

PERIOPERATIVE REFLEX BRADYCARDIA AND CARDIAC ARREST

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Introduction

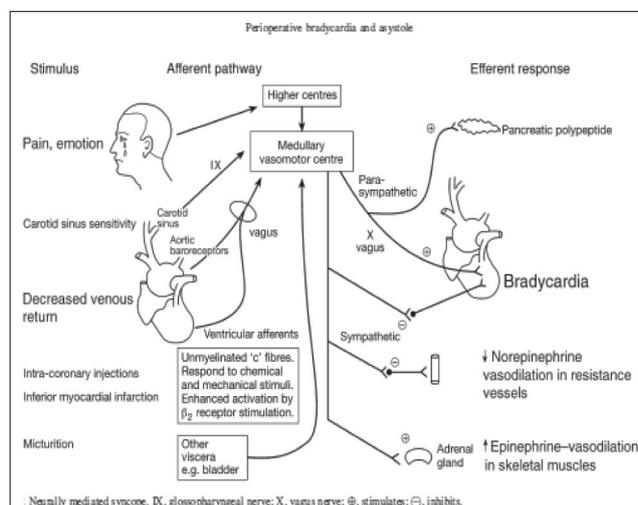
Vasovagal syncope or Neurocardiogenic syncope refers to the loss of consciousness that occurs secondary to hypotension resulting in reduced blood supply to the brain. It is the most common form of unexplained syncope (50-60%) in the outpatient setting. Bradycardia and vasodilation are the primary causes of this hypotension. Fear, pain, dehydration, alcohol consumption, anxiety, tight clothing and hot climate may be its triggering agents^{1,2}. Although it is benign, it can result in significant morbidity (falls, accidents); mortality is 5-10%. Treatment varies from drugs to pacing².

Bezold-Jarisch reflex (BJR) is a term that describes perioperative bradycardia with hypotension that result from activation of cardiac mechanoreceptors^{1,3}. The afferent limb of this reflex are the nonmyelinated, type C vagal fibers. Activation causes inhibition of sympathetic outflow coupled with bradycardia, peripheral vasodilation and hypotension^{1,3}.

Mechanism

Cardiac unmyelinated sensory fibers and non cardiac afferents namely arterial baroreceptors constitute the afferent limb of this reflex^{1,3}. These afferents enter the brain via the vagus and glossopharyngeal nerves, synapse in the nucleus tractus solitarius and the ventro-lateral medulla (Figure 1).

Fig. 1
Neurally mediated syncope.



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These cardiac unmyelinated sensory fibers are mechanically sensitive, whereas stimulation of the chemosensitive afferents occurs secondary to cardiac pathology^{1,3}.

In addition, there is evidence that endogenous opioids are important neurotransmitters in the nucleus tractus solitarius^{1,4}. Naloxone pretreatment did not stop this reflex^{1,5,6}. The delta receptors subtype may be more important than the mu receptor^{1,7}. Further studies are needed to document whether delta specific antagonists may be beneficial.

The efferent responses include increase vagal activity especially to the heart and decrease sympathetic activity resulting in bradycardia and vasodilation causing hypotension. Increased parasympathetic activity occurs not only in the heart, the gastrointestinal tract is affected which account for the nausea that accompanies syncope^{1,8}.

The vasodilation is caused by sympathetic inhibition. There is a decrease in the concentration of norepinephrine along with the sympathetic inhibition with an increase in the epinephrine concentration. The vasodilation that occurs results in a reduction of systemic vascular resistance. However, at the same time, there is evidence of cerebral vasoconstriction^{1,8}. Figure 1.

Risk Factors:

Patient Related Factors

Some patients have an increased risk of intraoperative reflex bradycardia due to enhanced cardiac vagal modulation that, at the same time, is associated with markedly increased mortality⁹⁻¹⁴. This “altered autonomic balance” is related to physiological factors, pathological factors and extrinsic factors (table 1).

