By Adam Hollingworth

4.CVS Regulation

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Introduction

- Different levels of control of circ:
  - Local control – caters for specific organs
  - Central control – caters for whole body – putting brain first
  - Systemic Regulation by Hormones
- Generally there is a hierarchy in these control levels

Physics Reminder

$$Q = \frac{\Delta P}{R} \qquad (\text{Ohm's law})$$

Thus, for the whole circulation: $CO = \frac{(MAP - RAP)}{SVR}$

→ for a specific organ (simple): $Q_{organ} = \frac{(P_a - P_v)}{R_{organ}}$ where P_a = MAP

→ for an organ where a *Starling resistor* applies: $Q_{organ} = \frac{(P_a - \text{larger of } P_v/3^{rd} P)}{R_{organ}}$

- The different mechanisms that control the circulation (whether whole body or individual organ) will influence either ΔP or R .
- Remember factors that determine resistance (R) :

→ From Poiseuille's flow equation, resistance: $R = \frac{8 \eta L}{\pi r^4}$

η = viscosity
L = length
r = radius of tube
NB power of 4 effect…

↳ above applies for *laminar* flow in *rigid* tubes, be it blood, air, urine etc…

Local Control of CVS

- Aka autoregulation
- Autoregulation consists of:
  - Pressure autoreg:
    - ↑pressure ⇒ ↑distension of walls ⇒ ↑contraction of vasc smooth mm
      - ↳Law of Laplace – wall tension ∝ distending pressure x radius
      - ↳∴ maintenance of a specific wall tension: if pressure ↑s requires a ↓ in radius
  - Metabolic reg:
    - ↓blood flow ⇒ ↑Metabolites accumulate ⇒ ↑VD
    - ↑blood flow ⇒ ↓metabolite ⇒ ↑VC

Vasodilator Metabolites

- causes of VD:
  - ↓O2 tension:
    - ↑hypoxia inducible factor 1α (HIF 1α) ⇒ VD gene expression
  - ↓pH
  - ↑pCO2 – most pronounced in brain & skin
  - ↑temp
  - ↑k+ - causes hyperpolarization of smooth mm ⇒ VD
  - lactate
  - adenosine – in cardiac muscle only
    - ↳also inhibit's NA release

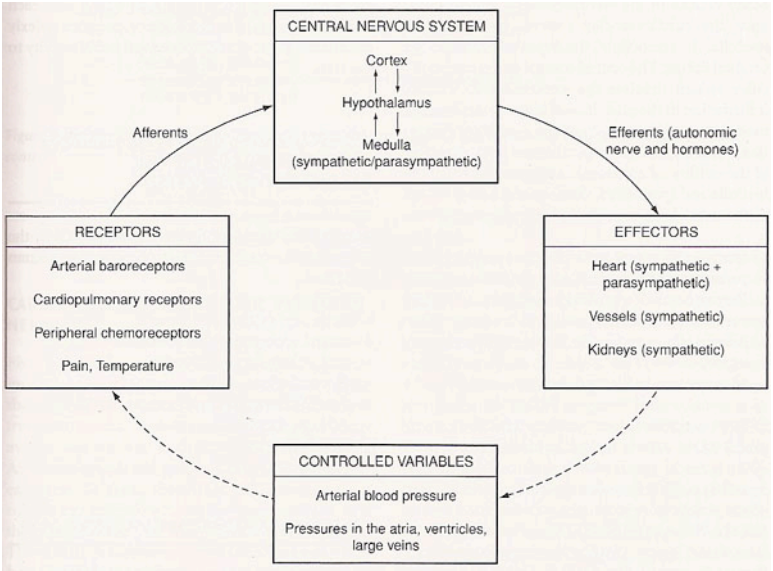
Local Vasoconstriction

- causes of VC:
  - injury to vessels– 2nd to local release of serotonin from activated platelets
    ↳veins constrict weakest as least smooth mm
  - ↓temp

Other Substances Effecting VD/VC

- independent VDs:
  - Adenosine
  - ANP
  - Histamine – via H1 & H2
  - Bradykinin
  - Vasoactive intestinal peptide (VIP)
- Independent VCs:
  - Ach
  - Substance P

Neural Control of CVS



Receptors & The Afferent Limb

- Various variables are measured:
  - Baroreceptors - Arterial bp
  - Cardiopulmonary Receptors
  - Periph chemoreceptors –temp & chemical changes
  - Others:
    - Periph nociceptors – pain
    - Stretch – lung receptors
    - Activity - mechanoreceptors

