Pheochromocytoma

Pheochromocytomas are pharmacologically volatile, potentially lethal catecholamine releasing tumors of chromaffin tissue that present hemodynamic challenges to anesthesiologists.

ANESTHETIC CONSIDERATIONS:

- Pathophysiologic changes:
  - Potential for life-threatening multisystem crisis:
    - HTN, tachycardia, arrhythmias
    - MOSF
    - Temp > 40°
    - Encephalopathy
  - Relative severe volume depletion
  - End-organ dysfunction
    - Hypertrophic cardiomyopathy & IHD
    - Dilated cardiomyopathy
  - Hyperglycemia
- Associated endocrinopathies:
  - MEN 2a = hyperparathyroid, medullary thyroid CA
  - von Hippel-Lindau Syndrome
  - Neurofibromatosis type II
- Interactions w/ anesthetic drugs:
  - Desflurane increased SNS outflow induced HTN
  - Histamine releasing (morphine, meperidine, atracurium / mivacurium)
  - Droperidol induced HTN
- Post-operative complications:
  - HTN or hypotension
  - Hypoglycemia
  - Hypoadrenalism

ANESTHETIC GOALS:

- Adequate pre-operative optimization
  - Alpha-blockade if time permits
  - Volume replenishment
  - Anxiolysis and reassurance
- Stable hemodynamics throughout procedure:
  - Risk of HTN, hypotension, tachycardia and arrhythmias
  - Avoid precipitants of catecholamine release (e.g. pain, intubation, drugs etc.)

HISTORY

- Classic triad of diaphoresis, tachycardia & H/A in HTN patient
- Pheochromocytoma is essentially r/o by:
  - Absence of triad
  - Flushing
- Paroxysmal or sustained HTN hints at type of circulating catecholamines
- Orthostatic hypotension d/t chronic volume depletion
- Any indications of ischemic heart disease
- Hyperglycemia
- Polycythemia
- Associated endocrine syndromes (see above)
- Cardiac pheochromocytoma
- Can remember 5 Ps of pheochromocytoma:
  - Pressure (HTN, paroxysmal in 50%, severe and treatment resistant)
  - Perspiration (profuse)
  - Pallor (vasoconstrictive spell)
  - Pain (headache, chest pain)
  - Palpitations (associated with tremor, weight loss and fever)

PHYSICAL

- **GENERAL**
  - VITALS and orthostatic vitals (may have orthostatic hypotension)
- **CVS** – standard exam & BP q1min in stressful environment & orthostatic maneuvers with BP / HR q1min
  - Assessment of intravascular volume status
  - Examination for evidence of CHF and cardiomyopathy (displaced apex, JVD, S3 or S4)
- **GI – remember** palpating abdomen can trigger pheochromocytoma crisis

INVESTIGATIONS

- **Labs**
  - CBC for polycythemia
  - Lytes, BUN, & creatinine for renal function & volume status
  - LFTs for liver function
  - Glucose for hyperglycemia
  - Plasma free metanephrines (99% sensitivity, 89% specificity: JAMA 2002)

- 24 hour urine catecholamines, metanephrines (90% sensitivity, 98% specificity….can get false +ve with severe illness, renal failure, OSA, labetalol can interfere with the assay, TCAs, or medications containing sympathomimetics)

- **Imaging**
  - EKG changes: LVH, ischemia, prolonged QTc, abnormal R wave
  - ECHO for evidence of hypertrophic or dilated cardiomyopathy
  - CXR – cardiomegaly
  - Adrenal CT or MRI
  - MIBI scan
  - PET scan (in the US) to localize a non-adrenal mass
- **Special**
  - Endocrine consult

