

PHAECHROMOCYTOMA: PERIOPERATIVE MANAGEMENT

ANAESTHESIA TUTORIAL OF THE WEEK 151

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SELF ASSESSMENT

1. Regarding adrenal glands
 - a. The medulla secretes adrenaline, noradrenaline and dopamine
 - b. The rate limiting enzyme of catecholamine synthetic pathway is tyrosine hydroxylase
 - c. The adrenaline:noradrenaline ratio in a normal adrenal gland is 15:85
 - d. $\alpha 2$ receptors mediate the presynaptic feed back inhibition of NA release
2. Regarding pheochromocytomas
 - a. Pheochromocytomas account for 1% of all cases of hypertension in adults
 - b. MEN 2a constitutes medullary carcinoma of thyroid, hyperparathyroidism and pheochromocytoma
 - c. The right adrenal gland is more involved than the left
 - d. The most common sites of extra adrenal pheochromocytomas are the neck and thorax
3. With regards to pheochromocytoma
 - a. Hypertension is the most common sign
 - b. The most common symptom is sweating
 - c. It is more common in males
 - d. The perioperative mortality of elective pheochromocytoma is around 2%
4. With regards to the diagnosis of pheochromocytoma
 - a. A total catecholamine plasma concentration greater than 2000pg/ml is diagnostic
 - b. MIBG scintigraphy is used for locating extra adrenal tumours
 - c. Plasma free metanephrines are the most sensitive test
 - d. Adrenaline secreting tumours are the most common
5. With regards to the management of pheochromocytoma
 - a. The use of ephedrine is contraindicated
 - b. Suxamethonium induced fasciculation can set off a hypertensive crisis
 - c. Tachycardia is a side effect of prazosin
 - d. Phenoxybenzamine is a non selective irreversible α blocker

6. Regarding pheochromocytoma
 - a. Hormone secretion is under neurogenic control
 - b. Familial pheochromocytoma is inherited in an autosomal recessive manner
 - c. Persistent hypotension after tumour removal can be due to persistent α blockade and down regulation of α receptors
 - d. The perioperative mortality of untreated pheochromocytoma can be as much as 50%

INTRODUCTION

Pheochromocytomas are catecholamine secreting neuroendocrine tumours that arise from the chromaffin cells of the sympathoadrenal system. They are usually found in the adrenal gland but extra-adrenal pheochromocytomas, though less common, are tumours that originate in the ganglia of the sympathetic nervous system. It is a rare tumour, being responsible for less than 0.1% of all cases of hypertension. These tumours although rare are important as they present a great challenge to the anaesthetist. The condition is potentially life threatening unless diagnosed and treated. The morbidity and mortality in an unexpected emergency situation is quoted to be 50% but less than 2% in planned surgery. Clear understanding of the pathophysiology is important to manage the condition safely.

PATHOLOGY

The word pheochromocytoma in Greek means “dusky coloured tumour” referring to the colour it acquires when stained with chromium salts. Pheochromocytoma is often referred to as the ‘10% tumour’ because 10% are extra adrenal, 10 % are malignant, 10% are inherited as an autosomal dominant trait and 10% present bilaterally. Though usually found in the adrenal medulla these tumours can be found anywhere in association with the sympathetic ganglia. The organ of Zuckerkandl near the aortic bifurcation is the most common extra adrenal site. Pheochromocytomas are usually solid highly vascular tumours. Malignant spread can occur in 10% cases, with a predisposition for the liver.

Ten percent of pheochromocytomas are inherited as an autosomal dominant trait. Familial pheochromocytomas can be part of the multiple endocrine neoplastic syndromes (MEN) and can also occur in association with neuroectodermal dysplasia. Patients with MEN2a (Sipple's syndrome) have pheochromocytoma, medullary carcinoma of the thyroid and hyperparathyroidism. Almost 100% of patients with MEN2a have or will develop pheochromocytoma and they are frequently bilateral. MEN2b is characterised by medullary carcinoma thyroid, pheochromocytoma and a specific phenotype consisting of a marfanoid body habitus, mucosal neuromas and intestinal ganglioneuromas. The neuroectodermal dysplasias associated with pheochromocytomas are Von Hippel-Lindau Syndrome and Von Recklinghausen's Disease.

