The Cardiovascular Autonomic Nervous System and Anaesthesia

W Pearce
MBBCh (Witwatersrand) MMed (Anaesth) (Pretoria) FCA (CMSA)
Department of Anaesthesiology, Pretoria Academic Hospital and the , University of Pretoria

Once awareness, our seat of deliberate action and movement, is temporarily extinguished by sleep or a loss of consciousness, we rely on a primordial, indispensable, and autonomous ("vegetative") system that continues to sustain and control our vital organ systems. This vegetative system is never allowed to rest. The Cambridge physiologist J N Langley referred to it as the autonomic nervous system in a paper on the superior cervical ganglion in 1898.[1] The term and concept did not receive immediate and overwhelming acceptance, but what they refer to has since been revealed as something astonishingly complex and nuanced in both its central organization, and its peripheral responses to external stimuli.

Anaesthesia has as its sine qua non the reversible abolition of a patient's so-called "nocifensive" movement response to potential, or inflicted, tissue damage.[2] This abolition, as well as the subsequent surgery it allows, is always accompanied by a degree of physiological stress that leaves the patient's autonomic nervous system neither unprovoked nor untouched. Successful anaesthesia paradoxically both perturbs and relies on the integrity of the autonomic nervous system. Anaesthesia is autonomic medicine. The greater part of our training and practice is spent acquiring skills in averting or utilizing the autonomic nervous system effects of anaesthetic drugs or surgical procedures under a variety of pathophysiological conditions. Moreover, many of these pathophysiological conditions may be associated with impaired preoperative autonomic function. Therefore, almost every aspect of clinical anaesthesia can be discussed with some reference to the autonomic nervous system.

Considerations of space preclude an exhaustive, systematic treatment of the autonomic nervous system in anaesthesia. The approach here is, firstly, to assume that the reader has a fundamental grasp of the physiology and anatomy of the cardiovascular autonomic nervous system as they relate to anaesthesia. Secondly, the extrasynaptic non-innervated hormonal receptors that mediate part of the autonomic response and that are relied on whenever inotropes are administered, are not strictly part of the autonomic nervous system and will not be elaborated on. Similarly, a description of the comparative autonomic pharmacology of the anaesthetic agents belong more appropriately in a separate monograph.

Autonomic dysfunction can manifest in protean ways, and involve many organ systems, that are decisively relevant to anaesthesia. Lists, for example, of the relevant autonomic manifestations of diabetic autonomic neuropathies (Table I), of those in multiple system atrophy (MSA – formerly known as Shy-Drager syndrome) (Table II), and in Parkinson's disease (Table III) serve to illustrate this. This discussion will consider the assessment of the autonomic nervous system and outline the principal aspects of the importance of autonomic dysfunction for the anaesthetist under aspects of perioperative circulatory stability.

Correspondence:
Dr W Pearce
aether@icon.co.za

ASSESSING THE AUTONOMIC NERVOUS SYSTEM

A large battery of tests for autonomic function exists. No single test can provide a global assessment of autonomic function. Even if directed towards a single system, testing often involves a variety of procedures. The autonomic nervous system innervates every organ

TABLE I: Manifestations of diabetic autonomic neuropathies

Cardiovascular
Orthostatic intolerance
Resting tachycardia
Cardiac dysrhythmias
Prolongation of the QT interval
Impaired heart rate and blood pressure circadian rhythm
Painless myocardial ischaemia or infarction
Reduced distal vasoconstrictor tone
Exacerbation of cardiac failure
Gastrointestinal
Oesophageal motor incoordination
Reflux and heartburn
Gastric dysrhythmia, hypomotility (diabetic gastroparesis)
Respiratory
Sleep apnoea
Reduced hypoxic drive
Sudomotor
Deranged sweating (diminished, excessive or gustatory)
Neuroendocrine
Impaired glucose counterregulation
Reduced noradrenaline release
Reduced motilin release

TABLE II: Autonomic Signs/Symptoms in MSA.

Cardiovascular
Postural hypotension
Postprandial hypotension
Exercise-induced hypotension
Alcohol-induced hypotension
Supine hypertension
Sleep
REM behavioural sleep disorder (RBD)
"sleep talking"
sleep apnoea
laryngeal stridor
Sudomotor
Global (>80%) anhidrosis
Segmental anhidrosis
Hyperthermia
Heat intolerance

TABLE III: Autonomic Symptoms in Parkinson's Disease

Gastrointestinal
Oesophageal hypomobility
Delayed gastric emptying
Sialorrhoea
Dysphagia

Thermoregulatory failure
Hyperthermia
Akinetic crisis
Levodopa withdrawal symptoms
Hyperhidrosis

Cardiovascular
Postural hypotension
Postprandial hypotension
Supine hypertension

Neuromuscular
Weight loss

Pain
"off" period related
Neuralgic pain
Deep visceral ache

and in the generalized autonomic disorders there may be impaired function of virtually every organ in the body. A number of methods of assessment and analysis obtain in discussions and research on perioperative autonomic function. They often pertain to cardiovascular autonomic function. Of these, anaesthetists should be familiar with some aspects of autonomic reflex testing and the analysis of biomedical signal variability. Usually, however, it suffices to enquire about symptoms, especially those of orthostatic intolerance, and establish on preoperative assessment whether simple indicators of globally abnormal cardiovascular autonomic function are present (Table IV).[3]

Results obtained from investigation of autonomic dysfunction need to be interpreted in conjunction with the clinical state and confounding variables that relate not only to the autonomic nervous system but also to organs it supplies, as the majority of tests are dependent on target organ function. As a pertinent example, consider cardiovascular reflex tests. These measure the end-organ response to the activation of a neural reflex arc. Since the end-organ response to a stimulus depends on the integrity of all parts of the reflex arc, from stimulus to the end-organ, an abnormal response may result in any step of the reflex arc. Therefore, adequacy of the stimulus is very important. The patient's collaboration, instruction, and familiarization with tests are necessary to achieve a standardized stimulus, especially for the Valsalva manoeuvre and deep breathing test. Respiratory function can interfere with stimulus standardization. The greatest source of poor repeatability in tests based on heart rate is variation in respiration. Other factors exert their influence affecting end-organ function, such as cardiovascular disease or volume status (more important for the lying-to-standing test).[4,5]

TABLE IV: Practical Indicators of Abnormal Cardiovascular Autonomic Function

Resting heart rate > 90 beats/minute

Abnormal heart rate variability (failure to change heart rate, R-R interval by more than 10 beats/min by one minute of slow, deep breaths)

