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Dysautonomia

Perioperative Implications

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CME This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Severe autonomic failure occurs in approximately 1 in 1,000 people. Such patients are remarkable for the striking and sometimes paradoxic responses they manifest to a variety of physiologic and pharmacologic stimuli. Orthostatic hypotension is often the finding most commonly noted by physicians, but a myriad of additional and less understood findings also occur. These findings include supine hypertension, altered drug sensitivity, hyperresponsiveness of blood pressure to hypo/hyperventilation, sleep apnea, and other neurologic disturbances.

In this article the authors will review the clinical pathophysiology that underlies autonomic failure, with a particular emphasis on those aspects most relevant to the care of such patients in the perioperative setting. Strategies used by clinicians in diagnosis and treatment of these patients, and the effect of these interventions on the preoperative, intraoperative, and postoperative care that these patients undergo is a crucial element in the optimized management of care in these patients.

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SEVERE autonomic failure occurs in approximately 1 in 1,000 people.[1,2] Such patients are remarkable for the striking and sometimes paradoxic responses they manifest to a variety of physiologic and pharmacologic stimuli. Autonomic failure may be secondary to other diseases, such as diabetes mellitus, amyloidosis, or bronchogenic carcinoma, or be due to a primary autonomic disorder such as multiple system atrophy (MSA) such as Shy-Drager syndrome, or pure autonomic failure.

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The authors will review the pathophysiology that underlies autonomic failure, with a particular emphasis on those aspects most relevant to the care of such patients in the perioperative and intraoperative settings. The authors will also discuss strategies that can be used to manage the symptoms of autonomic failure.

Proper functioning of the autonomic nervous system requires that both afferent and efferent limbs are intact. Afferent neurons detect changes in blood pressure, temperature, and the myriad other vital processes controlled by the autonomic nervous system, and communicate these changes centrally, whereas the efferent neurons engage effector systems to perturb or restore homeostasis. Dysfunction of the afferent limb is typically associated with labile hypertension, as seen in baroreflex failure, particularly during the postoperative period after endarterectomy or other neck surgeries affecting the carotid sinus nerve.[3] Abnormalities of central autonomic pathways such as in patients with MSA, of efferent effector systems as in patients with pure autonomic failure, patients with deficiency of dopamine β hydroxylase, or any combination thereof all can lead to clinical autonomic failure and disabling orthostatic hypotension.

Some of the most severely affected individuals have pure autonomic failure or multiple system atrophy. Such patients often have both extremely low blood pressures while upright and extremely high blood pressures while supine. Patients with MSA are perhaps the most vulnerable of all such patients to the complex and interacting responses to drugs and perturbations that occur during anesthesia.

Preoperative Evaluation of Autonomic Dysfunction

Common Features Associated with Autonomic Dysfunction

Orthostatic hypotension is the core feature of autonomic failure. Orthostatic hypotension is defined as a decrease in blood pressure of 20/10 mmHg on standing for 3 min. This definition is meant to capture initial or mild cases. Symptomatic orthostatic hypotension is more commonly encountered in subjects with decreases in blood pressure that may range from this figure to the severest cases where the decrease in blood pressure may be 100/50 mmHg. The most common symptoms of orthostatic hypotension are lightheadedness, dimming/tunneling of vision, and discomfort in the head (typically occipital), neck, shoulders, and sometimes the chest. It can be accompanied by various neurologic features in patients with MSA and Parkinson disease. Table 1 summarizes some of the seemingly trivial stimuli that can cause major blood pressure changes during autonomic failure. Other common clinical manifestations of autonomic failure include postprandial hypotension, urinary bladder dysfunction with urinary retention, decreased gastrointestinal motility (sometimes with severe constipation), and erectile dysfunction. Supine hypertension affects more than half of patients with autonomic failure; it induces pressure natriure-

Table 1. Commonplace Stimuli that Can Cause Blood Pressure Changes in Autonomic Failure

Decreases Blood Pressure	Increases Blood Pressure
Standing	Lying supine
Food	Water ingestion
Hyperventilation	Hypoventilation
Straining (Valsalva)	Abdominal binding
Fever and heat	Coffee
Dehydration	Water immersion
Exercise	Head-down tilt

sis and worsens orthostatic hypotension, often complicating management. Supine hypertension is characterized by an increase in peripheral vascular resistance. This is due to the residual sympathetic tone in patients with MSA, but the cause is not clear in patients with pure autonomic failure who have similarly increased vascular resistance despite very low levels of plasma norepinephrine and renin activity.[4,5] Due to absent or decreased baseline efferent neural traffic, patients with autonomic failure may also manifest denervation hypersensitivity to norepinephrine. Denervation hypersensitivity results in hyperresponsiveness of vascular smooth muscles to the chemical mediator that normally activates it (in this case, norepinephrine), due in part to up-regulation of adrenergic receptors secondary to the low levels of plasma norepinephrine in autonomic failure.[6,7]