OPTIMIZATION

- Pre-operative anti-HTN treatment:
  - Optimum time is 10-14 days required for optimization
  - Alpha-blockade:
    - Reduction in perioperative mortality w/ institution of pre-operative alpha blockade from 40% to <3%
    - **Phenoxybenzamine** 10-20 mg PO BID, increased by 10 mg daily until controlled:
      - Noncompetitive $alpha_1$- & $alpha_2$-antagonist
      - T½ > 24 hrs, requires 2-3 weeks for maximal effect
      - Disadvantages:
        - Non-selectively inhibits pre-synaptic $alpha_2$ post-ganglionic receptors causing increased release of norepinephrine resulting in tachycardia
        - Longer T½ results in:
          - Prolonged hypotension post-tumor removal requiring larger volumes of IV fluids to maintain preload resulting in increased incidence of edema
          - Somnolence post-op due to central $alpha_2$ blockade which causes further hypotension d/t decreased SNS outflow
    - **Prazosin** / **Doxazosin** / **Terazosin**:
      - Competitive, selective $alpha_1$-antagonists
      - Prazosin 1 mg TID or QID
      - Doxazosin 1 mg QHS titrated up to 8 mg QHS
      - Terazosin 1 mg QHS titrated up to 20 mg QHS
      - Advantages:
        - No reflex tachycardia which eliminates need for beta-blockade in norepinephrine secreting tumors
        - Decreased post-op hypotension d/t shorter T½
      - Disadvantages:
        - Pre-op night dosing may wear off prior to surgical start w/ prazosin or terazosin
    - Adequate alpha-blockade indicated by HCT decrease of 5% reflecting volume re-expansion
    - If EKG evidence of myocarditis, should be on α-blocker therapy 1-6 months preoperatively
  - Beta-blockade:
    - Only institute once adequate alpha blockade or risk of unopposed alpha causing pulmonary edema & decreased CO:
      - Blockade of $beta_2$ receptors = hypertension d/t vasoconstriction
      - Blockade of $beta_1$ receptors = severe bradycardia
    - Only required if EPI secreting tumor OR phenoxybenzamine $alpha_2$ blockade
    - Even **labetalol** (a mixed beta & alpha blocker) can precipitate unopposed alpha
  - Pre-op guidelines to adequate alpha-blockade (Miller and Barash):
    - **No in hospital BP > 165/90 x 48 hours**
    - **Orthostatic hypotension BP > 80/45 (standing)**
    - **EKG free of ST-T changes x 1 week**
    - **No more than 1 PVC in 5 minutes**
  - Others:
    - **CCB** - may be useful in normotensive paroxysmal HTN pts
    - **$MgSO_4$** - recommended in refractory HTN pts esp. in pregnancy or pheochromocytoma multi-system crisis
    - **AMPT** - inhibits tyrosine conversion into catecholamines may be useful in severe refractory cases but has a high risk of adverse events
    - ACEi - NO benefit since goal is to remove pheochromocytoma, which will treat LV dysfunction
- Judicious pre-operative anxiolysis and reassurance
- Volume resuscitation

ANESTHETIC OPTIONS

- GETA is required
  - If tumor < 8 cm usually MIS approach which necessitates a GA
- No data that regional is superior to general anesthesia
- Consider adjuvant RA but this does not protect from catecholamine release from tumor

ANESTHETIC SETUP

- **Drugs**
  - Agents to treat hypotension = phenylephrine (may require very large doses d/t alpha-blockade)
  - Agents to treat hypertension = phentolamine, SNP or NTG

- Agents to control tachycardia & arrhythmia = esmolol or labetalol

- **Equipment**
  - Standard CAS + 5-lead EKG
  - PRE-INDUCTION art line
  - CVP +/- PAC +/- TEE
  - Foley
  - Temperature
  - Glucometer

MANAGEMENT OF ANESTHESIA

- **Induction**
  - Every anesthetic drug technique has been used despite concerns (see above) - just be prepared to deal w/ effects
  - High risk times during anesthetic:
    - Endotracheal intubation
    - Manipulation of tumor
    - Ligation of tumor's venous drainage
  - Anxiolysis for line placement
  - Ensure deep state of anesthesia prior to intubation & incisions
  - Avoid ketamine, ephedrine & hypoventilation
- **Maintenance**
  - Maintain deep plane of anesthesia
  - No agent / method shown to be superior
  - Avoid halothane as can sensitize the myocardium to catecholamines
  - Avoid pancuronium as it can inhibit the PSNS
  - Avoid histamine releasing agents (atracurium and morphine)
  - ?avoid desflurane as is can independently cause the release of catecholamines
  - Excellent communication with the surgeon (asking her / him to avoid manipulation or delay resection if unfavorable hemodynamics)
  - Pre-pheochromocytoma removal:
    - Be prepared to rapidly correct HTN / tachycardia / arrhythmias d/t tumor manipulation:
      - Alpha-blockers: phentolamine 1-2 mg IV boluses
      - Direct vasodilators: SNP or NTG infusion
      - Tachycardia / arrhythmias:
        - Labetalol 10 mg IV boluses
        - Lidocaine 1 mg/kg IV boluses
      - Consider $MgSO_4$ 50 mg/kg bolus followed by infusion of 2g/h
  - Bilateral adrenalectomies require steroid replacement
- **Emergence**
  - Post-pheochromocytoma removal expect **hypotension** that may require very large volumes of infusion d/t:
    - Relative hypovolemia
    - Residual alpha- / beta-blockade
    - Decreased catecholamine stores
    - Down regulation of catecholamine receptors
  - 50% may still be HTN post op if circulating catecholamines need to be cleared

DISPOSITION & MONITORING

- Post-op HDU

COMPLICATIONS

- HTN before removal
- Hypotension after removal
  - Most serious concern when tumor veins are ligated during surgery, and sudden drop in circulating catecholamines can lead to v/d
  - Also the catecholamine output of the contralateral adrenal may be suppressed from previous catecholamine excess.
  - In the hypovolemic patient, this can lead to hypotension, shock, and death
  - Ensure euvolemia
  - Phenylephrine is easy and safe to use
- Hyperglycemia before removal
- Hypoglycemia after removal
- Failure to localize additional tumors perioperatively

PATHOPHYSIOLOGY

- Pheochromocytomas = catecholamine secretion tumor of chromaffin cells:
  - 90% = adrenal medulla
    - 90% = sporadic
      - 10% are bilateral
    - 10% = familial:
      - 50% are bilateral
      - Occurs in:
        - MEN 2a: pheochromocytoma, medullary thyroid carcinoma, hyperparathyroidism
        - von Hippel-Lindau Syndrome: retinal angiomatosis, cerebellar hemangioblastomatosis, pancreatic / renal cysts, pheochromocytoma

