AANA Journal Course

Update for Nurse Anesthetists

A Tour of Autonomic Reflex Activity Relevant to Clinical Practice

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The reflex arc is the functional unit allowing the human body to continuously, and unconsciously, adapt to its internal and external milieu. We review a broad range of autonomic reflexes controlling blood pressure, ensuring tissue oxygenation, and otherwise acting in concert to maintain homeostasis. Normal activity, pathophysiologic insult, and pharmacologic impairment of this reflex activity are discussed, with special consideration to the care of the anesthetized patient.

Keywords: Autonomic reflexes, clinical practice, external milieu, reflex activity.

Objectives
Upon completion of this course, the reader will be able to:
1. Describe the role that autonomic reflex activity plays in maintaining blood pressure.
2. Identify pathophysiologic factors that impair autonomic reflex activity.
3. Identify pharmacologic factors that impair autonomic reflex activity.
4. Explain how autonomic reflex activity optimizes oxygenation of blood in the lung.
5. Develop a plan of care for patients that is based on an understanding of autonomic reflex activity.

Introduction
The autonomic nervous system (ANS) has at its disposal a wide range of reflex responses designed to maintain homeostasis. The reflex arc is the functional unit allowing humans to continuously, and unconsciously, adapt to their internal and external milieus. Pathology, polypharmacy, and surgical manipulation often challenge the integrity of these mechanisms. Providing high-quality, patient-centered care necessitates understanding the ANS and its associated reflex arcs. This AANA Journal Course surveys those reflexes that exhibit the greatest clinical significance during the perioperative period.

Baroreceptor Reflex
Marey’s law, which states that blood pressure elevation reduces heart rate in a predictable manner, is the basis for the baroreceptor reflex. Arterial baroreceptors are stretch-sensitive nerve endings embedded in the walls of the carotid sinus, aortic arch, myocardium, and pulmonary vessels. Vascular deformation (increased pressure equals increased stretch) begins the process of mechanosensory transduction. Activation of epithelial sodium channels generates action potentials, where the frequency of action potentials is directly proportional to the degree of receptor stretch. These electrical signals propagate along 2 afferent pathways. The nerves of Hering innervate the carotid sinus, and these fibers converge with the glossopharyngeal nerve. Vagal afferents innervate the extracarotid baroreceptors. Both pathways terminate in the nucleus tractus solitarius (Figure 1). After processing in the nucleus tractus solitarius, the signal spreads to the caudal ventrolateral medulla (CVLM). Until now, the signal has been excitatory; however, it becomes inhibitory inside the CVLM. Increased baroreceptor stimulation enhances inhibitory CVLM output, ultimately depressing the rostral ventrolateral medulla and sympathetic outflow. Input from the hypothalamus, cerebral cortex, and arterial chemoreceptors modulates rostral ventrolateral medulla activity as well. The vagus nerve, cardiac accelerator fibers, and sympathetic vascular fibers work in concert to form the efferent limb of the baroreceptor reflex.

The baroreceptor reflex attenuates acute hypertension by reducing heart rate, inotropy, and vascular tone.

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Conversely, the opposite occurs when blood pressure declines. Many factors common to the perioperative period impair the baroceptor reflex, including halogenated anesthetics, propofol, and β_1-antagonists. Although classic teaching suggests that the baroceptor reflex regulates blood pressure only over the short term, emerging evidence challenges this dogma. Indeed, electrical baroreflex stimulation shows promise as a viable treatment of chronic hypertension that resists medical therapy. From tachycardia in the setting of acute hemorrhage to bradycardia during mediastinoscopy or balloon inflation during percutaneous carotid interventions, the effect of the baroceptor reflex is apparent throughout the perioperative course.

Chemoreceptor Reflex
Central chemoreceptors are located beneath the ventral surface of the medulla and are sensitive to hydrogen ion concentration. Peripheral chemoreceptors, found in the carotid and aortic bodies, are principally stimulated by decreased arterial oxygen concentration. Hypoxia, hypercarbia, and acidosis initiate a reflex increase in minute ventilation and blood pressure from increased sympathetic outflow. Both respiratory rate and tidal volume increase via afferent signals sent from the Hering nerve and the vagus nerve to the nucleus tractus solitarius. The chemoreceptor reflex is similar to the baroceptor reflex, in that it is attenuated by opiates, propofol, barbiturates, benzodiazepines, volatile anesthetics, and nitrous oxide in a dose-dependent manner. Therefore, the anesthesia provider should be cognizant that if residual volatile agent is present during emergence, a higher Pa\text{CO}_2 will be necessary before spontaneous respirations.