Inability to attain 85% of predicted maximal heart rate on treadmill testing

Abnormal heart rate recovery (inability to decrease heart rate by more than 12 beats/min in the first minute after peak exercise)

Autonomic Reflex Testing

An example of autonomic reflex testing is a battery of tests used to detect cardiovascular autonomic neuropathy in diabetes. The best known is the now almost classical Ewing battery of five tests of short-term cardiovascular reflex control[6,7,8] – it is still widely loved by some of our examiners in anaesthesia today, but requires some pertinent physiological footnotes (Table V). The first four tests listed are the most widely used, validated, and best known in their physiological bases. Therefore, they are always encountered in some form in any research article on diabetic autonomic neuropathy under the rubric of its methodology. A recent example: "The following tests were done to detect diabetic autonomic neuropathy: Valsalva maneuver, HR response to deep breathing, immediate HR response to standing, BP response to standing, and BP response to sustained handgrip. The heart rate tests reflect cardiac parasympathetic nerve damage. The BP tests reflect cardiac sympathetic nerve damage."[9] But this approach may hide an incorrect assumption. In fact, tests based on cardiovascular reflexes generally involve both parasympathetic and sympathetic pathways, although to different degrees, and, therefore, it is an oversimplification to consider them as "pure" vagal or sympathetic tests.[10]

With the Ewing battery outcomes of various tests were scored and points were awarded per score; all scores are added to find a final autonomic label, namely, normal, borderline, or pathological. The Ewing battery was designed for the early detection of subtle autonomic dysfunction. It has been suggested to be important for

TABLE V: The Ewing Battery

Heart rate response to the Valsalva manoeuvre
Heart rate response to standing up (30:15 ratio)
Heart rate response to deep breathing (maximum-minimum heart rate
Blood pressure response to standing up (postural BP change)
Blood pressure response to sustained handgrip.

Valsalva manoeuvre. The subject sits quietly and then blows into a mouthpiece at a pressure of 40 mmHg for 15 seconds. An immediate heart rate decrease during the rise in systolic and diastolic blood pressure at the onset of straining is observed. The heart rate then normally increases during and directly after the manoeuvre (withdrawal of vagal tone and increased sympathetic outflow to the sinus node due to the fall in blood pressure), followed by a rebound bradycardia (vagal reflex dependent on a blood pressure overshoot relative to control blood pressure) after release. The ratio of the longest R-R interval shortly after the manoeuvre to the shortest R-R interval during the manoeuvre is then measured. *Currently considered by most autonomic laboratories to provide mainly confirmatory information.*

Heart rate to standing up. The subject lies quietly on a couch and then stands up unaided. Normally an immediate increase in heart rate occurs that is maximal at about the 15th beat after starting to stand, followed by a relative bradycardia, maximal around the 30th beat. This can be quantified as the 30:15 ratio, which is the ratio of the longest R-R interval around the 30th beat to the shortest R-R interval around the 15th beat.

Heart rate response to deep breathing. The subject sits quietly and then breathes deeply and evenly at 6 breaths/min. The maximum and minimum heart rates during each breathing cycle are measured, and the mean difference during three successive breathing cycles is taken to give the maximum-minimum heart rate. *Today considered by many to be the sensitive measure to assess vagal heart control. The combination of abnormally low test scores for this manoeuvre and for the change in heart rate (measured from its baseline) upon standing is eminently suited to identify definite cardiac vagal neuropathy.*[14]

Postural blood pressure change. Orthostatic hypotension is defined as a reduction of systolic blood pressure of at least 20 mm Hg or of diastolic blood pressure of at least 10mmHg within three minutes of standing. It may or may not be symptomatic and represents a physical sign, not a disease. Typically, both systolic and diastolic blood pressure fall without a corresponding reflex increase in heart rate. A modest fall of systolic blood pressure without any fall in diastolic pressure usually signifies a non-neurogenic disturbance such as central hypovolaemia.

risk stratification and subsequent management in patients with cardiovascular disease. But since there is neither efficacious treatment for autonomic dysfunction (despite recent encouraging evidence of reversibility of early diabetic cardiovascular autonomic neuropathy or gastroparesis with tight glycaemic control), nor for the associated increase in sudden death, screening for impairment of short-term cardiovascular control is generally not routinely indicated. Further, cardiovascular reflex testing is more difficult to interpret than, for example, nerve conduction studies since both autonomic nerve function and cardiovascular haemodynamics are involved. Moreover, age, medication and unstable clinical conditions can influence test scores greatly.[11,12]

What then is the role of cardiovascular reflex testing in the preoperative evaluation of the patient with possible autonomic dysfunction? Does abnormal reflex testing predict anything in the perioperative period? Not much beside that for which every anaesthetist should be vigilant in all patients with pathophysiological conditions where autonomic dysfunction may be considerable. Other considerations may derive from the clinical setting of the patient's symptoms. A patient with preoperative cardiovascular autonomic reflex impairment is vulnerable to periods of hypotension during general anaesthesia that may require vasoactive drugs, but reflex testing cannot identify those that will develop perioperative arrhythmias. Pronouncing on the implications of demonstrable autonomic neuropathy for perioperative outcome should probably draw heavily from the insights of an analysis of the Pittsburgh Epidemiology of Diabetes Complications Study. Here, even though the presence of autonomic neuropathy in these patients was associated with a higher mortality, this is largely explained by associated complications (e.g. nephropathy) and increased cardiovascular risk factors (e.g., hypertension).[13] These findings suggested that the increased mortality is related to vascular complications, which may itself underlie the autonomic neuropathy.

Power Spectral Analysis[14,15,16,17,18]

Unlike autonomic reflex testing, the analysis of cardiovascular signal variability has been shown to discriminate between patients that are prone to develop perioperative (sometimes life-threatening) neurocardiogenic syncope (the "Bezold-Jarisch" reflex), and those that are not.[19] This analysis of biomedical signal variability has established itself firmly as a method of characterizing aspects of perioperative autonomic function. A recent study[20] on the effect of the preoperative administration of the a_2–agonist, clonidine, on the intraoperative autonomic balance of a particular patient population with autonomic dysfunction (hypertensives), not only elicited a thought-provoking editorial entitled, "Is gaining control of the autonomic nervous system important to our specialty?",[21] but also illustrates the particular elegance of this computer-oriented method of analysis even when it is not fully exploited.