Basic Evaluation of Patients with Autonomic Dysfunction

Basic evaluation of patients includes obtaining a detailed clinical history and examination, and measurement of blood pressure and heart rate while supine and again after 1 and 3 min of standing. Blood pressure measured while seated can sometimes be useful for those patients who cannot stand for even 1 min. More detailed autonomic function testing is usually performed in specialized centers, using multiples methods such as the following procedures: orthostatic and tilt-table testing; blood pressure and heart rate are measured twice in the supine position. The patient then is instructed to stand for 5 min. Blood pressure and heart rate are again determined at 1, 3, and 5 min in the upright position. In most instances of autonomic failure, there may be little or no increase in heart rate even though the blood pressure may decrease more than 50 mmHg on the upright position. Results from the tilt-table test in general are analogous but not identical to those of the orthostatic test. Although the tilt-table test offers little diagnostic advantage over carefully done upright hemodynamic data, many investigators use the tilt-table test because of its convenience and safety for the patient.[8]

The Valsalva maneuver is performed by blowing through a closed mouthpiece with a tiny leakage (16-gauge hole) to maintain 40 mmHg for approximately 15 s. It tests several components of the baroreflex arc. The cardiovascular response has been subdivided into four phases. During phase I, there is a transient increase in stroke volume and blood pres-
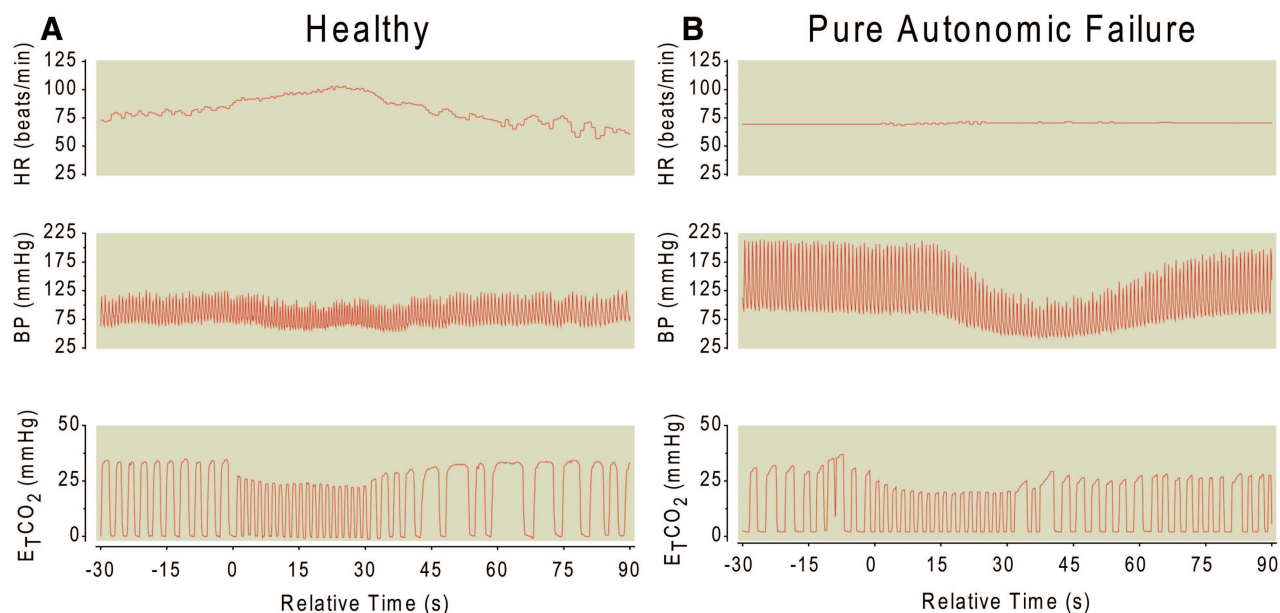
Fig. 1. The effect of hyperventilation on a healthy subject (*A*) and a pure autonomic failure patient (*B*). In response to hyperventilation, the compensatory heart rate (*upper trace*) increase is blunted despite the greater fall of blood pressure (*middle trace*) in the autonomic failure patient compared to a control subject. The E_TCO_2 (*bottom trace*) is decreased with hyperventilation. Signals from top to bottom, *upper trace* = heart rate (HR; beats/minute), *middle trace* = blood pressure (BP; mmHg), and *bottom trace* = end tidal carbon dioxide (E_TCO_2; mmHg).

sure secondary to the sudden increase in intrathoracic pressure being transmitted to the aorta. In phase II, as continued strained expiration is maintained, venous return is reduced and cardiac output decreases. This produces a decrease in blood pressure with reflex tachycardia. With the release of increased intrathoracic pressure, blood pressure abruptly decreases during phase III. During phase IV, there is a marked rise in blood pressure that exceeds basal levels. This blood pressure overshoot is the result of both an increase in cardiac output and peripheral vascular resistance. In patients with autonomic failure, the normal tachycardia in phase II is blunted or absent. The phase IV blood pressure overshoot seen in normal people also fails to occur in patients with autonomic failure.[8]

The cold pressor test evaluates efferent sympathetic function. It is carried out by placing the hand in a basin filled with 50% ice and 50% water for approximately 1 min. The normal average response is an increment of 20 mmHg in systolic blood pressure. The blood pressure increase is blunted in patients with autonomic failure.[8]

Deep breathing evaluates the vagal function on heart rate modulation during slow inhalation for 5 s and exhalation for 5 s over 90 s. The sinus arrhythmia ratio of the longest to the shortest interval is attenuated in those with autonomic failure.[8]

Hyperventilation tests the sympathetic response during deep and rapid (one breath per second) breathing for 30 s to counteract the hypocapnea-induced systemic vasodilation. A significant decrease in blood pressure indicates autonomic failure[8] (fig. 1).

