AUTONOMIC NEUROPATHY- PREDICTION OF COMPLICATIONS AND ITS RELEVANCE TO ANAESTHESIA

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The human internal environment is regulated in large measure by the integrated activity of the autonomic nervous system and endocrine glands. Much of the action of the body in maintaining cardio vascular, gastro intestinal and thermal homeostasis occurs through the autonomic nervous system. The components of autonomic nervous system namely the sympathetic and parasympathetic nervous system have their own functions designed and control the homeostasis. Even though sometimes it appears both of them act in an opposite way, most often they work together to maintain the body function against the challenges imposed on it. The "fight or flight" response is activated by the sympathetic system. It also causes redistribution of blood flow from the viscera to the skeletal muscle, increased cardiac function, sweating, salivation and papillary dilatation. These actions of sympathetic system are designed to help the animal to fight against the stress. So during anaesthesia and surgery, it can be expected that the sympathetic response will be high.

The parasympathetic system governs activities of the body and more closely associated with maintenance of function, such as digestive and genitourinary function. Disease status may impair ANS function to a significant extent and may thereby alter the expected responses to surgery and anaesthesia.

The most striking characteristic of the ANS is the rapidity and intensity with which it can change visceral functions, for instance, within 3-5 seconds it can increase the heart rate to twice normal and within 10-15 seconds the arterial pressure can be doubled; or at the other extreme, the BP can be decreased low enough within 4-5 seconds to cause fainting. These extremely rapid changes explain the rapidity of changes occurring during anesthesia like hypotension during spinal anaesthesia and stress response occurring during intubation.

The function of ANS- Relevant to Anaesthesia

Autonomic nervous system controls the entire visceral function of the body. The two components of ANS viz. sympathetic or parasympathetic system are responsible for either inhibition or stimulation of particular organ. The smooth muscles in the walls of the hollow viscera is generally innervated by both nor-adrenergic and cholinergic fibres and activity in one of these systems increases the intrinsic activity of the smooth muscle whereas activity in the other decreases it. However there is no uniform rule about which system stimulates and which inhibits. In case of sphincter muscle, both noradrenegic and cholinergic innervation are excitatory, but one supplies the constrictor component of the sphincter and the other dilator.

There is usually no acetylcholine in the circulating blood, and the effects of localized cholinergic discharge are generally discrete and of short duration because of the high concentration of acetylcholinesterase at cholinegic nerve endings. Whereas the catecholamine like adrenaline, NA and dopamine are found in plasma in substantial levels and have a more prolonged and widespread action.

Actions on the Heart:

The stimulation of parasympathetics cause decrease in HR, decrease in contractility and a general decrease in conductivity. There is a propensity for a sinus arrest on extreme stimulation. The coronary arteries constrict whereas the arterioles supplying skin, mucosa, skeletal muscle, brain, lungs dilate on stimulation of parasympathetics.

In contrast, the sympathetics act as a stimulator. It causes increase in heart rate, contractility and conduction velocity. The action on the arterial system is variable and depends upon the type of receptors(α or β) predominate in the particular organ system. Generally α receptors cause constriction of blood vessels and β receptors cause dilation. As the sympathetic stimulation is responsible for overcoming the stress situation, it is so designed that the blood flow to the unimportant organs can be cutoff by making them to have predominant α receptors and the organs necessary to tackle the stress situation are supplied with β receptors. That's why the blood flow to the organs like brain, heart and skeletal muscles increase, whereas the flow to skin and gut decreases. When these nerves get affected by a disease process, the ability of the organ to tackle the stress response diminishes.
The maintenance of blood flow to the cerebral circulation when the person gets up from supine position is by the immediate activation of α receptors of sympathetic system. When these nerves get affected, the person experiences dizziness when he adopts erect posture suddenly. In conditions where sympathetics are diseased or blocked as in regional anaesthesia, the ability of the individual to maintain blood pressure in postural variation is lost. So shifting the patient who is under the effect of anaesthesia has to be done carefully.

Segmental distribution of the sympathetic nerves:
The sympathetic pathways that originate in the different segments of the spinal cord are not necessarily distributed to the same part of the body as the somatic spinal nerve fibres from the same segments. Instead, the sympathetic fibres from cord segment T_1 generally pass up the sympathetic chain to the head; from T_2 into the neck; from T_3, T_4, T_5 and T_6 into the thorax; from T_7, T_8, T_9 and T_{10}, T_{11} into the abdomen; and from $T_{12}, L_1,$ and L_2 into the legs. This distribution is only approximate and overlaps greatly.