The analysis is either that of heart rate (R-R interval) or of blood pressure variability. The most common method is known as power spectral analysis. The power spectral analysis of heart rate variability has been used in studying not only the epidemiological aspects of autonomic balance in heart disease, but also in exploring aspects of autonomic balance in diabetic autonomic neuropathy and after the administration of neuraxial anaesthesia.

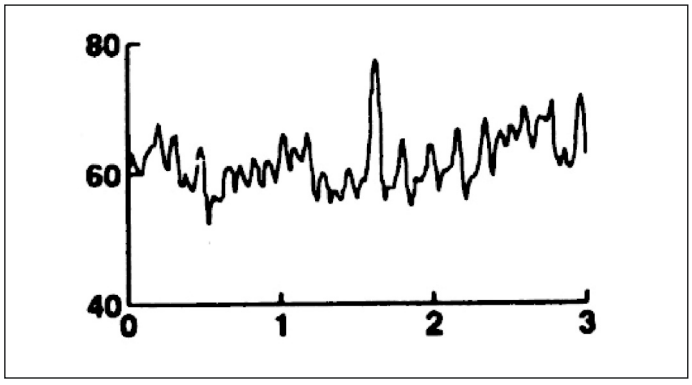
A short and simple primer of power spectral analysis aids in the understanding of much of the anaesthetic literature where analysis of signal variability features.

When heart rate variability is plotted as a time series (the heart rate – here in beats per minute - on the y-axis and time – in minutes - on the x-axis), a fluctuating, seemingly random, waveform results.

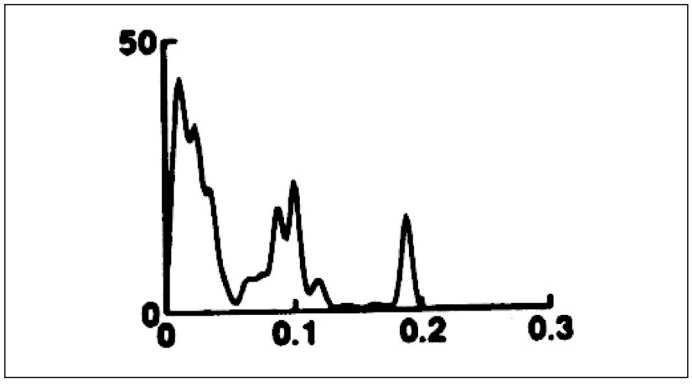
This time series waveform can, by means of Fourier analysis, be broken down into component sinusoidal waves (a series of sinus waves, the dominant and its harmonics, that, when superimposed will yield a wave identical, or very similar, to the time series wave). These component waves have different amplitudes and frequencies. When the power of these waves (in its simplest interpretation, the square of the amplitudes of the component waves) is plotted against frequency, i.e., when a plot is drawn in order to determine how the different waveforms' amplitudes are distributed across the frequency spectrum, three "peaks" result (= frequency domain analysis). The figure below shows these three peaks clearly. The y-axis represents power (square of the amplitude) and the x-axis, frequency (in Herz).

These three peaks possess distinct physiological correlates.[22,23]

A peak in the very low frequency band (below 0.03 Hz) is due to thermoregulatory or renin-angiotensin influences or both. The low frequency component (0,04 – 0.15 Hz) is jointly mediated by sympathetic and parasympathetic activity, it reflects baroreceptor activity and corresponds to "Mayer" waves. The high frequency component (0.14 –4.0 Hz) is solely affected by parasympathetic activity and coincides with respiratory rate. The concept of autonomic balance recognizes both reciprocal and non-reciprocal parasympathetic and sympathetic influences on heart rate, with an additional measure, the low frequency to high frequency (LF/HF) ratio. Augmentation of the ratio indicates the predominance of sympathetic activity,



and the reduction of it, predominance of parasympathetic activity. It has been shown that the sympathetic nervous system has the nature of a low-pass filter and has a slow response time, and the parasympathetic nervous system has the nature of a broad-band filter, with a relatively rapid response time. This may explain the finding that suppression of the parasympathetic activity decreases both the low frequency component and the high frequency component, and that of sympathetic activity decreases only the low frequency component.



Power spectral analysis is, a useful epidemiological tool for the detection of autonomic imbalance in autonomic dysfunction (e.g., it could demonstrate an established sympathetic predominance after repeated episodes of hypoxaemia in those with obstructive sleep apnoea[24]), as well as for research on the perioperative effects of autonomic drugs.[25]

This type of analysis is only valid during steady state periods, so it is required to use stable signals (i.e. changes of the mean value <10% or of the standard deviation <30%).

To overcome the problems of characterizing "non-stationary" phenomena (such as the Valsalva manoeuvre, irregular breathing or in general signals continuously changing with time) in the frequency domain, a time-varying spectral algorithm, the Wigner-Ville transform, has been introduced in the analysis of cardiovascular signals. This method is able to provide instantaneous characterization of the frequency components in each signal.[26]

Studies in autonomic failure suggest that these methods, apart from their tremendous value in research, may be complementary to, and sometimes even more sensitive and specific than, traditional laboratory tests.[27] However, the clinical impact of these methods in the diagnostic, monitoring, and prognostic evaluation of patients with autonomic dysfunction needs to be tested in longitudinal controlled studies.

Imaging Myocardial Sympathetic Innervation

A modality of assessing of the autonomic nervous system that deserves mention is imaging of the myocardial sympathetic innervation by means of I^{123}-meta-iodobenzylguanidine (MIBG) scintigraphy. Reduced myocardial MIBG accumulation is seen in diabetic autonomic neuropathy. Irregular regional sympathetic innervation or denervation of the left ventricle is thought to cause a prolongation of the QT interval, and to result in systolic and diastolic dysfunction especially at the posterior myocardium leading to arrhythmias.[28]

PERIOPERATIVE CIRCULATORY STABILITY

Many anaesthetists regard the importance of autonomic dysfunction to revolve around sympathetic dysfunction. Some common disease states are associated with sympathetic dysfunction (Table VI)[29] and these must be taken into consideration when planning for the administration of general anaesthesia. But dramatic manifestations of altered autonomic function in the perioperative period are sometimes brought about by the disruption of sympathetic function by the anaesthetist. A reversible sympathetic denervation follows the administration of neuraxial anaesthesia. The level of sympathetic denervation determines the consequent degree of alteration of normal physiology, and the anaesthetist must be vigilant for "danger signs" indicative of serious autonomic disruption, not least the pernicious but rare accompaniment of neurocardiogenic syncope.[19]

TABLE VI : Pathological States Associated with Sympathetic Dysfunction

Sympathetic Hyporesponsiveness	Sympathetic Hyperresponsiveness
Diabetes	Guillian-Barré
Hypertension	Spinal cord injury¶
Sleep apnoea	Tetanus
Heart failure*	Acute drug withdrawal
Chronic renal failure*	Complex regional pain syndrome II
Spinal cord injury	(previously reflex sympathetic dystrophy)
Chronic alcoholism	
Multiple system atrophy (previously Shy-Drager Syndrome)	
Pure Autonomic Failure (previously idiopathic orthostatic hypotension	
Familial dysautonomia (previously Riley DaySyndrome)	

***** Basal levels of sympathetic traffic are elevated but reflex control is impaired
¶ During somatic or visceral stimulation below the level of transection.