Arterial Baroreceptors

- = stretch receptors
- found in:
  - carotid sinus
    - just off origin of internal carotid in adventitia
    - carotid sinus nerve (branch of IX)
  - aortic arch

  - aortic depressor nerve (branch of X)
  - transverse aortic arch
  - in adventitia
- stretch stimulates receptors ⇒ impulse to medulla release +ve glutamate onto nucleus of the tractus solitarius (NTS).
- NTS ⇒
  - +ve Glutamate on caudal ventrolateral medulla (CVLM) ⇒ ↑PNS output
  - –ve GABA on RVLM ⇒ ↓SNS output

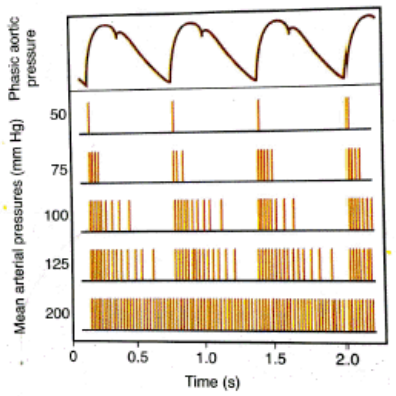
↳∴ ↑baroreceptor ⇒ ↓symp & ↑parasymp output ie ↓CO & ↓SVR ⇒ ↓bp

- baroreceptors much better at vasoC than venoC

Firing Activity

- Receptors ↑sensitivity to pulsatile pressure than constant pressure

↳drop in pulse pressure (ie narrowing) with no change in MAP ⇒ ↓s rate of receptor discharge ⇒ ↑bp & ↑hR



- MAP thresholds for firing: 60mmHg to 200mmHg
- Each baroreceptor neuron fires over a narrow pressure range but collectively cover wide range:
  - C fibres – higher threshold
  - Myelinated A fibres = lower threshold ie more sensitive to low pressures

Receptor Resetting

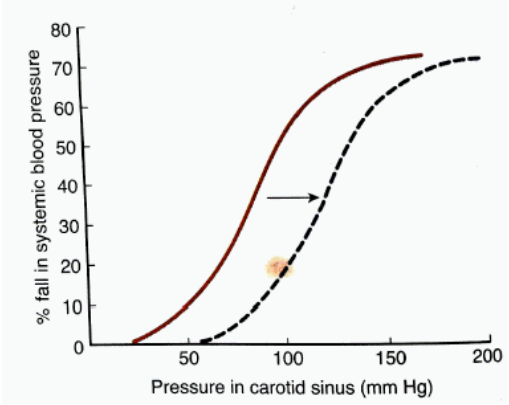
- Baroreceptor mechanism is reset in chronic HTN
- ?due to opening of K channels ⇒ return of membrane potential to baseline
- Resetting occurs rapidly in animals and is rapidly reversible

↳∴ thought baroreceptor reflex responsible for changes in HR and bp on lying/standing

↳opposite to long term regulation of bp = balance of fluid in/out ie volume regulation

↳ shows importance of renal function in bp control

- If remove baroreceptors:
  - Rapid rise in bp but mean pressure then drifts back to norm



Cardiopulmonary Receptors

- 3 main groups:
  - Veno-Atrial Stretch Receptors –
    - aka low P or volume receptors
    - Myelinated
    - vagal
  - Cardiac mechanoreceptors
    - Unmyelinated
    - Vagal & symp
  - Central Chemosensitive fibres:
    - Vagal & symp
- If stimulated as a group:
  - NET inhibitory effect: reflex brady & vasoD ⇒ ↓bp
    ↳ = Bezold Jarisch reflex – may see in Acute MI
- If stim individually == diff CVS effects

Veno-Atrial Stretch Receptors

- Located in endocardium @ junction vena cava & pulmon vein with atrium
- Two types:
  - A –
    - discharge in atrial systole ie with 'a' wave
  - B –
    - d/c in late diastole/atrial filling ie with 'v' wave
    - give info to CNS of degree of distension of atrial walls ie CVP
- stim of both receptors ⇒
  - immediate: ↑HR via ↑SNS to SAN
  - late: ↑urine volume & Na excretion ⇒ ↓bp
    ↳ via Bainbridge effect:
    - ↓ADH
    - ↓renal SNS activity ie RAAS
    - ↑atrial ANP production

↳ ∴ main function of Veno-Atrial stretch Rs = regulate cardiac size when CVP high