Physiological factors

Age and physical fitness: Advanced age causes a decrease in vagal control of heart rate and is generally lower among women; however it results in more evident

Table 1
Risk factors

Patient related factors	<ul style="list-style-type: none"> ● Pediatrics ● Athletics ● Hypertensive ● B-blockers, calcium channel blockers, and ACEI... ● Inferior MI ● History of syncope ● Secondary hypothyroidism ● Atopic dermatitis ● Electrolytes imbalance
Anesthesia related factors	<ul style="list-style-type: none"> ● Light anesthesia ● Spinal, epidural anesthesia ● Hypercapnia, hypoxia ● Drugs (remifentanyl, propofol, dexmedetomidine, suxamethonium) ● Airway manipulation
Surgical related factors	<ul style="list-style-type: none"> ● Strabismus ● Zygomatic fracture, facial surgery ● Endoscopic sinus surgery ● Laparoscopic surgery (CO2 insufflation) ● Neurosurgery ● Abdominal surgery ● Electroconvulsive therapy ● Cervical and anal dilation

impairment of vagal function at rest^{9,10}. The decrease in vagal modulation, often attributed to increasing age, may instead be the result of a decline in fitness¹¹. Young, healthy and vagotonic patients are more frequently associated with severe bradycardic episode and cardiac arrest during neuraxial anesthesia¹⁵⁻¹⁷.

Pathological factors

Cardiac: Myocardial ischemia: Acute inferior myocardial ischemia often provokes transient bradycardia and hypotension “Bezold-Jarisch Reflex” and, has been explained by the preferential distribution of unmyelinated cardiac fibers with chemosensitive afferent vagal pathways in the inferior wall of the left ventricle^{1,3,12,13}.

Myocardial infarction: Infarct location is a major determinant in the short term prognostic implications of third degree atrio-ventricular block. Anterior infarction is associated with an adverse prognosis¹⁸.

Others:

Secondary hypothyroidism: Patients with low heart rate caused by secondary hypothyroidism are prone to intraoperative severe bradycardia if no preoperative treatment is given^{19,20}.

Atopic dermatitis: Patients with atopic dermatitis have also been linked to increase vagal modulation due to shift of autonomic balance towards parasympathetic predominance¹⁴.

Electrolyte imbalance: Atropine resistant bradycardia was also reported in cases during which there is electrolyte imbalance especially potassium disturbances²¹.

Extrinsic factors

Drugs associated with reflex perioperative bradycardia are: beta-blockers, digitalis, other cardiac glycosides, lithium, calcium antagonists, cholinesterase inhibitors, clonidine, other centrally acting alpha 2-adrenergic agonists, tricyclic antidepressant agents and phenytoin²².

Anesthesia related factors

Several anesthetic drugs administered mainly during induction of anesthesia such as propofol²³⁻²⁹, suxamethonium³⁰⁻³², opioids^{26,32-33} contribute to a remarkable decrease in heart rate and at times cardiac arrest. On the other hand, ketamine, a drug with vagolytic activity, has not been shown to improve the incidence of the oculocardiac reflex³⁵. In addition, spinal, epidural and regional anesthesia can cause severe reflex bradycardia and in some cases resulting in asystole^{36,37}, (table 1).

Drug related anesthetic factors

Propofol: Several data have shown that propofol increases the risk of bradycardia compared with other anesthetics. This bradycardia can lead to atrioventricular block, asystole and cardiac arrest²³⁻²⁵. Its incidence can be decreased by anticholinergic drugs prophylaxis²³ and increased in combination

with administration of other drugs such as opioids^{26,27}, beta blocker²⁹, suxamethonium^{31,32}, or any drug that potentiates vagal stimulation. Propofol induced bradycardia can also be evident in the presence of any risk factor such as previous syncope, light anesthesia, preoperative conduction abnormalities, and in the presence of procedures that increase risk of bradycardia such as laparoscopy^{23,38}. This bradycardia is more evident in old patients²⁸, and in children less than 2 years³⁹.

Dexmedetomidine: has been used for its sedative, anxiolytic and analgesic effects. However, this alpha 2 agonist can cause hypotension and bradycardia leading to pulseless electrical activity. This can be potentiated when the dose and rate are increased, as well as, in the presence of hypovolemia, and the use of beta adrenergic blockade^{40,41}.

Opioids: Fentanyl and other potent opioids are well known for their vagotonic effects through the inhibition of sympathetic outflow²⁶. Several reports have described heart rate slowing and sinus arrest when opioids were given alone or in combination with other drugs such as propofol^{26,27} and succinylcholine^{31,32}.

Succinylcholine: is known to cause bradycardia mainly by stimulating afferent vagal receptors. Its incidence increases by subsequent injected doses as the choline produced by its hydrolysis sensitizes patients to subsequent doses^{31,32}. In addition, administration of central vagotonic or sympatholytic drugs can exaggerate the muscarinic effects of suxamethonium^{31,32}.

Cholinesterase inhibitors: Acetylcholine esterase inhibitors produce an elevation in acetylcholine that stimulate cardiac muscarinic receptors and prolong the refractory period and conduction time at the sinoatrial (SA) and atrio-ventricular (AV) nodes causing bradycardia⁴². This can result in a decrease in cardiac output, blood pressure and sometimes cardiac arrest⁴³.