Each of these states will have some impact on blood

Sympathetic Hyporesponsiveness

Diabetic Autonomic Neuropathy

With diabetic autonomic failure, a number of additional considerations to those that are mentioned under the assessment of the autonomic nervous system pertain. The causes of an increase in mortality in diabetics attributed to cardiovascular autonomic neuropathy are not without relevance to perioperative management (Table VII).[30] Both somatic and autonomic diabetic neuropathy influence the clinical manifestations and prognosis of cardiovascular disease in diabetics. The loss of afferent nerve fibres in ischaemic areas of the heart is thought to be responsible for the "defective anginal warning system" in individuals with myocardial ischaemia and diabetic autonomic neuropathy. Not only can acute myocardial infarction occur without symptoms, but chronic silent ischaemia is also common. The severity of heart failure in diabetic patients appears to correlate with degree of cardiovascular autonomic impairment.[31]

Resting tachycardia is frequently observed in diabetic patients. It is similar to the tachycardia of the transplanted heart in that the heart rate response to breathing, changes of posture, Valsalva manoeuvre, or carotid sinus pressure is either non-existent or minimal. It is the result of early parasympathetic neuropathy. With the extension of denervation to the sympathetic nervous system, the heart rate becomes fixed or myocardial electrical instability results. Heterogeneity in sympathetic innervation has recently been shown, with reduced innervation in the left ventricle but proximal myocardial sympathetic hyperinnervation. It may be associated with malignant ventricular arrhythmias and sudden cardiac death. Approximately one-third of deaths in diabetics with symptomatic cardiovascular autonomic impairment are sudden and unexpected. Some investigators have suggested cardiac denervation supersensitivity as a cause. Other suggested explanations for sudden death in diabetic autonomic neuropathy include cardiac arrhythmias, QT interval abnormalities, silent infarction, sleep apnoea, and an abnormal ventilatory response to hypoxia, particularly in association with lung infection, surgery and anaesthesia.[31]

Apart from an expected sympathetic hyporesponsiveness manifested by a reduced distal vasoconstrictor tone, diabetics also manifest localized sympathetic cardiac hyperinnervation, or a sympathovagal imbalance, that leads to a vulnerability to arrhythmias. Prolongation of the QT interval is thought to be the result of an imbalance between right and left sympathetic innervation (underactivity of the right stellate ganglion and overactivity of the left stellate ganglion) leading to ventricular arrhythmias. Several studies have identified a relationship between the degree of autonomic neuropathy and QT interval prolongation (or dispersion) in diabetic patients. This effect is further exacerbated by exercise. Despite these interesting observations, a clear cause and effect relationship be-

TABLE VII: Causes of Increased Mortality Attributed to Diabetic Cardiovascular Autonomic Neuropathy

Asymptomatic Cardiac Ischaemia
Respiratory Arrest
Prolongation of QT interval
Abnormalities in sympathetic-vagal and blood pressure circadian rhythm
Denervation supersensititivy causing increased blood pressure

tween QT interval prolongation or dispersion and sudden death in diabetic autonomic neuropathy has not yet been established.[32]

Sympathetic hyporesponsiveness can manifest as orthostatic hypotension. It is symptomatic in diabetics when the fall in systolic pressure on standing is greater than 50mmHg. The contributing factors to the development of orthostatic hypotension in diabetics include reduced total splanchnic and cutaneous vascular resistance, as well as diminished heart rate and cardiac output. Of these, the failure of the splanchnic vascular bed to constrict is considered the most important. Such failure may be exacerbated by the vasodilating effect of insulin.

Recent studies have shown that one in four diabetic patients with autonomic neuropathy suffers from obstructive sleep apnoea. It has its own constellation of perioperative considerations. These patients also demonstrate a reduction in hypoxic drive. Impaired vagal input to inspiratory phasic dilator muscles has been suggested as the mechanism for the sleep apnoea.[33]

In some diabetic patients with autonomic neuropathy and hypoglycaemia, awareness of hypoglycaemia may be absent or blunted, and impaired congnition may the first sign of a drop in blood glucose level. Hypoglycaemia may itself lead to a reduced adrenaline, noradrenaline, growth hormone, and cortisol response to a second episode of hypoglycaemia 24 h after a first episode. This has been termed "hypoglycaemia associated autonomic failure"[34]

Familial Dysautonomia

Some instances of peripheral autonomic dysfunction generally tend to be mild (e.g., the autonomic dysfunction that accompanies uraemia or human immunodeficiency virus infection). However, a particular rare condition, familial dysautonomia, originally termed the Riley-Day syndrome, manifests with extensive central and peripheral autonomic perturbations.[35,36] Diagnosis in this disorder is based on ascertaining the presence of five "cardinal" criteria, i.e., the absence of overflow emotional tears, absent lingual fungiform papillae, depressed patellar reflexes, lack of an axon flare following intradermal histamine, and documentation of Ashkenazi Jewish extraction. Further supportive evidence is provided by findings of a decreased response to pain and temperature, orthostatic hypotension, periodical erythematous blotching of the skin, and increased sweating. In addition, cine-oesophagrams may reveal delay in cricopharyngeal closure, tertiary contractions of the oesophagus, gastro-oesophageal reflux, and delayed gastric emptying.