        - NF type I: peripheral nerve NF + cafe-au-lait spots
    - 10% are malignant
  - 10% = paraganglia cells of SNS (celiac, mesenteric, renal, hypogastric, testicular, and paravertebral) & organ of Zuckerkandl
- Pathophysiology:
  - Mutation in RET proto-oncogene in the chromaffin cells causes:
    - 80%-90% release norepinephrine:
      - Sustained hypertrophic cardiomyopathy
    - 10-20% release EPI or DOPA:
      - Paroxysmal hypertension
      - Palpitations, trembling, diaphoresis & blanching
      - Feelings of DOOM
  - Massive sustained or paroxysmal catecholamine release causes:
    - Arteriolar vasoconstriction & venoconstriction
    - Severe relative hypotension that is unmasked by loss of SNS
    - Down-regulation of normal adrenal catecholamine production & peripheral catecholamine receptors
    - Hypertrophic cardiomyopathy is commonly seen in sustained hypertension individuals (resolves post-op)
    - Dilated cardiomyopathy is rare but has poorer prognosis (MOA is unclear d/t alpha or beta stimulation)
  - Hyperglycemia 2° glycogenolysis & impaired insulin secretion
  - Life-threatening pheochromocytoma multi-system crisis:
    - Hypertension & tachycardia
    - Hypotension d/t arrhythmias or infarcts
    - MOSF
    - Temp > 40°
    - Encephalopathy & cerebral hemorrhage
    - Death
    - Treatment requires prompt diagnosis, Rx, & emergent surgery to remove pheochromocytoma if Rx fail to control symptoms
- Signs & Symptoms:
  - Most common is hypertension (1 in 400-800 hypertension have pheochromocytoma) followed by H/A, palpitations & diaphoresis
  - N/V
  - Slow palpitations (baroreceptor mediated)
- Catecholamines can be released during:
  - Emotional stress
  - Exercise
  - Postural changes
  - Procedures & intubations
  - Surgical manipulation of tumor
  - Certain drugs
- History has high mortality but w/ development of rapid, titratable HD agents, mortality has become rare
- Diagnosis is based on clinical suspicion (usually sustained refractory hypertension +/- H/A) and confirmed by:
  - Serum catecholamines have best sensitivity: free norepinephrine, normetanephrine, & metanephrine
  - Urine catecholamines: metanephrine > normetanephrine VMA (sensitivities)
- Localization:
  - CT = best for adrenal = 93% sensitive
  - MRI = best for non-adrenal
  - MIBG uptake in tumor cells = 95% specificity
  - PET
- Special considerations:
  - Pregnancy:
    - Can mimic PIH
    - Treatment = alpha +/- beta blockade +/- Mg w/ tumor removal (1^{st} / 2^{nd} trimester) or C/S followed by tumor removal (3^{rd} trimester)
  - Peds = 35% have extra-renal tumors & familial w/u
  - Cardiac pheochromocytoma = very rare but highly fatal
- Altered response to anesthetic drugs:
  - Volatiles OK but theoretical risk of Des causing catecholamine release, thus Sevoflurane preferred
  - Halothane must be avoided d/t interaction w/ EPI to cause arrhythmias
  - NMB:
    - SCh: theoretical risk of stimulation of tumor by fasciculations, however has been used successfully
    - Pancuronium: implicated in hypertension in 1 patient, however has been used successfully in majority of patients
    - Avoid atracurium d/t histamine release
    - Mivacurium not discussed in literature reviews, but likely avoid d/t histamine release
    - Roc = NDMR of choice
  - Opioids:
    - Avoid meperidine & morphine d/t histamine release
  - Droperidol has been associated with severe hypertension

- Surgical approach:
  - Open
  - Laparoscopic adrenalectomy is procedure of choice:
    - Less postoperative pain

        - Shorter hospital stays
        - Fewer incisional complications
        - BUT worse intra-op HD swings
- Distinguishing between MH, thyroid storm, & pheochromocytoma crisis:
    - All may have tachycardia, hypertension, increased $ETCO_2$, & increased temp intra-op
    - Pre-op history is very useful but if not already diagnosed pre-op, won't be available to you intra-op
    - Increased $ETCO_2$ is earliest sign in MH and is less dramatic in pheochromocytoma or thyroid storm
    - MH is assoc. w/ muscle rigidity (not seen in others), more severe acidosis, increased CK & myoglobinuria
    - Hypertension is more severe in pheochromocytoma than others

REFERENCES

- Stoeling
- Prys-Roberts. Pheo-recent progress in its Mx. BJA. 2000; 85: 44-57
- Kinney et al. Periop Mx of Pheo. J Caroiothoracic & Vascular Anes. 16(3) 2002: 359-369
- James et al. Pheo Crisis - Use of MgSO4. A&A. 2004; 99:680-686.
- Previous seminars