Pheochromocytomas are highly active tumours secreting adrenaline, noradrenaline and rarely dopamine. Most tumours predominantly secrete noradrenaline. (Normal adrenal secretion is 85% adrenaline). Familial pheochromocytomas are an exception because they secrete large amounts of adrenaline. Pheochromocytomas are not under neurogenic control but the trigger for catecholamine release is not clear although postulated mechanisms include changes in pressure or tumour blood flow. On rare occasions chromaffinomas can secrete intestinal peptides such as VIP and somatostatins.

The incidence is equal in both males and females, being most prevalent between the third and fifth decades of life.

CLINICAL FEATURES

The classical symptom complex of recurring attacks of headaches, sweating with hypertension strongly suggests a diagnosis of pheochromocytoma. In fact the occurrence of these combined symptoms is probably a more sensitive and specific indicator than any one biochemical test. Hypertension is the commonest sign and headache the commonest symptom. Hypertension is usually sustained but can less commonly be truly paroxysmal.

The overall clinical picture depends on the relative proportions of noradrenaline or adrenaline. The paroxysms of headache, palpitation and sweating are sometimes accompanied by facial pallor, anxiety and a feeling of impending doom, especially when the predominant catecholamine is adrenaline. Nausea and vomiting are features seen in dopamine secreting tumours.

The headache, anxiety and sweating accompanied by hypertension can be triggered by physiological factors such as changes in position, increased abdominal pressure (defecation, sneezing, voiding of urine and labour). Iatrogenic factors precipitating an attack include induction of anaesthesia, certain opioids (eg. pethidine), dopamine antagonists, cold medications, radiographic contrast media and drugs which inhibit catecholamine reuptake, such as tricyclic antidepressants and cocaine.

Cardiovascular system

Cardiovascular symptoms include palpitations secondary to a tachyarrhythmia. With excess secretion of noradrenaline, α adrenergic effects predominate and patients have systolic and diastolic hypertension and a reflex bradycardia. With adrenaline secreting tumours β effects predominate and patients have systolic hypertension and diastolic hypotension with a tachycardia. Acute presentation can be with ventricular dysarrhythmias, heart failure or myocardial infarction.

Untreated cases can present with pulmonary oedema or cardiomyopathy secondary to a chronic increase in vascular systemic resistance. High catecholamine levels can cause coronary vasoconstriction by their effect on α receptors leading to myocardial ischaemia. Prolonged exposure of the circulation to noradrenaline leads to constriction of arteriolar and venous circulation with a marked decrease in circulatory blood volume. This explains the raised haematocrit and apparent polycythemia. (Treatment often reveals an underlying anaemia.)

There exists a discrepancy between the degree of hypertension and blood catecholamine concentrations in patients with pheochromocytoma. Despite a 10 fold increase in circulating catecholamines, the degree of hypertension is not substantially different from patients with essential hypertension. This is explained by the fact that long term exposure to catecholamines leads to desensitisation of the vascular system, a down regulation of adrenergic receptors or changes in the receptor–effector coupling.

Central nervous system

Central nervous system manifestations include anxiety, psychosis, nervousness and tremors. Patients can present with cerebrovascular accidents either as a cerebral haemorrhage from uncontrolled hypertension or an embolic episode from a mural thrombus associated with a dilated cardiomyopathy. Uncontrolled hypertension can lead to hypertensive encephalopathy, which is characterized by an altered mental status, focal neurologic signs and symptoms, or seizures.

Metabolic disturbances

Glucose control is impaired because of the excessive glycogenolysis induced by the catecholamines, combined with an impaired release of insulin. Excessive adrenaline secretion can cause a state of hypermetabolism associated with weight loss.

Rare presentations

Bladder phaeochromocytomas can present with crisis symptoms precipitated by the voiding of urine. Phaeochromocytoma can present during pregnancy mimicking preeclampsia.

Phaeochromocytoma is an extremely rare tumour in children, but may be suspected in episodic hypertension especially in association with a family history of medullary carcinoma of the thyroid gland or phaeochromocytoma or both.

DIAGNOSIS: CLINICAL, BIOCHEMICAL, RADIOLOGICAL LOCALISATION

Clinical: symptoms and signs (as above)

Biochemical tests

Once a clinical diagnosis is made, an excessive catecholamine secretion must be demonstrated.