In familial dysautonomia there can be extreme variability in clinical expression. Clinical features include diminished pain sensation, unexplained fevers, recumbent hypertension, and postural hypotension. Patients have oropharyngeal incoordination and abnormal gastroesophageal motility, causing feeding difficulties, vomiting, and recurrent aspiration pneumonia, which in turn lead to chronic lung disease. Developmental milestones and maturation are delayed, and there is an increased prevalence of convulsions, especially at an older age. Musculoskeletal problems are related to gait disorders, foot deformities, arthropathies, fractures, and spinal deformities (scoliosis, kyphosis, and kyphoscoliosis). The spinal deformities are severe and these patients often need surgical correction of these abnormalities. At presentation for surgery the restrictive lung disease caused by the spinal deformity is superimposed on an obstructive component produced by chronic aspiration.

Common causes of early death in familial dysautonomia in one series of 136 patients[35] included acute aspiration and chronic pneumonia, sudden unexplained death during sleep, and surgical complications. The clinical features, most with anaesthetic implications, are listed in Table VIII.[35] General anaesthesia has the potential for inducing severe hypotension. With greater attention to stabilization of the vascular bed by hydrating the patient before surgery and titrating the anaesthetic to continuously monitored arterial blood pressure (both simple but essential principles of managemenet of any patient with autonomic dysfunction manifesting sympathetic hyporesponsiveness), anaesthetic risk has been greatly reduced. Prolongation of QT_c may be ominous. Inappropriate persistence of parasympathetic cardial activity under conditions of physiological stress may require attention from the anaesthetist intraoperatively.

Spinal Shock

Spinal shock, [37] another condition associated with sympathetic hyporesponsiveness, occurs only with physiological or anatomical transection or near transection. There is an inter-species difference in autonomic disturbance after spinal cord injury with human beings manifesting the most profound spinal shock. In general, the more severe the transection of the spinal cord, the more profound the state of spinal shock. During the acute stage of spinal cord injury the isolated spinal segment closest to the injury is the most severely affected. Spinal segments distal to transection may become depressed later. There is a well-documented upward spread of reflex depression after spinal cord injury (the Schiff-Sherrington phenomenon) in which there is transient loss of upper thoracic spinal cord reflexes.

Clinically, spinal cord lesions between C-1 and T-6 spinal segments can result in loss of sympathetic tone, hypotension, hypothermia, and bradycardia from unopposed vagal function. Spinal shock is usually characterized by mild hypotension, a mean arterial pressure of 70-75 mm Hg, and heart rate < 70 beats/min. This is not due to hypovolaemia since central venous pressures are high. The cardiac index is usually 50-100% above normal and is associated with a decrease in systemic vascular resistance index resembling the

TABLE VIII: CLINICAL FEATURES OF FAMILIAL DYSAUTONOMIA

Common symptoms	Frequency (%)
Ocular	
Decreased tears	> 60
Corneal analgesia	> 60
Gastrointestinal function	
Dysphagia	> 60
Oesophageal and gastric dysmotility	> 60
Gastroesophageal reflux	67
Vomiting crises	40
Pulmonary	
Aspirations	NA
Insensitivity to hypoxia and hypercarbia	NA
Restrictive lung disease	NA
Orthopaedic	
Spinal deformities	90
Aseptic necrosis	15
Vasomotor	
Postural hypotension	100
Blotching	99
Excessive sweating	99
Hypertensive crises	>60
Neurological	
Decreased deep tendon reflexes	95
Dysarthria	NA
Decreased pain and temperature sensation	NA
Decreased vibration sense (after 13 years)	NA
Progressive ataxia (in adult years)	NA
Less than average IQ	38

(NA = not established)

haemodynamic picture of septic shock. The dysfunctional sympathetic system of spinal shock patients is not able to shift volume from the musculoskeletal compartment to the renal-splanchnic compartment through peripheral vasoconstriction. As a result, renal perfusion is usually impaired despite nearly normal arterial, central venous, and capillary wedge pressures. Once the diagnosis of spinal shock is established it should be treated vigorously and aggressively. Initial treatment requires a negative Trendelenburg positioning, fluid administration, and possible inotropic support, followed by immediate invasive haemodynamic monitoring with a pulmonary artery catheter. The inotrope of choice is dopamine, but in patients with severe hypotension phenylephrine can be used. The goal is to establish adequate cardiac output as determined by oxygen consumption and delivery from oximetric calculation, and a mean arterial blood pressure over 90 mm Hg. These manoeuvres can diminish secondary spinal cord injury.

Bradycardia is reported in most patients and cardiac arrest in 15% of patients with complete cervical spinal cord injury. This is thought to be due to the dissociation of the parasympathetic from sympathetic responses during spinal shock. If bradyarrhythmia is refractory to atropine or b-adrenergic agonists, cardiac pacing may rarely be required.

Autonomic Balance in Neuraxial Anaesthesia

The anaesthetist is sometimes the cause of peripheral autonomic dysfunction. Following the administration of neuraxial block a temporal and craniocaudal segmental sequence of blocked physiological functions results[38]:

- vasoconstrictor, pilomotor and sudomotor responses (sympathetic denervation),
- cutaneous temperature discrimination,
- epicritic pain sensibility, and
- skeletal motor activity.

Of all the effects of neuraxial anaesthesia on the central nervous system, none is more important from a physiological perspective than the denervation of preganglionic sympathetic fibres. In general, the more extensive the degree of sensory anaesthesia, the more extensive the associated sympathectomy. The relationship is not linear for pharmacological and anatomic reasons. The pharmacological reason rests in the long-recognized fact that the effective concentration of local anaesthetic agent varies with the type of nerve to be blocked. Preganglionic sympathetic axons (B fibres) are amongst the most sensitive of the nerves in the subarachnoid or epidural space to the action of local anaesthetics. After the injection of local anaesthetic agents into the subarachnoid space the anaesthetic is diluted by cerebrospinal fluid so that its concentration decreases as the distance from the site of the injection increases

The anatomic reason underlying the differential axial blockade in neuraxial anaesthesia remains elusive, but appears to be related to two principles derived from in vitro study of individual myelinated axons, viz

1. Nerve conduction can leap two consecutive blocked nodes of Ranvier but not three. Differential blockade seems to have nothing to do with the size of nerve fibres in itself, rather on the internodal distance (that varies directly with fibre size). As the internodal length is the greater the thicker the axon, the probability of three successive nodes of Ranvier being bathed quickly by solution is the smaller the longer the internodal distance. Small nerve fibres would need a smaller puddle of local anaesthetic to block more than three consecutive nodes of Ranvier.
2. A fibre length with more than three consecutive nodes bathed by dilute anaesthetic (i.e. below the minimum concentration required to produce complete block) may be blocked by a phenomenon of decremental conduction block. If the local anaesthetic solution covers just a few successive nodes, the impulse may limp along the incompletely blocked segment, then resume at full speed when normally conducting membrane is reached again. If, however, a long string of nodes is partially blocked, the impulse fizzles out gradually until conduction is halted eventually.