The distribution of sympathetic nerves to each organ is determined partly by the locus in the embryo from which the organ originated. For instance, the heart receives many sympathetic nerve fibres from the neck portion of the sympathetic chain because the heart originated in the neck of the embryo. Likewise, the abdominal organs receive most of their sympathetic innervation from the lower thoracic segments because most of the primitive gut originated in this area.

This wide variability in the autonomic innervation has to be kept in mind especially in planning the regional anaesthesia like spinal or segmental epidural block. The operated area may be in the lower abdomen, but the autonomic innervation is from higher up. As the majority of visceral sensation ascends up in sympathetics, a regional block should extend to block the autonomics, so that the visceral sensation is not perceived. As we know, a pull on the mesentry during a surgery done in the lower abdomen, may provoke vomiting and retching.

GIT:
The next important action of ANS is on GIT as far as Anaesthetists are concerned. The sympathetic stimulation causes decrease in the mobility and tone of stomach and intestine. The sphincters contract and the secretions of GIT get inhibited.
The parasympathetics on the other hand increase the mobility and the secretions.
Autonomic neuropathy generally results in gastroparesis and stasis of food in the stomach, which may be regurgitated during induction of anaesthesia.

The effect of ANS on other organs:
In general, most of the endodermal structures, such as the ducts of the liver, gall bladder, ureter, urinary bladder and bronchi are inhibited by sympathetic stimulation but excited by parasympathetic stimulation. Sympathetic stimulation also has multiple metabolic effects, such as release of glucose from the liver, increase in blood glucose concentration, increase in glycogenolygis in both liver and muscle, increase in skeletal muscle strength, increase in basal metabolic rate and mental activity. They are also involved in execution of the male and female sexual acts.
These action of ANS are not generally directly linked to anaesthesia, but they help in the establishment of the presence of autonomic neuropathy, so that we can take necessary actions to avoid complications.

Clinical syndromes affecting the ANS

Diabetic autonomic neuropathy: (DAN)
Diabetes is the commonest cause of autonomic neuropathy and is responsible for a significant proportion of the mortality and morbidity associated with that disease. A broad spectrum of symptoms occurs, affecting cardiovascular, gastrointestinal, uro genital, thermoregulatory ,sudomotor and pupillo motor function. Out of these, the cardio vascular and gastro intestinal involvement worry the anaesthetist the most.

Clinical features of DAN

Cardiovascular symptoms:
-   postural hypotension
-   painless myocardial infarction
-   resting tachycardia
-   loss of heart rate variation
-Respiratory:
-   unexplained respiratory arrest
-Gastro intestinal
-   Impaired oesophageal mobility
-   Gastric atomy

- Diarrehoea
- Colonic atony
- Enlarged gall bladder

-Vasomotor:
  -Loss of skin vasomotor responses
  -peripheral vascular changes
  -charcots arthropathy
  -Dependant oedema

-Sudomotor:
    Diabetic anhydrosis
    Gustatory sweating

-Pupillary abnormalities:
    Reduced resting diameter
    Delayed or absent response to light

-Urogenital:
    Bladder dysfunction
    Impotence
    Reterograde ejaculation
    Loss of testicular sensation

The hypoglycaemic unawareness was once thought to be due to autonomic neuropathy which occurred due to decreased catecholamine release with loss of warning symptoms. Recent studies however suggest a different mechanism viz: a reduced hypoglycaemic threshold which activates the counter regulatory system.

The features of DAN with anesthetic importance:

Resting Tachycardia: An increased resting heart rate has frequently been observed in diabetic patients with the progression of disease. Some patients display a fixed heart rate like that of transplanted heart, responding minimally to physiological stimuli. The initial tachycardia is due to vagal cardiac neuropathy.

Orthostatic hypotension: defined as a fall in systolic BP of 20 to 30mmHg or diastolic blood pressure of 10-15mmHg. It occurs as a consequence of efferent sympathetic vasomotor denervation causing reduced vasoconstriction of the splanchnic and other peripheral vascular beds. Patients typically present with light headedness and presyncopal symptoms. Many patients however remain asymptomatic despite significant fall in BP.