Cardiac Mechanoreceptors

- =unmyelinated vagal & symp receptors
- fine network endocardium of:
  - RA & LA – only some fire at height of atrial filling with insp
  - LV – fire during vent contraction
- Combined effect is ↓HR & vasoD
  ↳ similar function to arterial baroreceptors
  ↳ loss of afferent input from either art baroreceptors or cardiac mechanorecptors no sig effect on bp BUT loss of BOTH ⇒ sustained ↑bp
- vasovagal syncope:
  - ↓VR and dehydration ⇒ ↓baroreceptors ⇒ ↑symp HR & SV ⇒ vigorous vent contractions against empty ventricle ⇒ ↑activation vent baroreceptor ⇒ further ↓bp & ↓SV ⇒ syncope

Central Chemosensitive Fibres

- vagal & sympathetic
- in heart
- stim by products from ischaemic heart mm
- symp ones implicated in pain cardiac ischaemia
- convergence with somatic pathways in spinothalamic tract explains referred pain into neck/arms

Periph Chemoreceptor Reflex

- found in carotid & aortic bodies
- very important in respiration (same receptors)
- have v high rate flow
- activated by
  - ↓PaO2
  - ↑PaCO2
  - ↓pH – only in carotid bodies
  - ↓blood flow to receptors:
    - stagnant flow 2nd to ↓MAP
- result of activation:
  - resp: ↑ventilation – main
  - direct CVS effects = ↑bp & ↓HR
    - ↳ but indirect NET effect is that the ↓HR is offset by ventilatory stim ie
      - stim of insp neurons ↳ inhibits central PNS cells
      - stim of lung stretch receptors

      ↳ ⇒ ↑HR
  - Mayer waves :
    - Slow reg oscillations (every 20-40secs) in blood pressure during hypotension
    - Created as ↓blood flow ⇒ hypoxia ⇒ ↑receptor d/c ⇒ ↑bp ⇒ ↑blood flow ⇒ ↓receptor d/c and cycle

- periph chemoreceptors vital in correcting MAPs <60mmHg
  (↳ NB arterial baroreceptors don't fire <60mmHg)
- periph chemoreceptor action explains clinical response to ↓↓bp of tachypnoea & tachycardia

Other Receptors

- Many other sensations ⇒ reflex CVS responses:
  - Somatic pain → ↑bp + ↑ HR
  - Severe visceral pain→ ↓HR + ↓bp
  - Bladder distension→ ↑HR + ↑bp
  - Cold→ ↑bp
  - Threatening sight/sound→ ↑HR, ↑ contractility, ↑ SVR
  - Facial nerve stimulation with cold water→ ↓HR + ↑SVR
    ↳ = diving response - sometimes used to try terminate SVT's