The thermoregulatory sweat test and the quantitative sudomotor axon reflex test both determine the sweat gland function and the integrity of efferent cholinergic sympathetic

nervous system function. Sweating abnormalities are common in autonomic disorders; large areas of anhidrosis are found in patients with autonomic neuropathy due to various causes.[8]

Autonomic function testing can be especially important in asymptomatic patients with autonomic failure. Autonomic function testing can help to determine the severity and extent of the autonomic impairment, and hence aid in the anticipation of potential complications during anesthesia and surgery.

Clinical Features of Specific Autonomic Disorders

Table 2 lists some of the common causes of autonomic failure.[4,5,9] Although various causes of autonomic failure share common clinical features, the pathology is quite different and distinct in individual disorders. Some of the most severe forms of autonomic impairment are the neurodegenerative disorders commonly known as synucleinopathies.[4,10] They are characterized by aggregates of α-synuclein protein in the cytoplasm of neurons or glia. This group includes multiple system atrophy, and Lewy body disease (central autonomic failure). A related neurodegenerative disorder with isolated autonomic involvement is pure autonomic failure (peripheral autonomic failure). Parkinson disease in certain cases is associated with peripheral autonomic damage in additional to the central extrapyramidal disease. Distinction of multiple system atrophy in its earliest autonomic manifestation can be very difficult and is not currently always possible. Pharmacologically, patients with central autonomic failure (*e.g.*, MSA) can sometimes be distinguished from those with peripheral autonomic failure (*e.g.*, pure autonomic failure) by

Table 2. Major Causes of Autonomic Failure

Autonomic Synucleinopathies
  Multiple System Atrophy
    A central nervous system cause of autonomic failure (with orthostatic hypotension) that may mimic some motor features of Parkinson disease but is associated with a more rapid and dramatic course
  Parkinson Disease
    A primary motor disease that can sometimes be associated with a peripheral autonomic neuropathy and orthostatic hypotension
  Dementia with Lewy Bodies
    A rapidly progressive dementia that is associated with
    a peripheral autonomic neuropathy and orthostatic hypotension
  Pure Autonomic Failure
    A peripheral autonomic failure that occurs in older patients and can exist in isolation without motor neurologic disorders
Other Major Autonomic Disorders
  Autoimmune Ganglionic Neuropathy
    A form of autonomic failure caused by a loss of function antibody targeting of the α 3 subunit of the nicotinic receptor in autonomic ganglia
  Diabetic Autonomic Neuropathy
    A peripheral autonomic neuropathy that can cause orthostatic hypotension, often in the setting of multiple other diabetic complications
  Familial Dysautonomia
    An autosomal recessive developmental autonomic disease seen most commonly in Ashkenazi Jews
  Dopamine β Hydroxylase Deficiency
    A rare genetic loss of the enzyme that is needed to convert dopamine to norepinephrine, so the patients lack both norepinephrine and epinephrine
  Amyloidosis
    Amyloid protein deposition on autonomic neurons can cause autonomic failure with severe hypotension
  Drug-induced Autonomic Dysfunction
    Autonomic failure mimicked by drugs such as ganglionic blockers
  Spinal Cord Injury
    Typically seen with cervical and thoracic spinal cord transections

their response to imaging studies such as cardiac metaiodobenzylguanidine scan and olfactory function (usually normal in MSA, but abnormal in Parkinson disease). Sometimes direct (norepinephrine or phenylephrine) and indirect (tyramine, which causes norepinephrine release from sympathetic neurons) sympathomimetics may also help. In patients with peripheral autonomic failure, tyramine infusion produces only a small increase in blood pressure (due to peripheral neuronal damage), whereas norepinephrine infusion elicits an exaggerated pressor response (due to denervation hypersensitivity). Patients with central autonomic failure have a normal pressor response to tyramine and a lesser degree of denervation hypersensitivity.[11–15] Autonomic failure

with profound orthostatic hypotension is the clinical hallmark of the rather rare pure autonomic failure. This is in contrast to MSA, whereby patients develop multiple neurologic features including parkinsonism, cerebellar dysfunction, and pyramidal signs. MSA is differentiated from Parkinson disease by the asymmetric resting tremor, the poor response to levodopa, and the rapidly progressive nature of disease. Lewy body disease is defined by the coexistent parkinsonism and progressive cognitive decline frequently accompanied by spontaneous recurrent visual hallucinations. Diabetic autonomic neuropathy complicates long-standing diabetes and has been linked to increased cardiovascular mortality. Apart from the common features of autonomic failure and widespread organ impairment, diabetic neuropathy is characterized by resting tachycardia and large fluctuations in blood glucose.[9]

Anesthetic Considerations for Patients with Autonomic Failure

Preoperative knowledge of autonomic failure is of considerable importance in these patients. Preoperative blood pressure is usually assessed in the seated position and is typically normal in patients with autonomic failure; supine and upright blood pressures, which would expose autonomic dysfunction, are not routinely determined. Ideally, blood pressure should be measured in the supine position and repeated after 1, 3, and 5 min of standing.