Other CVS abnormalities: includes a cardiomyopathy in patients without IHD, manifesting as impaired myocardial contractility and decreased LV diastolic filling. Silent cardiac ischaemia and prolongation of the Q-T interval have also been observed.
  Mechanisms that maintain the blood pressure on erect posture are altered and normal precapillary vasoconstriction in the foot on standing may be diminished. When healthy people stand, roughly 700ml of the blood volume may pool in the legs and splanchnic circulation with an associated 20% decrease in cardiac output. Barorecptors in the carotid sinus and aortic arch which normally detect the decrease and mediate sympathetic impulse to the heart and blood vessels are compromised by diabetic neuropathy. Systemic injury to the vasovasorum in patients with postural hypotension increases the risk of haemodynamic instability and cardiovascular collapse in the perioperative period

It has been noted that there is an increased frequency of sudden death in patients of DAN. (Diabetic Autonomic Neuropathy). Proposed etiologies have included cardio respiratory arrest caused by cardiac arrhythmias, silent cardiac ischaemia, sleep apnoea and an abnormal response to hypoxia, particularly in association with pulmonary infection, surgery and anaesthesia.

Gastro Intestinal Tract:

Gastro intestinal autonomic neuropathy results in disordered gastro intestinal motility, secretion and absorption. Autonomic dysfunction occurs throughout the GIT, producing several specific clinical syndromes.

Diabetic gastroparesis may manifest as nausea, postprandial vomiting, bloating, belching, loss of appetite and early satiety. Food residue is retained in the stomach because of an absence of or decrease in gastric peristalisis, compounded by lower intestinal dysmotility. This gastroparaesis is probably caused by vagal degeneration and is of clinical relevance because of the risk of pulmonary aspiration while induction. This may warrant an awake or rapid sequence induction.

. Diabetic diarhoea manifests as a profuse, watery, typically nocturnal diarrhoea which can last for hours or days and frequently alternate with constipation. The pathogenesis includes abnormalities in gastrointestinal motility, decreased gut transit time, α_2-adrenergic receptor mediated reduced fluid absorption, pancreatic insufficiency and abnormalities in bile salt metabolism. These episodes of diarrhoea may put the patient in risk of electrolyte abnormalities and dehydration. Short episodes may delay an elective surgery.

Other system: The involvement of other systems like sudomotor, and urogenital system may not pose any direct problems to the Anaesthesiologist even though they are most troublesome as far as the patient is concerned.

PREDICTION OF COMPLICATIONS:

Screening: The onset of symptom is usually insidious with no typical pattern in the early stages. Interpretation of these non-specific symptoms and identification of patients with asymptomatic DAN has been aided greatly by screening tests used on parasympathetic and sympathetic cardiovascular reflex. The abnormality in cardiovascular reflexes is assumed to reflect autonomic damage elsewhere and the evidence suggests that it does. These tests although indirect, are widely used because they are simple, non invasive, reproducible and give a clear distinction between normal and abnormal.

Practical bedside tests to detect DAN
There are five simple bedside cardiovascular reflex tests; out of them, first three reflect primarily cardiac parasympathetic damage, and the last two more extensive and widespread sympathetic damage. Parasympathetic damage is usually the first detectable sign of autonomic neuropathy and it is rare to find sympathetic damage alone.

1.Valsalva manoeuvre:

Physiology: The valsalva manoeuvre, a forced expiration against a closed glottis is an excellent demonstration of the effects of changes in intra thoracic pressure in heart rate and bloodpressure through an intact autonomic nervous system. With the initiation of forced expiration against a closed glottis, intra thoracic pressure rises to extremely high levels. Since this increase in intra thoracic pressure is directly transmitted to systemic blood vessels. there is a slight increase in systemic BP. Next, as the venous return reduces LV output because of sustained elevation of thoracic pressure, the BP falls.

The fall in the BP stimulates baroreceptor reflex to cause tachycardia and widespread vasoconstriction through sympathetic system. Once the closed glottis is released, intra thoracic pressure abruptly falls. As the venous return improves because of normal intra thoracic pressure and the compensatory vasoconstriction persists, the BP shoots up from the baseline. Because of the hypertensive response, HR falls to register a bradycardia.

This rise and fall of BP and HR requires the intact ANS. Any dysfunction can result in abnormal response.