Procedures related anesthetic factors

Spinal and epidural anesthesia: Bradycardia and asystole can occur unexpectedly in neuraxial block^{36,37,44,45,47}. Several risk factors have been identified such as, low baseline heart rate less than 60 beats/min^{37,44,45}, male gender^{37,44,45}, anesthetic

level above T6^{44,45} and prolonged PR interval in the electrocardiogram⁴⁶. One of its possible mechanisms is that neuraxial anesthesia causes inhibition of the preganglionic sympathetic efferent limb of the autonomic nervous system. The resulting decreased venous return may initiate bradycardia by a spared parasympathetic nervous system⁴⁷. This vagal reflex has also been reported in thoracic epidural anesthesia⁴⁸.

Interscalene block: Sudden profound hypotension and bradycardia may occur in awake seated patients who have interscalene block^{1,49-52}. It is postulated that the combination of increased levels of circulating epinephrine combined with the sitting position and a contracted blood volume may irritate the left ventricle, leading to parasympathetic outflow that is responsible for this reflex. Patients who receive epinephrine either for the interscalene block or for injection into the surgical sites are more likely to develop bradycardia. This could be the result of the β -agonist effects of epinephrine reducing systemic vascular resistance and stimulating the myocardium¹. Beta blocker pretreatment has been shown to be effective in reflex reduction⁵³. Stellate ganglion block and intraoperative administration of intravenous fentanyl contribute to the development of this reflex⁴⁹⁻⁵².

Laryngoscopy and intubation: are potent triggers for the sympathetic and parasympathetic afferents⁵⁴. The net result of airway stimulation ranges from severe hypertension and tachycardia to severe bradycardia and arrest⁵⁴⁻⁵⁸. Although hyperdynamic response is more common to occur, vagal reflex can cause bradycardia and asystole⁵⁷⁻⁵⁸. This vagal response is potentiated by drugs such as propofol and opioids⁵⁶. Other contributing factors including prolonged laryngoscopy, preexisting bradycardia caused by medications, athletics, severe hypoxemia, and elevated intracranial pressure⁵⁹. Severe bradycardia can also be induced by suspension laryngoscopy even after safely completing intubation with direct laryngoscopy⁶⁰.

Anesthetic Depth: MAC bar (1.5-2 MAC) is the concentration of inhaled anesthetics that inhibit the autonomic reflexes. Thus, there is an inverse relation between the anesthetic depth and the occurrence of reflexes. A deep anesthetic level attenuates the oculocardiac reflex⁶¹.

Surgical factors

Reflex bradycardia may occur in a variety of procedures, from neurosurgery to obstetrical, abdominal, ophthalmic, facial and anal surgery^{1,61-71,34,35}, (table 1). It is mostly described in ocular surgeries and involves a reflex arc known as oculocardiac reflex. The afferent arm of this reflex is via the ophthalmic branch of the trigeminal nerve⁷². Asystole can occur⁶⁴. Whereas, anesthetic depth, anticholinergic premedication and retrobulbar block prevent the occurrence of this reflex^{61,35}, ketamine induction does not³⁵. However, the ophthalmic division is not the only branch of the trigeminal nerve. Stimulation of the mandibular branch or the maxillary branch of the trigeminal nerve is also responsible for the trigeminocardiac reflex and manifest clinically as oculocardiac reflex⁷³. The incidence of this reflex is 10-18% in neurosurgical procedures around the trigeminal nerve⁷⁰. Subdural empyema can trigger this reflex⁷¹. The trigeminocardiac reflex has been described also during repair of a nasal fracture⁷⁴. Carotid sinus hypersensitivity (CSH) can be triggered by positioning during head and neck surgery causing asystole⁷⁵. Besides surgical stimulation, there is a strong evidence that hypercapnea facilitates the occurrence of the oculocardiac and trigeminocardiac reflex^{69,76-77}.

Parasympathetic afferents supply numerous organs in the abdomen. Surgical related causes of bradycardia are primarily due to stimulation of parasympathetic nerve endings that initiate the reflex (table 2). This could explain the vagal response seen in cases where there is peritoneal stretching and stimulation of coeliac plexus reflex during laparotomy⁷⁸. Severe bradycardia after high flow rate CO₂ insufflation also occurs in laparoscopic surgery⁷⁹. Reflex bradycardia can occur during colonoscopy⁶⁸ and sigmoidoscopy under general anesthesia⁶⁹. Stimulation of the pelvic splanchnic nerves supplying the anal canal initiate the reflex⁶⁸⁻⁶⁹.