General Preoperative and Postoperative Treatment Strategies for Autonomic Failure

General management must focus on ensuring hemodynamic stability perioperatively with adequate hydration, maintenance of euvolemia, and optimization of pharmacologic treatment. Simple maneuvers such as raising or lowering the head of the bed have proven to be helpful in ameliorating orthostatic symptoms for patients with autonomic failure in the outpatient setting. Hypotension during anesthesia is readily responsive to small doses of the α_1-adrenoreceptor agonist phenylephrine, especially in patients with pure autonomic failure.[16–18]

Supine hypertension is particularly responsive to transdermal nitrates, although short-acting intravenous vasodilators/venodilators such as sodium nitroprusside or intravenous nitroglycerin may be a better choice in treating extreme elevation of blood pressure to avoid profound hypotension. In one case report, the use of hydralazine for supine hypertension resulted in severe hypotension that was corrected by vasopressin.[19] Other agents that can be used judiciously for supine hypertension include intravenous dexmedetomidine and nicardipine.[20,21,22] Prolonged postoperative bed rest and inactivity should be avoided because they will worsen the already tenuous tolerance to standing.

Drugs Used in the Treatment of Autonomic Failure

Fludrocortisone

Fludrocortisone is a mineralocorticoid, which causes sodium retention and enhances the sensitivity of blood vessels to circulating catecholamines.[23] Most patients will need to gain approximately 1–2 kg of fluid to have the full benefit of this agent. Some of the benefit of fludrocortisone may be due to the support that increased interstitial fluid provides to the vasculature. Fluid overload is not generally a problem for patients with autonomic failure who are taking fludrocortisone. With more than 0.3 mg per day, some patients will experience a small amount of glucocorticoid effect, which might have unfavorable long-term consequences if they remain on the agent for many years. Fludrocortisone use can cause hypokalemia in up to 50% of patients, and hypomagnesemia in perhaps 10%. Chronically, blood volume is often supported with the use of fludrocortisone, a mineralocorticoid agonist that promotes renal sodium reabsorption. At higher doses, >0.3 mg/qd, fludrocortisone can result in suppression of the hypothalamic-pituitary axis.[2] Even though these higher doses of fludrocortisone rarely provide added benefit, they are often used. Thus, the risk of adrenal insufficiency from fludrocortisone therapy must be considered preoperatively in these patients.

Fludrocortisone may be useful in the 1–2 weeks before an elective procedure to optimize the volume status of a patient with profound autonomic failure.[23] In the face of these weight changes, it might be expected that fluid overload and pulmonary edema would commonly occur in patients with autonomic failure who are taking fludrocortisones. In practice this is rarely seen, perhaps because weight gain beyond 2 kg is avoided, and also because seated or upright posture provides rapid relief if mild symptoms of shortness of breath begin to occur.

Midodrine

Midodrine is a prodrug that acts by stimulating α-1 adrenoreceptors to constrict blood vessels and increase blood pressure. The pressor effect of midodrine comes on within approximately 30 min and wanes after 4 or 5 h. Other than excessive hypertension due to denervation hypersensitivity, the most troublesome side effect of midodrine is gooseflesh (chill bumps). This is due to the drug's α-1 effect to cause hair to stand on end. Some patients experience this as a numbness or "strange" sensation in the scalp or neck. Midodrine may be a very useful agent for management of orthostatic hypotension in the perioperative period in patients with autonomic failure, although there are reports of excessive rise in the supine blood pressure of a patient taking midodrine preoperatively. In the latter case report the supine hypertension was corrected quickly with the reverse Trendelenburg position. In patients with preexisting supine hypertension, it might be safe to hold the drug perioperatively to avoid an excessive increase in supine blood pressure.[24]

Pyridostigmine

Pyridostigmine is sometimes beneficial in patients with autonomic disorders. Early studies showed that blood pressure was increased by anticholinesterase drugs, whether they crossed the blood-brain barrier (physostigmine) or not (neostigmine), in patients with autonomic failure. Pyridostigmine is now the most widely used drug of this class for this purpose. The drug has long been used for the treatment of myasthenia gravis by preventing the destruction of acetylcholine by acetylcholinesterase. Inhibition of acetylcholinesterase enhances sympathetic ganglionic neurotransmission particularly in the standing position, with a lesser increase in supine blood pressure compared with other pressors.[25] The overall effect of pyridostigmine is a modest increase in upright blood pressure in patients with orthostatic hypotension. However, occasionally other aspects of autonomic failure such as constipation, urinary bladder dysfunction, and dryness of secretions may also be improved by this agent. This agent may be useful in the postoperative period for management of the symptoms of autonomic failure. However, the effect of an acetylcholinesterase inhibitor in the operating room may lead to unpredictably decreased or altered efficacy of neuromuscular blocking drugs. In addition, the beneficial effects of pyridostigmine in patients with autonomic failure, while notable, are not dramatic, and the medication can be held safely in most cases. Therefore, discontinuation of pyridostigmine in the preoperative period should be considered in patients with autonomic failure.[25]