VALSALVA MANEUVER IN A NORMAL PERSON

Small increase in B.P
Sustained expiration causing a fall in B.P
Overshoot of B.P on release
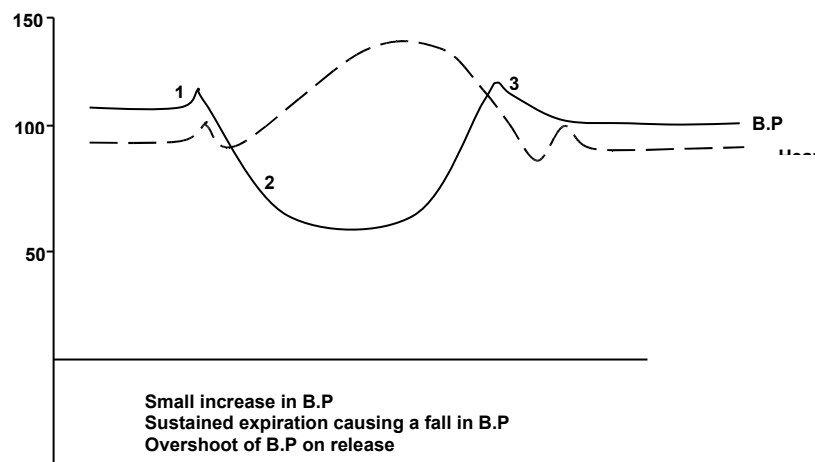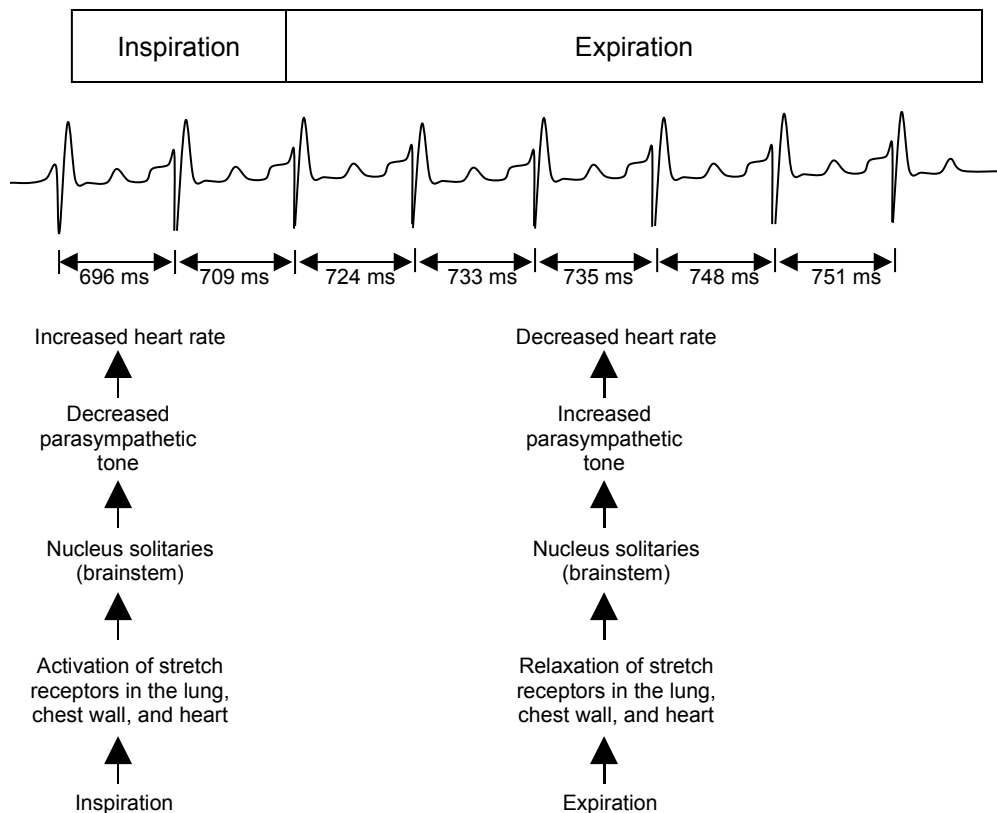
Technique: The subject sits quietly and blows into a mouthpiece at a pressure of 40mmof Hg for 15 seconds. The heart rate, measured from an ECG, normally increase during the manoeuvre, followed by a rebound bradycardia after the pressure has been released.
Result: The ratio of the longest R-R interval after the manoeuvre to the shortest while blowing is measured and the result expressed as the 'Valsalva ratio'. The result is usually expressed as the mean ratio of three successive tests.