No single test is perfect as the measurement of plasma catecholamines reflects only that single moment when the blood sample is collected. Catecholamines are metabolised into free metanephrines within the tumour cells and are continuously released into the circulation. Tests are usually carried out to estimate either the 24 hr catecholamine level in urine and random blood concentrations, or urine metanephrines.

- Free catecholamine level in a 24 hr urine sample: best confirmatory test. High performance liquid chromatography allows accurate measurement of free adrenaline, noradrenaline and dopamine in body fluids.
- Plasma or urine catecholamine metabolites such as metanephrines (free urine catecholamine estimation has superseded this investigation)
- Plasma free metanephrines: a sensitive test for high risk patients e.g.: familial phaeochromocytoma.
- Urine metanephrine levels: the single best urine screening test
- Urinary vanillylmandelic acid (VMA) levels: the oldest and least expensive test, but nonspecific.
- Clonidine suppression test: clonidine lowers plasma catecholamines in patients without phaeochromocytoma whilst having no effect on patients with the tumour.
- Provocative testings with histamine and tyramine are not used anymore due to concerns over precipitating hypertensive crises.

Localisation

MRI and CT both provide accurate and consistent identification of the majority of phaeochromocytomas.

MIBG scan. Meta-iodobenzyl guanidine is a radiopharmaceutical agent which is an analogue of guanethedine, similar in structure to noradrenaline and hence taken up by adrenergic neurons and concentrated in catecholamine secreting tumours. MIBG is detected by scintigraphy. and such scans can help to localise recurrent tumours, metastases and tumours in unusual sites.

Other useful tests include positron emission scans and selective venous catheterisation and catecholamine sampling.

Preoperative investigations

A clinical evaluation of the cardiac status of the patient, especially if a catecholamine induced cardiomyopathy is suspected

FBC, and serial haematocrit values: normalisation of the haematocrit is indicative of the adequacy of α blockade as the intravascular volume is corrected. Occult anaemia might be revealed on correction of the vascular tone.

Hyperglycaemia is common.

ECG: ST and T changes secondary to myocardial ischemia, ventricular hypertrophy, arrhythmias. Most changes are reversible on treatment.

2D Echo: to estimate myocardial function if cardiomyopathy is suspected.

PREOPERATIVE MANAGEMENT

Early multidisciplinary involvement is recommended in order to optimise the outcome. The occasional management of pheochromocytoma is now deemed to be inappropriate and patients should be referred to an experienced team.

Perioperative optimisation includes the use of adrenergic receptor blocking drugs. The value of preoperative α blockade has not been subject to any randomised studies, but the mortality of patients undergoing surgery has dropped from 50% to less than 6% since α receptor blockade was introduced.

Preoperative adrenergic blockade achieves the following objectives:

- Lowers blood pressure,
- Increases intravascular volume,
- Reduces the chance of hypertensive crises during induction and tumour manipulation,
- Allows resensitisation of adrenergic receptors
- Reduces myocardial dysfunction in the perioperative period.

Criteria for optimal control include:

- Blood pressure readings consistently less than 160/90
- Presence of orthostatic hypotension (not less than 80/45)
- ECG should be free of ST-T changes
- No more than one premature ventricular contraction every 5 minutes
- Nasal congestion

Nonselective α blockers

Traditionally phenoxybenzamine has been used for achieving adrenergic blockade. Phenoxybenzamine is an irreversible non selective α blocker which alkylates α receptors permanently. This confers a degree of protection against blood pressure surges during tumour manipulation when catecholamine levels can rise by a factor of several hundred. (A competitive reversible blockade would be overwhelmed by this catecholamine surge!) The long half life of phenoxybenzamine confers the advantage of twice daily dosage. Disadvantages, however, include an undesirable α_2 receptor blockade which causes inhibition of presynaptic NA reuptake and therefore causes a tachycardia, and the persistent α blockade which can be responsible for resistant hypotension after tumour removal. For these reasons many clinicians choose to stop phenoxybenzamine administration 48 hrs prior to surgery. Phenoxybenzamine is started at least 14 days (sometimes even months) before surgery to increase the intravascular volume and restore myocardial dysfunction. The usual starting dose is 10 mg twice daily slowly increased up to 60 -250mg/day.

Selective α_1 blockers

Selective α_1 blockers, in comparison to phenoxybenzamine, do not block the α_2 receptors and therefore do not induce a tachycardia as a side effect. Because they are competitive blockers they are not as efficient as phenoxybenzamine in preventing surges in blood pressure during tumour manipulation when a massive release of catecholamines displaces the drug from the receptors.