Octreotide

Octreotide is a somatostatin analog, which has significant effects on gastrointestinal hormones and the gastrointestinal tract. The pressor action of octreotide is probably mediated via splanchnic vasoconstriction and elevation of systemic vascular resistance, although an effect of augmenting cardiac output has also been reported.[26,27] At quite low subcutaneous doses, 12.5–25 mcg, it often elicits an increase in blood pressure in patients with autonomic impairment, sometimes with very few side effects. After subcutaneous administration of octreotide, drug effects appear within a few minutes and last for few hours. Almost all patients experience some increase in blood pressure if they have baseline autonomic impairment, but occasional patients experience increases in systolic blood pressure of 40 mmHg or more. Administration of the long-acting somatostatin analog was associated with severe hypertension in one case report of diabetic autonomic neuropathy.[28] Excessively high doses may cause nausea or altered gastrointestinal motility. Gastrointestinal side effects are particularly prominent in patients with diabetes mellitus and who therefore can rarely tolerate octreotide for this reason.[26,29]

Atomoxetine

This drug inhibits the reuptake of norepinephrine by the norepinephrine transporter, producing an increase in norepi-

nephrine at the synapses of peripheral sympathetic neurons. In central autonomic failure (MSA), patients lack central modulation of sympathetic activity and this translates into an increase in blood pressure even at pediatric doses of atomoxetine. Therefore, atomoxetine can be used to effectively treat orthostatic hypotension in patients with central autonomic failure. This medication does not produce an increase in heart rate in patients with central autonomic failure despite its effect on blood pressure. In people with peripheral autonomic failure, the effect on blood pressure is minimal. The concomitant use of atomoxetine with a monoamine oxidase inhibitor may elicit especially large blood pressure elevations, but should only be undertaken with careful observation. Neuroleptic malignant syndrome also remains a theoretic possibility with these drug combinations and should be grounds for extreme caution.[30]

Acarbose

Patients with severe postprandial hypotension may benefit from the use of acarbose with meal ingestion. This α-glucosidase inhibitor is commonly used to treat postprandial hyperglycemia in patients with type II diabetes mellitus because it decreases the absorption of glucose in the small intestine. This effect seems to blunt the secretion of some gut peptides that act as vasodilators and might be responsible for the hypotensive effect of meals. Patients may complain of abdominal cramps, or of unusual or foul-smelling stools. This is likely due to an increased production of butyrate by gut bacteria. Acarbose usually attenuates postprandial hypotension by 20 mmHg and accelerates the blood pressure recovery to baseline values.[31] Obviously, acarbose has no benefit in patients with postprandial hypotension when oral foods and fluids are withheld perioperatively.

Droxidopa

Droxidopa (also known as L-DOPS or L-dihydroxyphenyl-serine) is the treatment of choice for dopamine β-hydroxylase deficiency, a rare congenital form of severe orthostatic hypotension caused by complete absence of the enzyme required for the conversion of dopamine to norepinephrine, which results in absence of both norepinephrine and epinephrine. Droxidopa is converted in one step into norepinephrine by dopa decardoxylase, an enzyme that is present in most tissues and sympathetic nerves. Droxidopa administration produces a moderate increase in blood pressure and a sustained dramatic relief of orthostatic symptoms.[32,33]

Drug Interactions in Patients with Autonomic Failure

Liver blood flow in human subjects is relatively posture dependent. In healthy subjects, liver blood flow is only reduced 5% in the seated posture compared with the supine posture. In patients with autonomic failure, the liver blood flow can decrease as much as 30% with upright posture. A consequence of this is that a hepatically cleared drug such as lido-caine may display plasma levels that are dramatically dependent on posture and blood pressure. When patients with orthostatic hypotension are receiving intravenous lidocaine, the plasma drug levels are almost twice as high while seated *versus* supine, and this change in posture can occasionally result in a toxic seizure despite an unchanged infusion rate.[34]

The response to various cardiovascular vasodepressor drugs also may be exaggerated, whereas the response to other vasoactive agents is unpredictable.[13,14] Tyramine infusion results in a slight increase in blood pressure in pure autonomic failure and normal pressor response in MSA, whereas norepinephrine infusion elicits an exaggerated pressor response in pure autonomic failure.[11–15] Ephedrine is another sympathomimetic agent with lesser effect on blood pressure increase due to mixed stimulation of α_1, β_1, and β_2 adrenergic receptors.[35] In addition to blood pressure effect, there is a concurrent increase in mean heart rate mediated by β_1-receptors stimulation.[36] Due to its mechanism of action that includes release of norepinephrine from the postganglionic neurons, this agent might only be effective in patients with residual sympathetic activity and capacity to release norepinephrine. Clonidine has a paradoxic action in the severest cases of pure autonomic failure, instead of the typical central sympatholytic effect and blood pressure reduction. The stimulation of the postsynaptic α_2-adrenergic and possibly some α_1-adrenergic receptors may predominate over the presynaptic receptors on the norepinephrine-depleted neurons. Therefore, doses above 0.2 mg clonidine can occasionally increase blood pressure significantly.[37] Table 3 lists the responses to some drugs in autonomic failure patients.