VALSALVA MANEUVER IN A PATIENT WITH DAN

Small increase in B.P
Fall of B.P with slow regaining
No overshoot on release
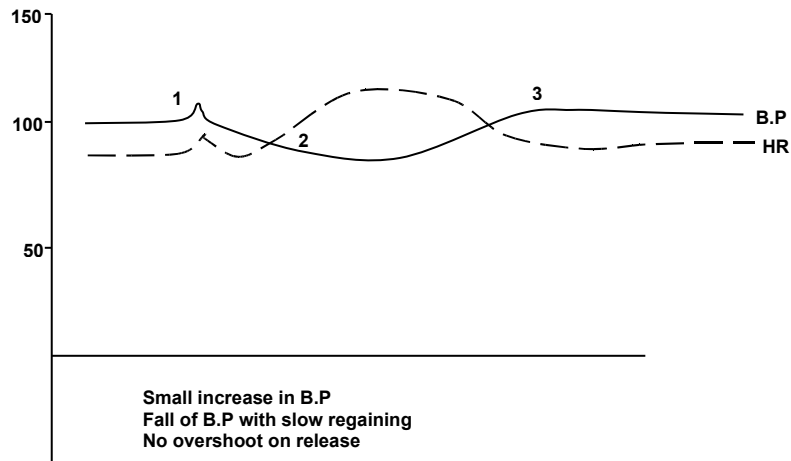
2. Heart rate response to deep breathing:

    <u>Physiology</u>: The heart rate is not constant from beat to beat in subjects with a healthy autonomic nervous system. There is a balance between sympathetic excitation and parasympathetic inhibition of the SA and AV nodes in the heart, lending to heart rate variability. Subjects exhibiting autonomic neuropathy show a reduction and eventual loss of Heart Rate Variability(HRV). The high frequency variation of heart rate which coincides with breathing is called ' Respiratory Sinus Arrythmia-RSA'.During RSA, heart rate increases during inspiration and decreases during expiration.

Technique: The subject sits quietly and breathes deeply and evenly at six breaths per minute, a rate which produces maximum variation in heart rate. Heart rate is measured by an instantaneous heart rate monitor or more simply from an ECG.

Result: Maximum and minimum heart rates during each breathing cycle are measured and the mean of the differences during three successive cycles taken to give the maximum-minimum heart rate.

3. Immediate heart rate response to standing:

Technique: The patient lies quietly on a couch and then stands unaided with an ECG continuously recording. On changing from horizontal to vertical, there is a reflex vagally mediated response whereby a rapid increase in heart rate occurs, maximal at about the 15th beat after standing and followed by slowing , maximal after the 30th beat.

Result: This is expressed as the 30:15 ratio, the ratio of the longest R-R interval around the 30th beat to the shortest around the 15th beat.

4. Blood pressure response to standing:

Technique: Blood pressure is measured with an ordinary sphygmomanometer while lying and again after standing for at least one minute. On standing there is immediate pooling of blood in the lower limbs and splanchnic bed with a fall in blood pressure but, if baroreflex function is normal, this is rapidly corrected by peripheral vasoconstriction.

Result: The difference in systolic BP is taken as the measure of postural blood pressure change.

5. Blood Pressure response to sustained handgrip:

Technique: Sustained (isometric) muscle exercise causes a heart rate-dependent increase in cardiac output and systemic BP. A simple test based on this reflex uses a handgrip dynamometer with handgrip maintained at 30% of the maximum voluntary contraction up to a maximum of five minutes with BP measured every minute.

Result: The difference between diastolic BP just before release of the handgrip and that after starting is a measure of the response.

Interpretation of results:

Table given below, gives normal, borderline and abnormal values for these five tests based on 500 patients seen over 10 years. One may not be able to perform all five tests but at least two, based on heart rate changes, should be done to detect parasympathetic damage which usually occurs earlier than sympathetic. If only two are done, heart rate response to deep breathing and heart rate response to standing are easiest as they require only an ECG. A postural fall in blood pressure is the simplest test of more widespread sympathetic damage but may be 'masked' by oedema from nephropathy or cardiac failure.

To follow the natural history of DAN (which once established is irreversible), these tests are both reproducible and quantitative. If all five are used, patients can be categorized as:
1. Normal: all five tests normal or one borderline.
2. Early involvement: one of the three heart rate tests abnormal or two borderline.
3. Definite involvement: two or more of the heart rate tests abnormal.
4. Severe involvement: two or more of the heart rate tests abnormal plus one or both blood pressure tests abnormal, or both borderline.