Doxazosin has been successfully used instead of phenoxybenzamine and the long duration of action of doxazosin means daily dosing is sufficient. Oral dosing starts at 1 mg and is titrated up to 16 mg if required.

Prazosin, another selective α 1 blocker, is favoured by some clinicians because of its shorter half life and ease of titration to the desired end point. However this may also render it relatively ineffective in the intraoperative control of blood pressure especially if the last dose was given on the night before surgery. Profound first dose hypotension may be seen with this drug.

Beta blockers

The role of β blockers is to control the tachycardia. Tachycardia can be secondary to α 2 receptor blockade from phenoxybenzamine or it could be due to secretion of adrenaline or dopamine from the tumour. Most tumours, however, are predominantly noradrenaline secreting and β blockers are added to counteract the side effects of non selective α blockade. In a pure noradrenaline secreting tumour controlled by a selective α 1 blocker such as doxazosin, β blockers are not necessary.

The choice and timing of β blockade is important. A non selective β blocker should not be prescribed before α blockade is achieved as blockade of β 2 vasodilatory receptors leads to unopposed stimulation and worsening of hypertension. The removal of β 1 stimulation following β blockade means the heart has to cope with an increased after load with less ability to contract and this can precipitate heart failure in patients with myocardial dysfunction. This is another reason why β blockade should only be started after appropriate arteriolar dilatation has been achieved with α blockers. Selective β 1 blockers, including atenolol and bisoprolol, are useful in patients with reactive airway disease or peripheral vascular disease. Popularly used non selective β blockers include propranolol, with most patients requiring 80-120 mg/day and pure adrenaline secreting tumours may require up to 480mg/day. β blockers with additional α blocking properties are synergistic with α blockers in reducing blood pressure. Examples include labetalol (100-400mg/day) and carvedilol (12.5-50mg/day).

Other drugs

α - methylparatyrosine (Metyrosine) is an inhibitor of tyrosine hydroxylase enzyme. It can reduce catecholamine production by 50 – 80% but, unfortunately, its side effects have limited the use of this drug except in malignant and inoperable tumours

Calcium channel blockers and ACE inhibitors have been used in the preoperative control of blood pressure but clear evidence to support their use as primary agents is lacking.

INTRAOPERATIVE MANAGEMENT

Most anaesthetic drugs and techniques have been tried with success and any technique based on sound pharmacological principles and clear understanding of the pathophysiology of the condition should lead to a favourable outcome. Close communication amongst team members is important to anticipate and treat periods of instability.

The choice of surgery can be either an open (retroperitoneal or transperitoneal) approach or laparoscopic. Hospital stay is reduced and postoperative pain control is better with the latter although the incidence of catecholamine surges would appear to be the same with both procedures. Unfortunately gas insufflation during laparoscopy can produce a hypertensive crisis due to the increased intra-abdominal pressure.

The intraoperative goals are to:

- Avoid drugs or manoeuvres which produce a catecholamine surge
- Maintain cardiovascular stability with short acting drugs
- Maintain normovolaemia and haemodynamics after tumour resection

Periods of instability include:

- Induction and intubation
- Surgical incision
- Pneumoperitoneum during laparoscopic approach
- Abdominal exploration and tumour manipulation
- Ligation of venous drainage

Monitoring and vascular access

- ECG (CM5)
- Pulse oximeter
- EtCO₂
- Temperature probe
- Invasive blood pressure – Arterial line (inserted prior to induction of anaesthesia) and CVP monitoring
- Cardiac output monitoring in patients with cardiomyopathy (Pulmonary artery catheter, TOE)
- Large bore peripheral venous access
- Urinary catheter

ANAESTHETIC TECHNIQUE

Technique: General ± epidural anaesthesia have been successfully used. A low thoracic epidural blocks sensory and sympathetic discharge in the area of the surgical field, but it cannot prevent the effect of the catecholamines released during surgical manipulation of the tumour.

Factors which release catecholamines should be avoided: stress, anxiety, pain, hypoxia, hypercarbia. Consider premedication (e.g. Temazepam 20mg). Endotracheal intubation should be attempted having achieved a satisfactory depth of anaesthesia as catecholamines released from stored nerve terminals often produce an exaggerated pressor response.