Special Considerations in Intraoperative Clinical Management

Airway Management

Several features related to the pathophysiology of autonomic failure may complicate airway management in the anesthetic care setting. Impaired gastrointestinal motility should be taken into consideration during airway management. Rapid sequence induction should be considered. Patients with MSA have muscle rigidity similar to patients with Parkinson disease, which may make intubation difficult. Vocal cord paralysis due to laryngeal muscle dysfunction[38,39] may be seen in central autonomic disorders such as MSA. As with any structural or functional disorder involving the vocal cords or glottic apparatus, this can result in difficult tracheal intubation. Oshima *et al.* reported a transient deterioration in laryngeal function following anesthesia in a patient with MSA, resulting in complete glottic obstruction and sudden death.[40] The combination of impaired gastrointestinal motility and laryngeal dysfunction make aspiration a particular concern in these patients.

Apnea in patients with autonomic failure, either due to upper airway obstruction (such as that seen in obstructive sleep apnea) or impaired central regulation of respiration, could be aggravated postoperatively. One author has postu-

Table 3. Drugs with Unusual Effects in Autonomic Failure

Drugs	Effects
Pressor effect	
Phenylephrine	Markedly increases blood pressure (even eye drops)[14]
Norepinephrine	Markedly increases blood pressure
Vasopressin	Markedly increases blood pressure[63]
Atomoxetine	Excessive pressor effect (approximately 25 mmHg) in MSA but not pure autonomic failure
Octreotide	Low dose (12.5 mg) may increase blood pressure for several hours
Saline	Increases blood pressure
Oxymetazoline	Increases blood pressure
NSAID (indomethacin)	Increases blood pressure by 5–30 mmHg[64]
Ephedrine	Increases blood pressure[35]
Clonidine	High dose (>0.4 mg) paradoxically increases rather than decreases blood pressure[37]
Depressor effect	
Salbutamol/terbutaline	Can reduce supine systolic blood pressure up to 50%[65]
Insulin IV	Decreases blood pressure
Tizanidine	Depressor first, then pressor (overshoot) when drug concentrations are gone
Propranolol	Usually little effect on blood pressure
Narcotics/Barbiturates	Depressor
Atropine	Large IV dose (3 mg) may transiently decrease blood pressure because of the drug's small α-1 antagonist effect, especially if α agonist is being administered
Dexmedetomidine	Blood pressure decrease may not always occur
Dopamine	May be depressor
Nitrates	Depressor effect, with significant blood pressure drop
Chronotropic effect	
Isoproterenol	Sixfold β-1 hypersensitivity and 17-fold β-2 hypersensitivity[65]
Epinephrine	Increases heart rate more than blood pressure–may be depressor
Pindolol	Increases HR 5–20 beats/min with mild elevation of blood pressure
Miscellaneous effect	
Lidocaine	Toxic levels and seizures if plasma concentrations increase with posture change

HR = heart rate; IV = intravenous; MSA = multiple system atrophy; NSAID = nonsteroidal antiinflammatory drug.

lated that the observed respiratory depression in autonomic failure was likely due to disordered central control of respiration during anesthesia rather than extreme respiratory center sensitivity to the anesthetic agent.[41] In addition to hypoxemia, apnea in these patients can have significant effects on blood pressure due to the resulting hypercapnea. The effect of hypercapnea on blood pressure should also be taken into consideration when titrating opioids or other respiratory depressants in the operating room and postoperatively.[40,42,43]

Gastrointestinal Function and Food Ingestion

Impaired gastrointestinal motility may impair gastric emptying. Patients with autonomic failure should be treated as if they have a full stomach. Gastroparesis in autonomic failure can predispose to aspiration upon induction of anesthesia.[44,45] Constipation, due to decreased gastrointestinal motility, and fecal incontinence are common in patients with autonomic failure; this may result in inadequate bowel preparation for colon surgery. Use of narcotics postoperatively may exacerbate the already sluggish intestinal motility and result in intestinal pseudoobstruction and toxic megacolon. In addition, distension of the rectosigmoid portion of the lower intestinal tract may worsen urinary retention. For these reasons, it may be prudent to minimize postoperative narcotics, although not at the expense of adequate pain control.[46,47]

Food ingestion can induce profound hypotension even in the supine position in patients with autonomic failure, especially with carbohydrate-rich meals.[48] Although this is often not an issue preoperatively for elective procedures, it may be of particular concern in the recovery room for same-day procedures, as patients are often given food and drinks that are high in carbohydrates to assess their ability to tolerate oral intake before discharge. Conversely, patients with supine hypertension may ingest food to attenuate the excessive blood pressure elevation.