Bainbridge Reflex
While studying anesthetized dogs, Bainbridge observed that an infusion of saline and/or blood of sufficient volume to cause atrial and ventricular dilation produced tachycardia. Bainbridge postulated this as a reflexive phenomenon, as he prevented it by denervating the heart and ligating the suprarenal veins, thus eliminating the potentially confounding role of endogenous catecholamine release. Stretch receptors in the atria, great veins, and pulmonary veins transmit afferent traffic along the vagus nerve to the vasomotor center in the medulla; vagal inhibition facilitates cardiac acceleration. Stretching of the sinoatrial node hastens its automaticity as well. Because the volume of blood ejected by the heart must equal the amount of blood returning to the heart, the Bainbridge reflex may confer protection against pulmonary vascular congestion in the face of increased venous return. The apparent contradiction to Marey’s law is best explained by the idea that intravascular volume loading obtunds the sensitivity of the baroceptor reflex. The Bainbridge reflex may manifest during intravascular volume expansion, during position changes that augment venous return, and with the use of vasoactive drugs that reduce venous capacitance. The Bainbridge reflex is impaired by factors such as polypharmacy, aging, altered sympathetic tone, and patient comorbidities.

Bezold-Jarisch Reflex
The Bezold-Jarisch reflex is an inhibitory reflex with origins in receptors located in the heart’s chambers sensitive to pressure, volume, inotropic state, and chemical stimuli. The afferent limb of this reflex is composed of unmyelinated elements of the vagus nerve; its efferent component inhibits the sympathetic system and activates parasympathetics, resulting in bradycardia and peripheral vasodilation (Figure 2). We may see profound bradycardia during severe blood loss, likely as a result of a falling (or absent) venous return. Although not agreed on by all, the Bezold-Jarisch reflex may promote diastolic filling during catastrophic declines in cardiac blood volume. Essentially, it informs the heart that there is no reason to contract if there is insufficient ventricular blood. It may slow the heart to the point of asystole. Some speculate that the Bezold-Jarisch reflex plays a major role in explaining cardiovascular collapse resulting from diminished venous return during neuraxial interventions and in the supine inferior vena cava compression syndrome in pregnancy. The role of the Bezold-Jarisch reflex remains speculative in these scenarios and requires further research; for obvious ethical reasons, the Bezold-Jarisch reflex is difficult to study in humans.

Autoregulation of Blood Flow
Autoregulation refers to the intrinsic ability of an organ...
to maintain a constant blood flow despite changes in perfusion pressure. It is a reflex response particular to the target organ not reliant on humoral factors. Upper and lower limits of autoregulation vary among different organs in the individual, and therefore we generally default to that of the brain in discussions related to anesthetic care. Recent evidence implicates hypotension and altered renal autoregulation in some cases of acute kidney injury during cardiac surgery.7

Autoregulation is under the influence of a variety of factors and mechanisms. The myogenic influence is a reflex change in muscle tone itself, induced by a change in the perfusion pressure, also termed the Bayliss effect. A metabolic influence on autoregulation occurs as a direct effect of accumulating metabolites (eg, carbon dioxide, adenosine, electrolytes) on cerebral vasculature. A neurogenic influence results from action on the cerebral vasculature mediated via the superior cervical ganglion.8

Traditional teaching that cerebral autoregulation occurs over a range of mean arterial pressures of 50 to 150 mm Hg (lower and upper limits, respectively) may be flawed given the variation in the physiology of the cerebral circulation. For example, cerebral autoregulation is shifted rightward in hypertensive patients (Figure 3), and the so-called plateau may not exist at all, with cerebral blood flow becoming highly dependent on systemic blood pressure in a linear manner.9

A number of case reports and studies describe perturbations in cerebral function after head-up (eg, beach-chair) positioning during general anesthesia. The commonly quoted lower limit of autoregulation of a mean pressure of 50 mm Hg may be too low to adhere to, because it suffers from substantial interindividual variation.10