Sympathetic block extends beyond the level of analgesia in neuraxial anaesthesia, and even "low" neuraxial anaesthesia may be associated with considerable sympathetic paralysis. The sympathetic block extends beyond the level of analgesia produced by neuraxial anaesthesia (= differential craniocaudal blockade). Neuraxial anaesthesia high enough for upper abdominal surgery will usually involve preganglionic paralysis to the first thoracic level. There will then be a complete sympathetic block. The more the thoracic sympathetic outflow is blocked by neuraxial anaesthesia, the more profound become the physiological alterations produced by the technique. However, sensory levels extending above the second or third thoracic segments are not usually accompanied by progressively greater disturbances.

The structure of the sympathetic nervous system dictates that a diffuse peripheral response results from its preganglionic denervation. The cardiovascular effects are summarized in table IX.[39]

TABLE IX

Mechanism	Effect
"Peripheral" sympathetic block (T10 –L2) Blockade of vasoconstrictor fibres to lower limbs	Arteriolar dilatation. Increased venous capacitance and pooling of blood in lower limbs leading to decreased venous return and a decreased cardiac output.
Reflex increase in vasoconstrictor fibre activity in upper limbs via baroreceptors	Increased vasomotor tone in upper limbs with increased venous return and cardiac output.
Reflex increase in cardioaccelerator nerve activity	Increased heart rate and cardiac output.
Reduced right atrial pressure due to decreased venous return.	Can cause a decrease in heart rate. Marked decrease in right atrial pressure can cause a sudden bradycardia (Bezold-Jarisch reflex).
Adrenal medullary sympathetic block (T6-L1) (Blockade of splanchnic nerves)	Pooling of blood in gut leading to decreased venous return.
Vasoconstrictor fibres to abdominal viscera	Decreased levels of circulating catecholamines leading to decreased heart rate and cardiac output.
Adrenal medullary catecholamine secretion	
"Central" sympathetic block (T1-T4) Blockade of	Decreased heart rate and cardiac output.
Cardiac sympathetic outflow from vasomotor centre and at segmental level	Vasodilatation in upper limbs. Blockade of compensatory lower limb vasoconstriction with epidural anaesthesia if T5-L1 is also blocked.
Vasoconstrictor fibres to head, neck, and arms	"Inappropriate bradycardia"; "sudden bradycardia"; vagal arrest. Also referred to as the Bezold-Jarisch reflex or neurocardiogenic syncope.
Vagal predominance	
Abolition of increase in renin activity in response to arterial hypotension (but activates the vasopressin system in response to hypotension)	

The treatment of the sympathetic denervation relies on correcting for the degree of physiological disruption caused by the neuraxial blockade. An approach to the treatment of hypotension is outlined in Table X.[39]

The Bezold-Jarisch reflex[19] (reflex cardiovascular depression with vasodilation and bradycardia) has a particularly pernicious association with neuraxial anaesthesia. Haemodynamic instability is often associated with the onset of a block, but delayed bradycardia or asystole may be more sinister when initiated by reduced venous return (more likely with a high block and hypovolaemia). Outcomes are usually good but delays in instituting corrective treatment and resuscitation may cause permanent cerebral damage or death. The risk of such life-threatening vasovagal reactions during regional anaesthesia may be in the order of three per 1000, compared with 5% of patients who have both bradycardia and hypotension during spinal anaesthesia. Risk of death is significantly associated with higher age, higher ASA physical status class, later occurrence of cardiac arrest (neuraxial anaesthesia-induced bradycardia or alterations in atrioventricular conduction may, at least partly, outlast sensory or motor blockade), and total hip arthroplasty. Adrenaline must be used early in established cardiac arrest after high regional anaesthesia.

Although the mechanism of lumbar neuraxial anaesthesia-induced bradycardia or asystole is presently unknown, the final pathway is most likely an absolute or relative increase in parasympathetic activity. This would slow conduction through the nodal region of the AV node. Higher degree than first-degree heart block has been described during neuraxial anaesthesia in the presence or absence of pre-existing conduction abnormalities.

Studies of cardiac neurovegetative balance in neuraxial anaesthesia by means of power spectral analysis of heart rate variability supports the notion that the sympathetic and parasympathetic systems modulate each other and that the reduction in "sympathetic outflow" is associated with a reduction in "parasympathetic outflow".[40,41,42] There also seems to be a decrease in the complexity of heart rate dynamics with neuraxial anaesthesia as measured by non-linear analysis of heart rate variability.[43]

Heart rate variability studies indicate that a rearrangement of autonomic tone takes place in normal pregnancy, either as the result of a shift of autonomic balance toward a relative vagal predominance or as the consequence of the attenuation of baroreflexes.[44] In pregnancy, regional anaesthesia combined with inferior vena cava compression introduces significant risk because of interference with cardiovascular control, and the inability of the patient to move herself. Cardiac arrest (either asystole or a non-perfusing bradycardia) in the gravid patient is a special situation that easily admits of fatal errors.[45]

Table X

In "normal" patients *treat* if systolic blood pressure decreases by 30%

In "essential hypertension" *treat* if systolic blood pressure decreases by 20%
However monitor cardiovascular and central nervous system function.

Principles of use of vasopressors

Peripherally acting vasoconstrictors, e.g. a-agonists phenylephrine, methoxamine, not ideal (but not contra-indicated!) because of: increase in afterload, increased left ventricular work, increased left ventricular oxygen consumption, whereas the problem is decreased preload and cardiac output.
The ideal is a pure venoconstrictor (+ mild vasoconstrictor): it would increase preload and cardiac output; no such drug exists

Treatment steps

Use ephedrine: this would increase the preload and thus the cardiac output.
Elevate legs or Trendelenburg, but not more than 20 degrees (more increases internal jugular pressure and decreases cerebral perfusion pressure)
Administer oxygen
Administer IV fluids but:
If normovolaemia ephedrine more effective
IV fluid "preloading" not very effective as prophylaxis against hypotension (but some studies have shown better placental perfusion (demonstrated by colour Doppler) after "preloading")

Multiple System Atrophy

Unfortunate patients with multiple system atrophy (MSA), previously referred to as the Shy-Drager syndrome, present a formidable challenge to the anaeshetist.[46,47,48] It occurs in two forms, MSA-P, in which parkinsonian features predominate, and MSA-C, where cerebellar features are dominant. The disease presents between the fifth and seventh decades of life, is more common in men than women, and does not appear to be an inherited disorder. It is a slowly progressive illness that leads to death, often as a result of post-syncopal cerebral ischaemia.