Blood Pressure and Volume Control

Although orthostatic hypotension may not be evident in the operating room, the interventions associated with anesthetic management disturb cardiovascular equilibrium even in healthy individuals. The maintenance of baroreflex control of the circulation serves as a crucial counterregulatory mechanism in the face of surgical blood loss. Anesthetic agents can suppress the residual capacity to release catecholamines and can induce diminished baroreflex gain, which further compromises the pressor response during surgery.[18,49–52] The magnitude of these changes can be greatly enhanced in patients with efferent baroreflex impairment due to their inability to buffer changes in blood pressure. Furthermore, denervation hy-

persensitivity makes the pressor response to norepinephrine and its analogs very unpredictable.

In addition, a seeming paradox (but evidently part of the pathophysiology of dysautonomia) is that apprroximately 50% of our patients also have supine hypertension, often with systolic blood pressure more than 200 mmHg. These increased pressures occur despite extremely low levels of both plasma norepinephrine and plasma renin activity.[53] Even minor physical and pharmacologic perturbations in these patients may increase or decrease blood pressure and/or cardiac output to dangerous levels.

The loss of cardiovascular reflexes in autonomic failure can complicate anesthesia and predispose patients to life-threatening changes in blood pressure.[54] The volume status of the patient is one of the most important factors in determining hemodynamic stability in patients with autonomic failure. Consequently, acute changes in blood volume (such as may be seen with rapid saline infusion or with rapid blood loss) can result in a substantial increase or decrease in blood pressure. A relatively fixed heart rate in response to cardiovascular stimuli is characteristic in these patients. Bradycardia in patients with autonomic failure may not respond to atropine (because vagal tone is already diminished in these patients), and alternatives such as isoproterenol or a temporary pacemaker can be life-saving. Supine hypertension is present in more than half of patients with autonomic failure. Although this condition may complicate surgery when patients are supine, it usually responds to changing position (reverse Trendelenburg) or judicious use of antihypertensive agents such as transdermal or intravenous nitroglycerin without causing unwanted hypotension. Prone position during surgery as an alternative to the traditional supine position is known to obstruct venous return and may result in hypotension.[55] Supine hypertension has been noted to be especially prominent in patients taking midodrine. Omitting midodrine or other acute pressor agents the day of the surgery should be considered.[24]

Ventilatory Management

The inability of patients with autonomic failure to increase cardiac output through sympathetic activation makes them exquisitely sensitive to the effects of positive pressure ventilation on venous return and cardiac output. Similarly, these patients may be less tolerant of the pneuomoperitoneum associated with laparascopic procedures. Using smaller tidal volumes and volume loading to control hypotension would be appropriate management.

In patients with autonomic failure, hyperventilation and the resulting decrease in blood carbon dioxide levels causes a rapid decrease in blood pressure, sometimes ≥40 mmHg within 60 s.[42] Conversely, hypercapnea (such as can be seen with hypoventilation or increased dead space ventilation) can rapidly increase blood pressure 20 mmHg or more.[43] In fact, some patients with autonomic failure are able to increase their tolerance of upright posture by increasing dead space

ventilation as by breathing through a length of tubing.[56] These observations imply that blood pressure in patients with autonomic failure can at least partially be modulated by manipulation of minute ventilation.

Response to Infection

Patients with severe autonomic failure respond to infection with an acute decrease in blood pressure and a greatly reduced functional capacity of standing and ambulation. Such infections are most commonly in the urinary tract or the lungs. If a patient with autonomic failure experiences greater than usual blood pressure lability, new-onset recurrent syncope, or an acute decrease in performance status, the presence of occult infection should be determined with emphasis on evaluation for urinary tract infection or aspiration pneumonia. Suspicion for urinary tract infection should be especially high because urinary bladder dysfunction and chronic urinary retention are part of autonomic failure.

Temperature Regulation

Patients with autonomic failure often lose the ability to sweat. Early on in the clinical course, this sweating can be patchy, and paradoxically present as apparent "increased sweating" in less involved areas such as the head and neck. Impaired perspiration can lead to an inability to dissipate heat adequately. When patients are exposed to hot weather, this condition may be a problem and also contribute to a persistent high fever postoperatively. This increase in body temperature can cause a decrease in blood pressure that is accompanied by a feeling of extreme fatigue. The patient may only be able to tolerate this temperature for a few minutes. Contemporary operating rooms have carefully controlled temperatures, but with aggressive warming measures (*e.g.*, heavy bedding with blankets, use of convective air warmers, and heated intravenous fluids) temperature elevation may sometimes occur and lead to thermally induced hypotension. Conversely, the lack of vasoconstriction in patients with autonomic failure to vasoconstrict in response to a cool environment may result in excessive heat loss and hypothermia.[57] The lack of thermoregulatory vasoconstriction is especially reported in patients with diabetic neuropathy; it predisposes patients to intraoperative hypothermia, excessive blood loss, and postoperative infections.[58]