Pathophysiology (eg, hypertension, diabetes) and drug effects (autonomic modifiers) have a unique, patient-specific impact on autoregulation. During general anesthesia, anesthetists should not universally assume that a lower limit of 50 mm Hg ensures adequate cerebral perfusion in all patients (see Figure 3). The wide variation, substantiated by recent sophisticated measurement tools, suggests that anesthetists should consider maintaining mean pressure at higher levels, especially in those patients who are older or have disorders that may obtund the ANS.11

Hypoxic Pulmonary Vasoconstriction

The task of optimizing pulmonary transfer of oxygen to blood rests in part with hypoxic pulmonary vasoconstriction (HPV), a vascular smooth-muscle response occurring when a decreased pressure of alveolar oxygen...
(PAO₂) is sensed regionally in the lung. This reflex encourages perfusion only to alveoli that are ventilated. When the reflex is pathologically or pharmacologically impaired, pulmonary function suffers.

Hypoxic pulmonary vasoconstriction can be organized into 2 distinct phases. In the acute setting of regional hypoxia, phase 1 manifests immediately, reaching its zenith in 10 to 15 minutes; if hypoxia persists, a more generalized and sustained pulmonary vasoconstriction occurs, so-called phase 2, peaking in about 2 hours.¹² In a persistent state of hypoxia, HPV is greatly enhanced, which is well described in high-elevation mountaineers.

Various factors are known to obtund HPV. Among these are acetazolamide, nitric oxide, prostacyclin, angiotensin-converting enzyme inhibitors, nitroglycerine, nitroprusside, potent inhaled anesthetic agents, and phosphodiesterase inhibitors.¹³ The latter is clinically relevant because it is a mainstay therapy in patients with pulmonary hypertension.

As a rule, drugs with vasodilating effects will negatively affect HPV. Volatile anesthetics inhibit HPV in a dose-dependent manner.¹³ Curiously, propofol, which causes systemic vasodilation, appears not to inhibit HPV.¹⁴

**Thermoregulation**

Thermoregulation consists of afferent thermal sensing, central control, and efferent responses. Peripheral sensors relay information to the brain, where the hypothalamus regulates body temperature to around 37°C. Awake patients warm themselves by shivering, brown fat thermogenesis, and vasoconstricting cutaneous vascular beds. Likewise, they reduce body temperature via sweat glands that provide evaporative cooling and vasodilation of cutaneous vascular beds.¹⁵

All general and regional anesthesias inhibit thermoregulatory mechanisms, rendering patients unable to regulate core body temperature.¹⁶ Temperature monitoring and measures to conserve and deliver heat are routinely employed during anesthetic care. Figure 4 is a timely reminder that radiation, conduction, convection, and evaporation can lead to hypothermia during surgery if not minimized.¹⁷

Age-related impairment of the ANS in both the young and old includes a decrement in heat generation, impaired shivering and vasoconstriction, and reduced insulation from subcutaneous fat. Young children are at particular risk of thermoregulatory reflex impairment because of a large ratio of body surface area to body mass, ANS immaturity, a high metabolic rate, and low subcutaneous fat.

**Oculocardiac Reflex**

There are many reports of severe bradycardia and even cardiac arrest associated with the oculocardiac reflex (OCR). Also known as the Aschner reflex and the trigeminal-vagal reflex, the OCR is induced by mechanical stimulation on the eyeball, frequently seen by traction on the extraocular muscles (medial rectus in particular) during strabismus surgery.¹⁸ The afferent limb begins in the eye, as the long and short ciliary nerves join the ophthalmic division of the trigeminal nerve. After synapsing in the ciliary ganglion, these fibers merge with the main sensory nucleus of the trigeminal nerve, descend the spinal trigeminal tract, and synapse in the motor nucleus of the vagus nerve, which serves as the efferent limb terminating at the sinus and atrioventricular nodes.

The reflex is advantaged with gentle pressure on the eye to treat supraventricular tachycardia. Orbital and facial trauma may also elicit the OCR. Opiates, β-blockers, and calcium channel blockers may contribute or predispose to its occurrence. Baseline tachycardia induced by atropine or glycopyrrolate is not uniformly protective. The OCR is typically a fatiguing reflex, waning with repeated ocular manipulation. Retrobulbar anesthesia may be preventive, although performing the block may provoke the OCR.