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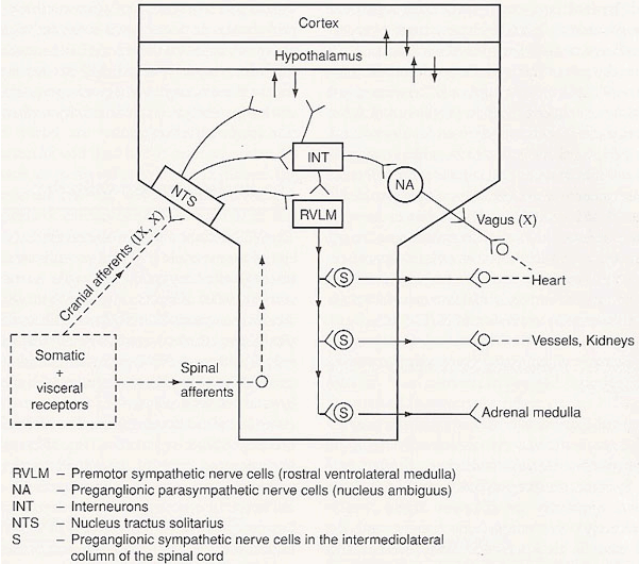
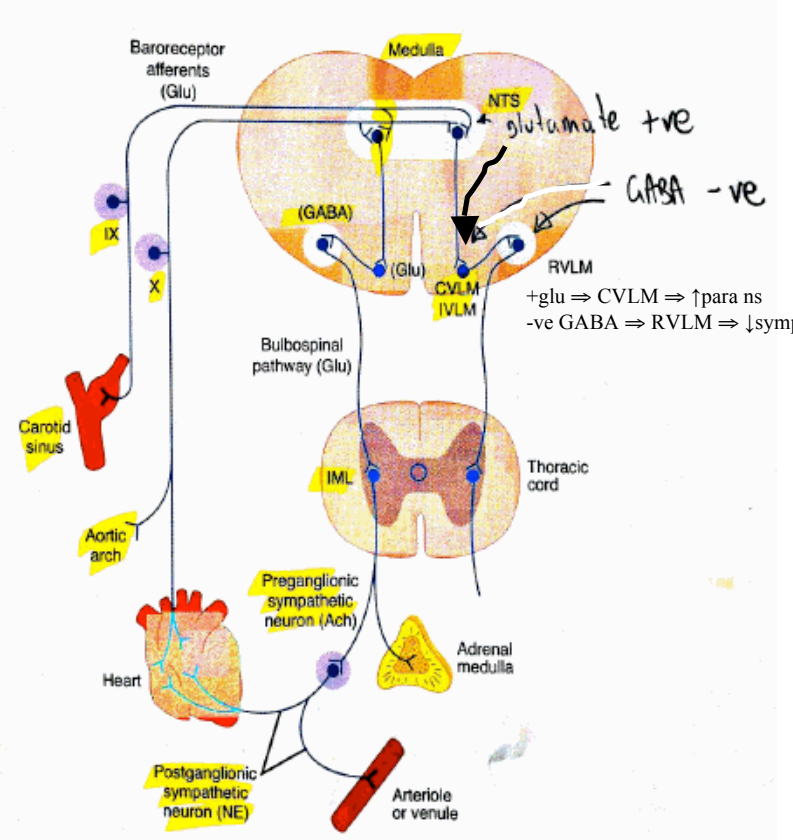
Central Integration





Central Centres

- Central neuronal axis group of cells in various locations with a lot if integrated central processing:
  - Medulla – most impt. Where 'vasomotor centre' exists
  - NTS
  - Cerebellum
  - Cerebral Cortex
  - Midbrain Periaqueductal grey (PAG)
  - Hypothalamus
  - Limbic system

  ↳ all control autonomic efferent limb
- Afferent limb fed back via NTS
- Central processing of afferent info in medulla & higher centres ⇒ modulation of medullary SNS & PNS neurons ⇒ altered balance SNS vs PNS autonomic output

Medulla & Spinal Cord Cells

- In medulla:
  - Premotor symp nerves
  - Preganglionic parasymp nerves
  - Medullary interneurons
- In spinal cord (intermediolateral column):
  - Preganglionic symp neurons

1. Central Sympathetic Output

Premotor Sympathetic Nerves

- 5 groups of cells which innervate preganglionic outflow to all symp ganglia in medulla:
  - RVLM – most impt in control of MAP aka vasomotor area
  - RVMM (rostral ventromedial medulla)

- Caudal raphe nuclei
- Paraventricular nucleus in hypothalamus
- A5 noradrenergic cell in caudal ventrlateral pons

- Rostral ventrolateral medulla (RVLM) –
  - Are +ve (excitatory) premotor fibres
  - Output to symp preganglionic cells in spinal column intermediolateral gray column (IML)
  - RVLM neurons are:
    - tonically active
    - responsible for resting SNS output to CVS
    - ↳ ∴ maintain CO & SVR at rest
  - Afferent input into RVLM arrive from:
    - Afferents from baroreceptors ⇒ -ve on RVLM
    - Carotid & aortic chemoreceptors ⇒ +ve on RVLM
    - Direct +ve stimulation by Co2, hypoxia
    - Area postrema (lacks bbb):
      - Vascular area on dorsum of medulla
      - Circulating angiotensin can directly stim RVLM ⇒ ↑MAP
    - Other input:
      - Cerebral cortex:
        - Limbic cortex via hypothalamus ⇒ ↑bp & ↑HR caused by emotions
      - Reticular formation - pain ⇒ +ve on RVLM
      - Somatic afferents – somatosympathetic reflex from exercising mm ⇒ +ve on RVLM

Sympathetic Preganglionic Cells in Spinal Cord

- Most symp preganglionic cells are in IML columns of Tx & Upper Lx segments
- Ach = neuro-transmitted at ganglia
- Have specificity for diff organ circulations
  - ↳ but symp ganglia & adrenal medullar are innervated from multiple cord segments