Afferent Baroreflex Failure

Multiple clinical disorders can result in baroreflex failure such as accidental trauma, trauma either from unilateral or bilateral carotid endarterectomy, or additional surgical therapy for pathology in the relevant anatomic areas, local tumor growth (carotid body tumor), and brainstem stroke are all recognized causes of baroreflex failure. Radiation therapy of head and neck carcinoma may also have the side effect of damage to cranial nerves, although this can occur months to years after the irradiation.[3]

Acute baroreflex failure clinically resembles pheochromocytoma more than it does autonomic failure, and excursions of systolic blood pressure to 320 mmHg or more is sometimes seen during stress. The blood pressure in these individuals is sensitive not only to usual perturbations of pain, anxiety, anger, and stress, but also to what for others would be a minor stress, such as exposure to bright light, sudden noise, or the appearance of the physician at the patient's door. The headache accompanying these large elevations in blood pressure sometimes places patients in a position to develop their own intuitive biofeedback-based mechanisms to decrease blood pressure. Some sensitive patients find that sunglasses can prevent headaches due to decreased exposure to sunlight.

When baroreflex impairment is due to disturbance of transmission up the vagal and glossopharyngeal nerves, there may also be complete loss of parasympathetic function. This results from the close physical relation of the afferent baroreflex nerves in the vagus and glossopharyngeal nerves, and efferent vagal nerves. However, certain individuals have intact efferent parasympathetic control so that stress can be fully appreciated and expressed in terms of both blood pressure and heart rate.[3,59] In this disorder, selective baroreflex failure, blood pressure and heart rate may fall quite low during sedation or sleep, sometimes with sinus arrest for several seconds, and pacemaker placement may become necessary.

Choice of Anesthesia in Autonomic Failure

Currently, there are no systemic studies that looked at the preference of general *versus* regional anesthesia in autonomic failure patients. Most of the information is based on individual case reports. Dose requirement of local anesthetic for adequate level of anesthesia was reported to be higher in autonomic failure patients,[49,60] although this finding has not been consistent in all case reports.[61] Marked hypotension can complicate spinal anesthesia in autonomic failure; it is usually preventable by adequate perioperative fluid replacement.[16,62] Postural hypotension may develop during placement of the spinal anesthesia in the sitting position,[60] which requires special attention. Bevan has concluded that the choice between regional and general anesthesia is less important than adequate volume replacement and hemodynamic monitoring.[16] Table 4 summarizes the preoperative intraoperative and postoperative aspects of dysautonomias and anesthesia.

Summary

Patients with autonomic failure are a special population with significantly perturbed homeostatic responses to normal physiologic and environmental stresses. Postural hypotension is the chief and most disabling symptom, but other neurologic disturbances are frequently encountered. Preoperative management of autonomic failure requires careful evaluation and control of blood volume. The absence of compensatory mechanisms exaggerates the response to vaso-

Table 4. Summary of Anesthesia Implications

Preoperative Factors
  Patients orthostatic hypotension with or without supine hypertension
  Be aware of gastroparesis and aspiration risk
  Be aware of blood volume status for the conduct of anesthesia
  Be aware of slight anemia due to reduced erythropoiesis
  Consider holding oral vasopressors to prevent drug interactions intraoperatively
Intraoperative Factors
  General *vs.* regional anesthesia choice would be dependent on procedure type
  Patients require adequate monitoring and constant vigilance
  Hypothermia and hyperthermia are both risks with poor thermal regulation
  Intubation may require rapid sequence with cricoid pressure
  Patient positioning may have significant effects on vital signs
  Nitroglycerine, prone positioning, or reverse Trendelenberg positioning can be used for supine hypertension
  Sudden blood volume changes may precipitate untoward blood pressure response (rapid infusions or rapid blood loss)
  Pneumoperitoneum should be applied with extreme caution or avoided if possible
  Vasopressors and inotropes can have resistance or undue sensitivity (see table 3.)
  Abnormal electrolyte values affect responses to medications
Postoperative Factors
  Anticipate volume changes in the postoperative period and observe with a higher level of care
  Orthostatic hypotension requires good blood volume and assistance with first ambulation
  Abnormal electrolyte values affect responses to medications
  Thermal regulation may be an issue in the recovery period
  Ileus can be worsened by opiate use in the postoperative period
  Restart home dysautonomia medications before discharge

active and cardiac depressant agents. The decision to withhold or continue medications perioperatively should be individualized and tailored for each patient.

Intraoperatively, patients need careful and attentive monitoring and are at risk for hypertension or hypotension with volume stimuli and also with positioning. Temperature regulation can result in hyperthermia or hypothermia and should be controlled for during either event. Postoperatively, orthostatic hypotension control necessitates the use of volume expansion, postural training, and occasionally vasoconstrictors. Patients should be placed on home medications for dysautonomia before discharge.

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