**Hiccup**

A surprisingly large literature exists on the reflexive nature of the hiccup, also known as singultus, which is the involuntary contraction of the inspiratory muscles, associated with a slightly delayed (approximately 35 milliseconds), abrupt closure of the glottis. Generally, episodes of hiccup are self-limiting in both children and adults, disappearing spontaneously or via simple measures such as breath-holding or home remedies such as swallowing a spoonful of sugar.

Chronic or prolonged hiccups require medical intervention because they can be debilitating, causing insomnia, exhaustion, impaired feeding, and depression. The management of intractable hiccups is challenging; a
variety of interventions (drug and mechanical) have been applied with varying success. Surprisingly little is known about its purpose or pathophysiology. When occurring during anesthesia and surgery, it can be a frustrating reflex to extinguish but usually is self-limiting.

**Swallowing Reflex**

If you have ever been to the dentist for cleaning or repair work, trying to remain still, you know how difficult it is to try to overcome the swallowing reflex. Swallowing is a complex sensorimotor event that can be voluntary but also is highly reflexive. Swallowing involves a highly coordinated, hierarchical interplay among the cerebral cortex and cranial nerves V, IX, X, and XII. It is highly dependent on sensory feedback for both initiation and modulation. A rather well-defined “swallowing center” is located in the nucleus of the solitary tract of the dorsal region of the brainstem.

There is a highly coordinated interplay between the pharynx and breathing that is designed to facilitate body nourishment, yet protect the glottis from aspiration, despite the close sharing of anatomy. A variety of pathologic and drug-induced dysfunctions of the swallowing reflex can occur.

Even subanesthetic levels of commonly used drugs (eg, propofol, opiates, nitrous oxide, sevoflurane, neuromuscular blocking drugs, barbiturates) impair swallowing. In a highly elegant study, morphine and midazolam impaired the interplay between breathing and swallowing, resulting in an elevated risk of aspiration even in healthy, young volunteers.19

**Autonomic Failure**

Injury to any component of the autonomic reflex arc places the patient at risk of autonomic dysfunction. Causes are listed in Table 1. Orthostatic hypotension is the hallmark feature of autonomic dysfunction, in which a reduction of systolic blood pressure greater than 20 mm Hg or diastolic blood pressure above 10 mm Hg occurs within 3 minutes of standing. Fludrocortisone (Florinef) is the mainstay of treatment. It enhances sodium retention, expands the plasma volume, and increases vascular sensitivity to catecholamines. Other consequential findings specific to the cardiovascular system include supine hypertension, postprandial hypotension, drug hypersensitivity, and excessive blood pressure fluctuation in response to hypo- and hyperventilation. Treatment targets the underlying cause; therapeutic options include midodrine, atomoxetine, acarbose, droxidopa, octreotide, and pyridostigmine.

Perioperative hemodynamic management requires considerable attention to detail. Acute alteration in central blood volume in response to position change or positive-pressure ventilation may affect end-organ perfusion. Maintenance of euvolemia is essential. Heart rate variability is reduced, with the rate usually elevated. Atropine may be of little benefit in the setting of bradycardia, whereas adrenergic agonists may produce an exaggerated response; therefore, slow, careful titration is vital. Supine hypertension can be alleviated by the reverse Trendelenburg position, transdermal nitroglycerin, or short-acting intravenous vasodilators. Minute ventilation strongly influences the hemodynamic state, in which hypocapnia can cause systolic blood pressure to decline as much as 40 mm Hg within 60 seconds. Conversely, hypercapnia can precipitate significant hypertension. One must remain cognizant of this when instituting mechanical ventilation or during carbon dioxide insufflation.20

**Orthostatic Hypotension**

Orthostatic hypotension is defined as a decrease in systolic blood pressure of 20 mm Hg or diastolic blood pressure of 10 mm Hg within 3 minutes of standing from a seated or supine position. Manifestations include blurred vision, weakness, syncope, and palpitations.21

Immediately following abrupt standing, there is gravity-related pooling of 500 to 1,000 mL of blood in the lower extremities and venous capacitance vessels. The consequence is a reduced venous return with a fall in stroke volume and cardiac output. An increase in sympathetic outflow restores blood pressure by augmenting heart rate, contractility, and peripheral vascular resistance. There are many causes of orthostatic hypertension (see Table 1), including diabetes, Parkinson disease, multiple system atrophy (Shy-Drager syndrome), and medications, including many anesthetic agents.22 Table 2 shows variables affecting the severity of orthostatic hypotension. Lifestyle changes, as well as drugs such as midodrine and droxidopa that stimulate α-receptors, are commonly used in treating orthostatic hypertension.