2. Central Parasympathetic Output

- Situated in
  - nucleus ambiguous (NA)
  - dorsal motor nucleus of vagus nerve
- stim:
  - baroreceptor via NTS ⇒ discharge in synchrony with cardiac cycle
  - direct input from medullary inspiratory neurons ⇒ ↓output of NA ⇒ tachycardia of inspiration (sinus arrhythmia)

3. Nucleus Tractus Solitarius (NTS)

- located in dorsomedial medulla
- = principle site of termination of:
  - primary CVS afferents – CN IX (carotid sinus) & X (aortic arch))
  - 2nd order afferents from other visceral & somatic receptors
- also receives input from higher centres which likely modulates output response
- = a gateway & relay station to:
  - spinal cord
  - medulla
  - hypothalamus
  - cerebral cortex
- Role:
  - If ablated ⇒ sustained HTN
  - ↑ed Afferent baroreceptor ⇒
    - stim NA ⇒ ↑PNS output to heart

- stim CVLM ⇒ inhibition of RVLM ⇒ ↓SNS output to heart, kidney, vessels & adrenal medulla

4. Cerebellum

- involved in regulation of CVS response to mm & joint activities in exercise
- input from:
  - cortex
  - brainstem via extrapyramidal tracts & vestibular system
  - ascending pathways via spinocerebellar tracts (dorsal & ventral)

5. Midbrain Periaqueductal Grey (PAG)

- roles in :
  - antinociception & reaction to threat
  - defence reaction ie ↑bp, skeletal mm vasoD & renal vasoC
- different areas of PAG have diff actions:
  - lateral ⇒ pressure response ie vasoC
  - ventrolateral ⇒ depressor effects ie vasoD
- connects with RVLM

6. Hypothalamus

- imp in general homeostasis
- discrete cell groups:
  - defense area – (short term control)
    - ant perifornical region
    - ↑HR, ↑CO, ↑bp, vasoD skeletal mm, vasoC GIT & renal vessels, rage/fear behaviour
    - inhibits the baroreflex at NTS, inhibits vagal output, stim the RVLM ⇒ ↑SNS>PNS output
  - depressor area: (short term control)
    - anterior hypothalamus
    - effects similar to baroreflex
  - supraoptic & paraventricular nuclei: (longer term control)
    - ant hypothalamus
    - produce ADH in response to:
      - stim of local osmoreceptors
      - input from art baroreflex
  - temp regulating area:
    - ant hypothalamus
    - ↑core temp ⇒ ↓vasoC outflow to skin & ↑sweating ⇒ vasoD & heat loss

7. Limbic System

- consists of:
  - ant cingulate
  - post orbital gyrus
  - hippocampus
  - amygdala
- amygdala stimulates hypothalamus defence area ⇒ fear/rage
- limbic may be responsible for playing dead behaviour in animals in danger

8. Cerebral Cortex

- role in rapid CVS changes at beginning of ex ie ↓PNS output
- connections into:
  - amygdala
  - hypothalamus
  - RVLM
  - NTS

Efferent Limb

- Pathway consists of:
  - Vagus
  - SNS
  - Hormones:
    - Adrenaline & Noradrenaline
    - ADH
    - Renin, angiotensin
    - Atrial natriuretic factor (ANF)
- Effectors:
  - Heart
  - Blood veseels
  - Kidneys
  - Thirst/water intake

Innervation of Blood Vessels

- Symph NA fibres ⇒ all vessels ⇒ VC
  ↳have background tonic activity
- Symp cholinergic fibres ⇒ skeletal muscle ⇒ VD
  ↳no tonic activity
- ∴ In most tissues VD is mediated by ↓symp NA activity
  ↳in skeletal mm active VD by symp cholinergic system

Neural Regulatory Mechanisms

- All vessels receive motor fibres from SNS except capillaries & venules
- Fibres to resistance vessels (arterioles) regulate flow & resistance (∴pressure)
- Fibres to capacitance vessels vary volume of blood stored

Output Effects

SNS & Adrenaline & NA

- Heart: ↑contractility & ↑HR ⇒ ↑CO
- Arterioles: vasoC ⇒ ↑SVR
- Veins: venoC ⇒ ↑VR ⇒ ↑CO (switch volume to art side of circuit)
- SNS:
  - renin release from juxtaglomerular apparatus (JGA) of kidney ⇒ renin-angiotensin-aldosterone activation ⇒ H20 & Salt retention
  - angiotensin 2:
    - potent vasoC:
      - direct on periph vessels
      - indirect ↑SNS via area postrema of medulla
    - stimulates thirst & ↑ADH ⇒ H20 retention ⇒ ↑MAP