For follow-up an empirical scoring system can be used to assess worsening, e.g. '0' for normal, '1/2' for borderline, '1' for definitely abnormal which, if all five tests are used will give a score from 0 to 5.

	Normal	Borderline	Abnormal
Tests reflecting parasympathetic Function Heart rate response to Valsalva Manoeuvre(Valsalva ratio)	≥ 1.21	1.11-1.20	≤1.10
Heart rate (R-R interval) variation during deep breathing (maximum Heart rate)	≥ 15 beats/min	11-14 beats/min	≤10 beats/min
Immediate heart rate response to standing (30:15 ratio)	≥ 1.04	1.01-1.03	≤ 1.00
Tests reflecting sympathetic function Blood pressure response to standing (fall in systolic blood pressure)	≤ 10mmHg	11-29 mmHg	≥30 mmHg
Blood pressure response to sustained handgrip (increase in diastolic blood pressure)	≥ 16 mmHg	11-15 mmHg	≤ 10mmHg

Autonomic Changes with Aging:

Aging is associated with alteration in vascular reactivity manifesting clinically as exaggerated changes in blood pressure-hypertension or orthostatic hypotension. Orthostatic hypotension is quiet common (20% incidence) in the elderly and may result largely from diminished barorecptor responsiveness. HR response to changes in BP, Valsalva manoeuvre and the respiratory cycle are blunted with aging. So the response to the sympathetic blockade by regional anaesthesia, vascular reactivity to vasoconstrictors and myocardial sensitivity to cardiac depressant anaesthesia may be variable and

unpredictable in the elderly. One has to keep this in mind to conduct safe anaesthesia in the elderly.

Autonomic changes in spinal cord transection:

The most drastic of all alteration in the ANS that an Anaesthetist may encounter is complete spinal cord transection. Apart from sensory and motor involvement, it also result in profound changes in autonomic activity that can alter anaesthetic care. The autonomic dysfunction depends on the site, extent and timing of the lesion. Many autonomic reflexes are inhibited by supraspinal feedback that is lost after spinal cord transection. In paraplegic patients, small stimuli can evoke exaggerated sympathetic discharges.

In cervical spinal cord transection, the autonomic consequences may be many and unpredictable, but sometimes they may not be apparent as the distal portion of the spinal cord may retain some function. During an acute injury of the spinal cord, the patient may be in a phase called "Spinal Shock" where there is generalized atony with depressed reflexes. The basal supine BP is usually low. Patients with recent low spinal injuries may exhibit compensatory tachycardia from intact parts of ANS. Patients with high spinal lesion may fail to respond to hypovolemia with an increased heart rate and may exhibit bradycardia. The only intact efferent component of barorecptor reflex pathways in quadiplegic patients is the vagus. The exaggerated vagal response to cause severe bradycardia can occur during postural change, Valsalva,tracheal suction and hypoexemia. Because the sympathetic nervous system may be dysfunctional in these patients, the rennin-Angiotensin-Aldosterone system compensates for the maintenance of BP. That's why these patients may be exquisitely sensitive to ACE inhibition.

Mass reflex: If a person is stimulated below the level of spinal cord transection, it can elicit what is called an'mass reflex'. This includes a dramatic rise of BP, marked reduction in flow to the periphery and flushing and sweating in areas above lesion. Even bladder and bowel distension can elicit a mass reflex. The pathogenesis being a supersensitivity to adrenoreceptors. There is also an exaggerated response to exogenously administered catecholamines in these patients.

Although the Anaesthetist may be tempted to opt for minimal anaesthesia in a patient without sensory or motor funtion, significant visceral reflexes can be evoked. The Anaesthetist may select spinal, general anaesthesia or a vasodilator to attenuate the reflex even if pain is not appreciated.

CONCLUSION:

Smooth conduct of anesthesia needs a good understanding of functions of autonomic nervous system. Many reflex activities are affected when the autonomic nervous system gets involved in disease states. Either an absence of reflex (reflex to maintain B.P on postural variation) or presence of an abnormal reflex (mass reflex) may make the anesthetic conduct risky and dangerous. The simple bedside tests already described may help in identifying the involvement of ANS thereby avoiding complications.

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