and associated loss of sensory and motor activity below the injury.

Injury to the spinal cord at or above T6 results in significant loss of sympathetic tone and if it is above T4, cardiac sympathetic supply is also lost. This causes hypotension due to vasodilatation and bradycardia, both resulting due to loss of sympathetic outflow. This is called neurogenic shock. 'Neurogenic shock=hypotension+bradycardia+peripheral vasodilatation'.[11]

Initial management of the patient with spinal cord injury should involve the same principles as is used for the management of trauma patients. Bradycardia can be treated with anticholinergics like atropine and glycopyrrolate. Care must be exercised when suctioning trachea as unopposed vagal activity may cause profound bradycardia. Treatment of hypotension includes fluid resuscitation and may require vasopressor administration. Catecholamine surge due to the initial injury must be borne in mind during fluid resuscitation as there is the risk of pulmonary oedema. Invasive haemodynamic monitoring should be established to guide the management of neurogenic shock.

Autonomic hyperreflexia

Supraspinal feedback and inhibition of many autonomic reflexes are lost after spinal cord injury. Small stimuli below the level of injury can cause exaggerated, disordered autonomic response. This phenomenon is usually seen between 3 weeks and 9 months of the initial injury and is a significant risk with lesions above the T6 level. The stimulation is usually bladder or bowel distension but can be cutaneous stimulation or pain from surgery. The response causes severe hypertension, with risk of seizures and brain haemorrhage. Severe reflex bradycardia may develop. Treatment consists of preventing or removing the stimulus and using short-acting anti-hypertensive drugs to decrease arterial pressure.

Guillian–Barré syndrome

Autonomic dysfunction involving both sympathetic and parasympathetic systems is seen in Guillian–Barré syndrome. Sinus tachycardia is the most common manifestation. Orthostatic and persistent hypotension, paroxysmal hypertension, fluctuations in heart rate, paralytic ileus, urinary retention, and abnormalities of sweating are commonly present.[6]

Tetanus

Basal sympathetic activity is higher and episodic sympathetic hyper responsiveness is seen in tetanus. Features of autonomic dysfunction present in tetanus are hypertension, tachycardia, arrhythmias, sweating, and fever. Epinephrine and norepinephrine levels are very high during episodes of autonomic hyperactivity. Combination of α and β adrenergic blockers are used during sympathetic crisis. Unopposed β-block can precipitate acute congestive cardiac failure and hence avoided. Sedatives in the form of benzodiazepines and morphine are also used to decrease catecholamine output. Magnesium sulphate is used in severe tetanus as an adjunct to sedation and adrenergic block.[6]

HIV infection

Autonomic dysfunction is a common occurrence in HIV infection. Awareness of this complication of HIV infection is important to decrease the morbidity and mortality in this patient group.[3]

Porphyria

Sympathetic hyperactivity is a feature of autonomic dysfunction in porphyria. Hypertension, tachycardia, abdominal pain, and altered bowel movements are some of the features present during the crisis.[6]

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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