The prinicipal pathological finding is primary degeneration of the preganglionic lateral horn neurons of the thoracic spinal segments. Later there is a degeneration of the nerve cells in the vagal nuclei and the nuclei of the solitary tract, locus coeruleus, and sacral autonomic nuclei. The cause is unknown. The manifestations are those of autonomic and urinary dysfunction, parkinsonism, cerebellar dysfunction, and corticospinal dysfunction. There is no response to levodopa.

Loss of sympathetic and parasympathetic tone in these patients is profound. The debility caused by hypotension progresses from blurry vision, dizziness on standing, to fainting on walking. Not only do these patients exhibit a failure to compensatory vasoconstriction, but also a minimal heart rate response to postural changes. Blood pressure in normal individuals exhibits a diurnal pattern in which pressure falls during sleep and rises prior to awakening. This pattern is reversed in autonomic failure, especially in those patients suffering from MSA. Recumbent hypertension develops in many patients with autonomic failure due to defective baroreceptor reflexes, supersensitivity of denervated blood vessels to circulating catecholamines, and fluid shifts from the periphery to the central compartment. The problem can be worsened by pressor or plasma volume expanding medications intended to compensate for orthostatic hypotension during waking hours. Disordered thermoregulation, unequal pupils, stridor, and difficulty in speaking and swallowing are reported. There is pathological involvement of central structures responsible for the control of breathing. Eventually, parkinsonian symptoms develop in most patients.

One of the primary concerns in the perioperative period is the autonomic failure associated with MSA. Preoperative preparation and meticulous intraoperative management are essential to prevent severe hypotension without causing massive volume overload. Management goals are aimed at decreasing venous pooling, increasing systemic vascular resistance, and increasing plasma volume.

Postural training by sleeping with a 25-degree head-up tilt (for recumbent hypertension), and elastic stockings (to decrease venous pooling in the lower extremeties) can be used. In addition, the application of 50 mm Hg positive pressure with a gravity suit has been used. It is, however, uncomfortable and impractical. Preoperative drugs to increase peripheral vascular resistance have met with variable success. It is essential to realize that indirect acting drugs such as atropine and ephedrine will provide little clinical response. Direct-acting agents such as phenylephrine will work. However, these drugs

need to be used cautiously because of possible risk of an exaggerated hypertensive response reflecting denervation hypersensitivity. The mineralocorticoid, 9-alpha-fluorohydrocortisone has been used to help maintain plasma volume through its sodium-retaining properties. During long-term administration it may actually work by increasing the sensitivity of the resistance vessels to the low concentrations of circulating catecholamines. Clearly the possibility of steroid dependence and other side effects must be considered in these patients.

Intraoperative management is primarily concerned with avoidance of severe hypotension. Because of the possibility of abrupt blood pressure changes resulting from the absence of intact cardiovascular reflexes, intra-arterial placement of a catheter is prudent. A central venous pressure monitor should aid volume assessment. Induction agents should be chosen that produce minimal cardiovascular changes. Volatile anaesthetic agents can cause exaggerated hypotension because of the absence of carotid sinus activity in these patients. Positive pressure ventilation may profoundly decrease cardiac output. Maintenance of anaesthesia may be complicated by the absence of autonomic "signs" of depth of anaesthesia, hyperpyrexia because of anhidrosis, and sluggish papillary reflexes or unequal pupils. The latter finding should be recognized preoperatively to avoid making an erroneous diagnosis of a severe neurological insult.

Vocal cord paralysis has been reported in MSA: it is usually a bilateral abductor paralysis with resultant glottic obstruction and ventilatory failure. The sign may be a presenting feature. The obstruction is not always total, and the patient may live uneventfully for some time after diagnosis. Of note, a patient with bilateral abductor vocal cord paralysis may have minimal stridor and normal phonation. Consequently, the diagnosis may not be considered in the preoperative evaluation. It may be prudent to arrange a vocal cord examination for any patient with MSA who is to undergo anaesthesia and surgery.

Parkinson's disease can be infrequently associated with autonomic dysfunction (Table 3) after many years. However, orthostatic hypotension in patients with parkinson's disease is common and is most often caused by drug therapy. The primary anaesthetic concerns in these patients involve understanding the medications used and their side-effects.

Sympathetic Hyperresponsiveness

Guillian-Barré Syndrome

Sympathetic hyperresponsiveness can be extremely dramatic in the patient with acute inflammatory demyelinating polyneuropathy (Guillian-Barré Syndrome)[49] and administering anaesthesia for a tracheostomy in such a patient can test skills like few other conditions. The cardiovascular manifestations can be benign or serious (Table XI). Only patients requiring ventilation develop arrhythmias and these are predicted by wide fluctuations in heart rate and blood pressure including transient asystole. Proposed schemata for the management of these patients have to attend closely to autonomic instability. Pulmonary artery catheter monitoring often need to be instituted early in those with autonomic cardiovascular dysfunction. Pulmonary thromboembolism, hypoxaemia, sepsis, gastrointestinal bleeding, and fluid and electrolyte disturbances must all be excluded. Demand pacing should be instituted in all patients with episodic non-sinus arrhythmias.

TABLE XI : Cardiovascular Complications of Guillian-Barré Syndrome

Common benign conditions
Sinus tachycardia
Postural hypotension
Minor ECG changes
Serious complications
Hypertension (sustained or episodic)
Episodic hypotension
Sensitivity to vasoactive drugs
Bradyarrhythmias (bradycardia, asystole)
Tachyarrhythmias

Porphyria

Autonomic dysfunction with a large component of sympathetic hyperresponsiveness is also a feature of porphyric neuropathy – a condition that anaesthetists are warned against in their training. Severe attacks of abdominal pain, nausea, constipation and perhaps diarrhoea have been attributed to autonomic neuropathy involving the enteric nervous system. Cardiovascular abnormalities are well described during these attacks and include tachycardia, hypertension, absence of bradycardia with the Valsalva manoeuvre, an abnormal 30:15 ratio, reduced heart rate variability to deep breathing, impaired blood pressure response to sustained hand grip and postural hypotension. These abnormalities are far more prominent during attacks than between attacks.