**Sympathovagal Imbalance in Hypertension**

Sympathovagal imbalance describes a syndrome in which sympathetic reflex overactivity predominates in the face of vagal withdrawal. Hypertension may be hallmarked by tachycardia secondary to reduced inhibitory influence (eg, vagal withdrawal) as well as direct effects from liberated adrenergic neurotransmitters. Contemporary views of hypertension focus on it being a microvascular disease with ANS impairment.23

Many associated comorbidities can predispose to alterations in the reflex relationships associated with the microvascular disorder of hypertension. Hyperinsulinemia, obesity, diabetes, inflammatory states, and poor nutritional habits are implicated. Both pharmacologic and nonpharmacologic approaches are employed to manage amplified sympathetic activity.23

**Autonomic Hyperreflexia: The Mass Reflex**

In the acute aftermath of spinal cord trauma, there is risk
of neurogenic shock due to loss of autonomic function below the injured level. In the ensuing weeks, the lower part of the spinal cord remains functionally isolated from inhibitory influences of the hypothalamus and brainstem; inappropriate remodeling of sympathetic reflex arcs below the injury level results in neurons persisting in a hyperexcitable state. Stimulation of these fibers may trigger intense vasoconstriction below the injury level, causing hypertension. Bradycardia and vasodilation above the lesion attempt to stabilize blood pressure. Hypertension may be severe enough to provoke seizures, intracranial hemorrhage, and myocardial ischemia. Even with absent sensory function, general or regional anesthesia is often provided to avoid provoking autonomic hyperreflexia. Should autonomic hyperreflexia manifest, prompt intervention includes removing the stimulus, deepening anesthesia, and instituting an intravenous arteriolar vasodilator.

**Diabetic Autonomic Neuropathy and Dysfunction**

Exerting a major negative impact on quality of life, diabetic autonomic neuropathy and dysfunction (DAND) may affect the entirety of the ANS. Vasomotor, visceromotor, and sensory fibers innervate all organ systems; dysfunction creates physiologic havoc that is diffuse and complex. Major manifestations include resting tachycardia, orthostatic hypotension, gastroparesis, constipation, exercise intolerance, erectile dysfunction, and impaired neurovascular function. Sudden death is a reported consequence. Major hypotheses of the neuropathic injury include a metabolic insult to nerve fibers, neurovascular insufficiency, and an autoimmune insult.

Impaired baroreceptor/hemodynamic function, dysrhythmias, delayed gastric emptying, myocardial ischemia, renal dysfunction, poor joint mobility, and skin vulnerability to pressure injury are major concerns in developing a plan of care for those with DAND. Although perioperative glucose control is vital, acute management will not offset the havoc of DAND.

**Vasovagal Phenomena**

Also known as neurocardiogenic syncope, the vasovagal reflex results in abrupt slowing of the heart and dilation of lower extremity vessels leading to light-headedness or even fainting. Although the vasovagal reflex may be triggered by a wide range of physical or emotional stimuli, (eg, pain, striking the ulnar nerve, emotion-generating news, the sight of blood), it is rarely serious as an independent event unless a resultant fall places
the affected individual at risk of harm.

We may observe vasovagal reflex activity in which surgical stimulation of afferent fibers in the celiac plexus from traction or pressure initiates bradycardia with hypotension. Anesthetists not infrequently observe the reflex precipitated by the start of venipuncture and intravenous catheter placement, particularly in children, young adults, and the elderly.

Conclusion
The ANS conveys impulse signals from the vasculature, the heart, and all the organs of the body via nerves to the central nervous system, most notably the medulla, hypothalamus, and pons. Nearly all these impulses do not reach our consciousness, rather eliciting a host of automatic reflex responses serving to maintain homeostasis. Imbalance or dysfunction in this intricate network of reflex activity may occur as a result of disease, long-term drug therapy, mechanical or surgical intervention, or the acute effects of drugs that we employ in the care of our patients. Knowledge of the structure and function of the ANS reflexes is vital to the safe planning and management of the anesthetized patient.

REFERENCES


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DISCLOSURES
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