Choice of agents: Avoid medications that can stimulate the sympathetic nervous system. Caution should be exercised when using histamine releasing drugs (Atracurium, Morphine). Suxamethonium can produce a catecholamine surge by virtue of muscle fasciculation and drugs such as metoclopramide, ephedrine, and chlorpromazine can also produce hypertensive responses

Drugs considered safe include: Propofol, Etomidate, Fentanyl, Alfentanil, Remifentanyl, Benzodiazepines, Vecuronium, Rocuronium, Isoflurane, Sevoflurane.

Blood glucose should be closely monitored (hypoglycaemia is common after tumour removal)

Normothermia should be maintained with the use of forced air warming devices.

Pharmacological options for intraoperative haemodynamic control

Despite preoperative α blockade almost all patients demonstrate haemodynamic disturbances during tumour manipulation. This can be a predominant hypertensive response in noradrenaline secreting tumours or a tachycardia in adrenaline secreting tumours. Vasoactive medications must be drawn up and ready to be used to control these surges. Tumour manipulation can result in blood levels of catecholamines up to 200,000 to 1,000,000pg/ml. (the pressor response to intubation in a normal patient can produce an increase to 200 to

2000pg/ml). The response to this huge surge should be anticipated and treated to avoid myocardial dysfunction. The pharmacological options are discussed below

- Phentolamine: A competitive α blocker and direct vasodilator, given as boluses of 1-5 mg for controlling surges in blood pressure. Tachyphylaxis and tachycardia are common. Phentolamine can be used on its own or in combination with labetalol.
- Sodium nitroprusside: A direct potent, vasodilator with an immediate onset and short duration of action make it a favourite of many clinicians. The toxicity of SNP is not seen at normal clinical doses.
- Glyceryl TriNitrate: A venodilator. Larger doses are generally required and the reflex tachycardia may present a problem
- Magnesium sulphate: Direct vasodilator, inhibits catecholamines from the adrenal medulla and nerve terminals, reduces sensitivity of α receptors and is a useful antiarrhythmic. A loading dose of 40-60mg/kg followed by 1-2g/hr has been described.
- Volatile anaesthetics: Increasing the depth of anaesthesia using volatile agents works at a cost of a persisting hypotension after tumour removal.
- Calcium channel blockers: Calcium ion transfer is needed for the release of catecholamines from the adrenal medulla. Nicardipine is the drug of choice from this group..
- β blockers: the selective, short acting β blocker, esmolol is useful for isolated tachyarrhythmias and tachycardia without hypertension. The rapid onset and offset of esmolol makes it the drug of choice in such situations. Labetalol: predominantly a β blocker with some α blocking effect, it is used to control blood pressure as well as tachycardias in adrenaline secreting tumours. When administered with phentolamine, the effects are synergistic.
- Antiarrhythmics: Lidocaine is useful for ventricular arrhythmias with amiodarone is an alternative.

Catecholamine withdrawal following venous ligation

A combination of factors is responsible for the refractory hypotension following ligation of the venous drainage of the tumour. A sudden drop in the catecholamine concentration, the residual α blockade from phenoxybenzamine, down regulation of adrenoceptors, suppression of the normal contralateral adrenal gland from excessive catecholamines, catecholamine induced myocardial dysfunction and hypovolaemia from blood and fluid loss are all causative factors.

A preventative measure involves volume loading before tumour ligation and fluid boluses should be tried before initiating vasoactive medications. When this is ineffective, treatment options include adrenaline, noradrenaline and phenylephrine. Vasopressin is also effective in refractory cases (0.04U/min increasing as required). One should consider glucocorticoids if hypoadrenalism is suspected or if bilateral adrenalectomy is performed.

Patients are usually extubated at the end of the procedure after ensuring haemodynamic stability. Morphine may be used for post operative analgesia in the absence of a working epidural.

POST OPERATIVE MANAGEMENT

These patients, ideally, are managed post operatively in an ITU/HDU. Anticipated problems include refractory hypotension (which might require large volumes of fluid and vasopressor therapy), and hypoglycaemia due to excess insulin release and inadequate glycogenolysis.

Consider steroid supplementation if bilateral adrenalectomy is carried out or if hypoadrenalism is suspected.

Post operative pain control depends on the type of incision. Epidural analgesia provides good post operative pain relief and may be supplemented by regular oral medications.