Autonomic Hyperreflexia

Autonomic hyperreflexia (AH)[36] is defined as widespread and massive paroxysmal reflex sympathetic discharge provoked by noxious stimuli that occurs in patients with a spinal cord injury level above the major splanchnic sympathetic outflow. Classically, patients with AH develop sudden headaches, paroxysmal hypertension, and bradycardia. This mimics phaeochromocytoma but without elevated catecholamine levels. Severe untreated hypertension can lead to confusion, seizures, hypertensive encephalopathy, strokes, retinal and subarachnoid haemorrhage and death. Besides bradycardia, left ventricular failure, cardiomegaly, tachycardia in high cervical cord lesion, and myocardial ischaemia can develop. Electrocardiographic changes associated with AH include increased PR interval, second degree atrioventricular block with nodal escape beats, atrioventricular dissociation, premature atrial and ventricular extrasystoles, and acute atrial fibrillation, all compatible with heightened vagal activity. Above the lesion there is flushing of the face and neck, mucous membrane and conjunctival congestion, intense diaphoresis, papillary mydriasis, lid retraction and hyperventilation. Below the lesion signs include intense somatic and visceral muscle contraction, increased spasticity, pallor and pilomotor erection. Symptoms and signs are highly variable and may also include severe headache, blurred vision, anxiety, agitation, shortness of breath, chest pain, and nausea.

Although the most severe episodes of AH occur in patients with high spinal cord lesions above the thoracic sympathetic outflow generally at or above the T6 or T7 level, it can also occur in patients with lower thoracic level lesions. For the pathological reflex activity to occur, the cord below the level of injury must be viable with an intact blood supply. Patients who are areflexic from the beginning of the injury usually continue to be areflexic past the spinal shock period and are not expected to exhibit findings of AH. Noxious stimuli below the injury activate the intermediolateral cell column up to the level of the injury by connections collateral to the dorsal and spinothalamic tracts, and this causes a heightened sympathetic outflow not checked by supraspinal inhibition. This results in the variable initiation of two reflex arcs: vagal and vasomotor. Slowing of the heart rate

and vasodilation, flushing and diaphoresis above the lesion.

Some of the common stimuli that can trigger AH include bladder and bowel distension (also tugging on the urinary catheter as, e.g., when the patient is turned prone in theatre before spinal surgery), cutaneous stimulation, tight clothing, strapping, uterine contractions, pregnancy and delivery, lower extremity surgery, sexual intercourse and urinary pathology. Since identification and rapid removal of the offending stimulus results in rapid resolution of symptoms, the initial management of AH focuses on the identification and the removal of the stimulus and the treatment of hypertension.

Nifedipine is the most prescribed medication for minor and major symptoms of AH. It has been shown to be effective when given for urological procedures, but ineffective at preventing AH when taken as prophylactic therapy twice a day. Hydralazine is recommended for treatment of acute AH and for AH occurring during pregnancy.

Anaesthetic management of patients with high spinal cord injury undergoing surgical procedures can be difficult. They are usually pretreated with nifedipine to ameliorate or prevent AH. Most common procedures that can trigger AH include cystoscopy, urodynamic studies, extracorporeal lithotripsy, percutaneous nephrolithotomy, renal pelvic stone removal, electroejaculation, and nephrectomy. The anaesthetic approach is controversial and includes both general and regional anaesthesia. Regional anaesthesia is preferred since it can block the afferent pathway to the spinal cord, thereby blocking the spinal reflex and preventing AH. Lumbar epidural block may not always provide (as opposed to subarachnoid anaesthesia) adequate sacral anaesthesia and has been reported to fail to prevent AH.

Tetanus[50,51,52,53]

All the manifestations of tetanus are caused by the effects of the soluble neurotoxin, tetanospasmin, on the neurologic system. It causes profound disinhibition of the nervous system. While dysfunction of the parasympathetic nervous system has been described in tetanus, sympathetic hyperresponsiveness is far more common. Cases suggestive of a component of sympathetic disinhibition have always been described, yet it was only in the late 1960s that sympathetic nervous system manifestations were recognized to be part of the spectrum of the disease. The constellation of sympathetic overactivity includes: labile hypertension, tachycardia, peripheral vasoconstriction, fever, cardiac arrhythmia, profuse sweating and a late-appearing hypotension, all associated with an increased output of urinary catecholamines. Patients who survive asphyxia due to muscle spasms or who have an adequate airway established may yet develop these sympathetic manifestations of disease which constitute one of the most serious complications of tetanus and carry a poor prognosis. Up to 60% of serious cases may develop such sympathetic nervous system findings. In one series, nearly 40% of these patients suffered unexpected (i.e. in the absence of preceding electrolyte abnormalities, hypoxaemia or known cardiac arrhythmias) cardiac arrest. Most of these patients were easily resuscitated with the previous heart rate and blood pressure restored.

Various caveats in the treatment of the sympathetic hyperactivity have been presented to intensivists and anaesthetists. Beta-blockade may leave unopposed alpha-adrenergic effects with severe hypertension and peripheral vasoconstriction; combined alpha and beta blockade has been associated with a higher incidence of cardiac arrest; alpha $_2$ –agonists have been used with success but are associated with hypotension; intravenous morphine produces effective central sympatholysis, but provides little cardiac protection against catecholamine-induced myocardial damage; and magnesium infusions provide an antidysrhythmic effect, myocardial protection, and sympatholysis, but require frequent measurements of magnesium levels – especially in those patients with impaired renal function. A recent suggestion of the use of an epidural infusion of local anaesthetics and sufentanil, together with sedation by means of a benzodiazepine, embodies an intuitively attractive and physiologically sensible approach.

CONCLUSION

Even a perfunctory survey of these aspects of the cardiovascular autonomic nervous system and perioperative circulatory stability leaves no doubt that cardiovascular autonomic dysfunction can present a wide spectrum of challenges to the anaesthetist. An anaesthetist that is equal to this would be an experienced and vigilant one who has been trained to recognize those patient populations where virtually moment-to-moment intervention may be required. Further, since the image of an "independent" autonomic nervous system turns out to be illusory, the anaesthetist must remember that the autonomic nervous system needs to be assessed in the context of every aspect of a patient's pathophysiology.

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