In late pregnancy some women suffer an acute circulatory collapse, severe enough to mimic haemorrhagic shock, in the supine position. This could be reversed by turning to the lateral recumbent position. The cause is compression of the inferior vena

cava by the gravid uterus, reducing venous return and right atrial pressure. Sudden bradycardia occurred in some cases¹.

Table 2
Surgery and related reflex

Ocular surgery	<ul style="list-style-type: none"> ● Oculocardiac reflex: - Afferent: ophthalmic branch of trigeminal nerve. - Efferent: depressor fibers of vagus nerve.
Maxillofacial surgery	<ul style="list-style-type: none"> ● Trigemino-cardiac reflex - Afferent: ophthalmic, maxillary, mandibular branches. - Efferent: depressor fibers of vagus nerve.
Laparotomy and laparoscopy	<ul style="list-style-type: none"> ● Celiac plexus stimulation
Anal, uterine surgery	<ul style="list-style-type: none"> ● Pelvic splanchnic nerve stimulation

Anesthetic Management

Preoperative management should include any history of vasovagal events, precipitating factors, drug intake and medical diseases such as cardiac^{1,3,12-14}, thyroid dysfunction^{19,20} or atopic dermatitis individuals¹⁴. Proper cardiac evaluation and consultation should be done to patients with potential cardiac events; for cardiopulmonary events causing bradycardia are more likely than other causes to be associated with cardiac arrest⁸⁰. Oral premedication with a sedative and anticholinergic should be considered^{1,81}. If one of the precipitating factors is venipuncture then topical local anesthetic cream should be applied before venipuncture⁸.

Induction of general anesthesia should avoid drugs associated with bradycardia and asystole such as propofol, fentanyl, suxamethonium and vecuronium¹. During maintenance of general anesthesia, although vasovagal syncope is not known to occur¹; reflex bradycardia can occur in response to surgical bleeding¹, oculocardiac reflex^{35,73}, anal dilation^{68,69}, laparoscopy^{38,78,79} and other surgeries (table 2). At this point, the stimulus should be removed and the problem is usually resolved⁸⁰. Also, the use of drugs which produce bradycardia like dexmedetomidine is

not recommended^{40,41}.

When regional anesthesia is performed, lateral position for insertion of the spinal or epidural is preferable to the sitting position^{1,82} at the same time, caution should be given to drug dosage, baricity and patient positioning to control cephalad spread of the anesthetic^{1,83}. Special care should be taken to hydrate the patient before the start of regional anesthesia for, preexisting hypovolemia before induction of regional anesthesia may lead to cardiovascular collapse¹. The treatment of the bradycardia during neuraxial blockade, which is associated with vasodilation and significant hypotension, is urgent correction of the venous return to prevent the occurrence of asystole^{1,84}. A special care is given to relieve the compression of the vena cava in obstetrical patients, the supine hypotensive syndrome observed in these patients can be aggravated with regional anesthesia and surgical bleeding¹.

Although ephedrine is the most logical choice of single drug to correct the changes because of its combined action on the heart and peripheral blood vessels¹, anticholinergic drugs are often the first line of treatment for slow heart rate during general anesthesia^{1,80}. Hypotension during vasovagal syncope may persist after the relief of bradycardia by atropine¹. On the other hand, sympathomimetic drugs can counteract the vasodilation present. Drugs like ephedrine, metaraminol and phenylephrine have been used^{1,80}. The direct sympathetic effect on the heart rate of ephedrine are advantageous¹, however if hypotension persists adequate doses of ephedrine, an alpha agonist might be considered¹. When bradycardia occurs and the patient is pulseless, or when asystole develops, then the cardiac arrest algorithm (pulseless arrest unshockable rhythm) should be followed with chest compressions and prompt treatment with epinephrine⁸⁰.

In summary, whenever bradycardia occurs in the perioperative period, the first step should be to withhold the stimulus if known, when vasodilation is suspected for example with neuraxial blockade, intravenous bolus fluids should be given along with a sympathomimetic drug like ephedrine. Whenever hypovolemia is not suspected the bradycardia can be treated by anticholinergic drugs like atropine. If the bradycardia is complicated by cardiac arrest then the

treatment becomes chest compressions, epinephrine and fluid resuscitation.

In conclusion, a proper preoperative history, adequate risk factor stratification, preventive measures

from premedication to avoidance of drugs that cause bradycardia and judicious patient care from positioning during regional anesthesia, involving the surgeon by stopping the insult, proper hydration and management when bradycardia occurs is warranted.

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