The majority of patients are restored to normotension although plasma catecholamine levels may still be elevated due to their slow release from the nerve terminals. Sustained hypertension after surgery could be due to residual tumour, renal ischemia or underlying essential hypertension.

Special circumstances

Pregnancy

The mortality from phaeochromocytoma in pregnancy is high. Undiagnosed cases can mimic preeclampsia. Labour can also precipitate crises and hence an elective Caesarean Section should be planned if the condition is diagnosed late in pregnancy. If diagnosed early, resection of the tumour can be considered before the second trimester with the risk of miscarriage. Phenoxybenzamine can be safely used during pregnancy.

Unexpected phaeochromocytoma

There is, unfortunately, no quick test to diagnose the condition in an acute situation. Patients can present with severe hypertension or tachyarrhythmia or even refractory hypotension following induction. Attempts to resect the tumour without prior optimisation can increase the mortality and hence the procedure should be abandoned pending investigation and adrenergic blockade. In an acute situation arteriolar dilatation is the main stay of management. Patients presenting with heart failure secondary to excess vasoconstriction present a diagnostic dilemma as vasoactive medications worsen the situation. The mortality in untreated cases undergoing anaesthesia is quoted to be around 50%.

CONCLUSION

The perioperative mortality associated with phaeochromocytoma is around 2%. A thorough grasp of the pathophysiology and pharmacology will enable one to develop an anaesthetic plan tailored to suit each patient. Good preoperative preparation and the judicious use of a combination of vasodilatory and vasoactive medications help in reducing the mortality and morbidity associated with surgery. Good communication between the surgeon, endocrinologist and anaesthetist is crucial for the safe management of these patients. Patients with this condition are best managed by a team experienced in dealing with such cases.

ANSWERS TO SELF ASSESSMENT

1. TTFT 2.FTTF 3.TFFT 4.TTTF 5.TTFT 6.FFTT

Explanation for select questions

1b True: Tyrosine hydroxylase is inhibited by Metyrosine which is used very rarely because of the side effect profile. It is used in malignant and inoperable tumours

1c False: In the normal gland the ratio is 85:15, the reverse is true for tumours where the predominant catecholamine is noradrenaline

1d True: $\alpha 2$ receptors are blocked by phenoxybenzamine resulting in tachycardia due to catecholamine release at cardiac nerve endings

2a False: Phaeochromocytoma accounts for less than 0.1% of all cases of hypertension.

2d False: Only 2% of extraadrenal phaeochromocytomas occur in the neck and thorax. The most common site of extra adrenal phaeochromocytoma is the organ of Zuckerkandl near the aortic bifurcation

3a True: 80% of patients with phaeochromocytoma are hypertensive

3b False: Headache is the most common symptom

3c False: It has an equal incidence in both sexes

4a True: 500-2000pg/ml is equivocal and <500pg/ml rules out the diagnosis

4d False: Noradrenaline secreting tumours are the commonest and dopamine secreting tumours are the rarest

5a True: Ephedrine can release stored catecholamines from nerve endings leading to a hypertensive crisis

5c False: Prazosin does not block $\alpha 2$ receptors so there is no tachycardia

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6a False: Secretion is autonomous, there are physical and iatrogenic triggers which can release catecholamines

6b False: Familial phaeochromocytoma is inherited as autosomal dominant

6c True: Hypovolaemia, myocardial dysfunction and suppressed function of normal adrenals contribute to the cause

REFERENCES AND WEBLINKS

1. Phaeochromocytoma- recent progress in its management C.Prys-Roberts. *British Journal of Anaesthesia* 85(1):44-57(2000)
2. Phaeochromocytoma: Nick Pace, Michael Buttigieg. *British Journal of Anaesthesia CEPD Reviews/Volume 3Number/ 20-23(2003)*
3. Russell T Wall. *Stoelting's Anesthesia and Co-existing disease*, fifth edition, Churchill Livingstone, Philadelphia, 2008; 388-393.
4. Anna Batchelor. *Oxford Handbook of Anaesthesia*. Oxford University Press, UK, 2006; 560-563.
5. Michael F. Roizen and Lee A. Fleisher. Anesthetic implications of concurrent diseases. Chapter 35; *Miller's Anesthesia*, Seventh Edition Churchill Livingstone, Philadelphia; 1084-1085.

Useful link:

<http://emedicine.medscape.com/article/124059-overview>