Vagal

- effects limited to heart
- mainly AVN/SAN/atria

ADH

- made in hypothalamus by supra-optic & paraventricular nuclei
- stored & released from ost pituitary
- effects:
  - H20 retention
  - Arteriolar constriction

ANF

- Released from atria in response to distension/stretch

- Effects = ↑renal salt & H20 excretion (Bainbridge response)

Balance of Output

- tonic activity:
  - mild amount symp
  - larger amount parasymp

  ↳if both blocked HR ~100/min

Summary Factors Effecting HR

- In general stim which ↑HR also ↑bp except:
  - Atrial stretch receptor ⇒ ↓bp & ↑HR
  - ↑ICP ⇒ ↑bp & ↓HR
- ↑HR by:
  - ↓arterial baroreceptor activity
  - ↑atrial stretch receptor activity
  - inspiration – inhibition of nucleus ambigious ⇒ ↓PNS:SNS output
  - excitement, anger pain
  - hypoxia
  - exercise
  - thyroid hormones
  - fever
- ↓HR by:
  - ↑arterial baroreceptors
  - expiration
  - fear, grief
  - ↑ICP

Direct Effects on RVLM

Cushing Reflex

- ↑ICP ⇒ ↓blood supply to RVLM ⇒ local hypoxia and hypercapnia ⇒ ↑RVLM d/c ⇒ ↑bp ⇒ restores blood flow to medulla
- ↑ in bp ⇒ ↑baroreceptor d/c ⇒ ↓HR which masks expected ↑HR
- ↑in bp ∝ to ↑ICP

  ↳= Cushing reflex

Hypercapnia

- ↑PaCo2 ⇒
  - ↑RVLM d/c (↑HR, VC)
  - direct peripheral VD

  } ∴ periph & central actions cancel each other so no VD or VC with slow rise in bp via HR effect
- moderate ↑RR ⇒ ↓↓PaCo2 ⇒ cutaneous & cerebral VC

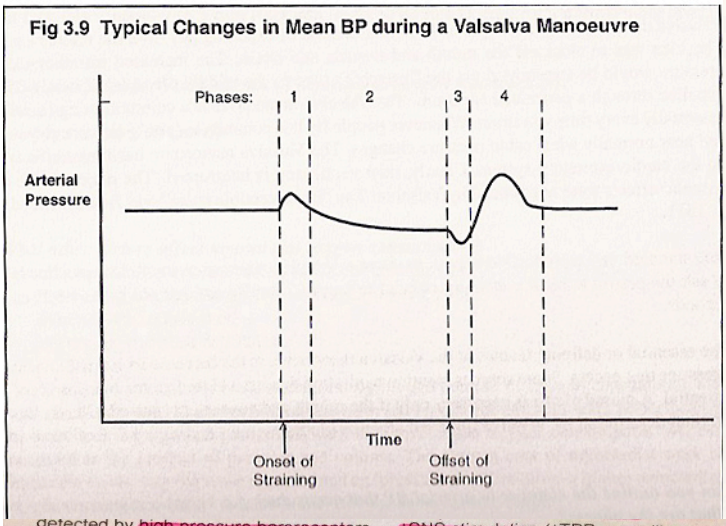
  ↳little change in bp

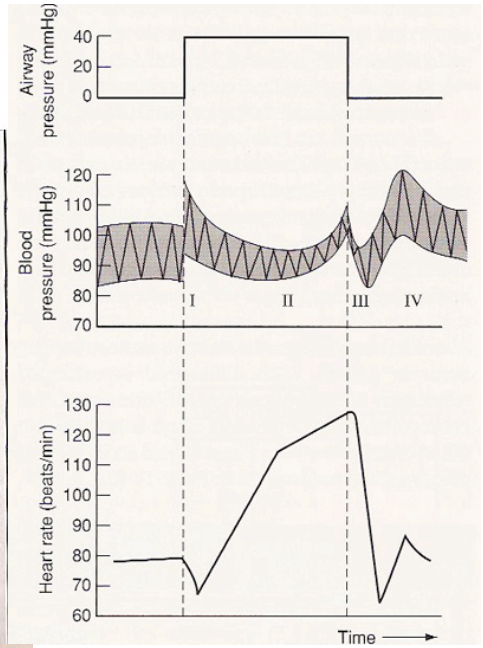
Valsalva Manoeuvre

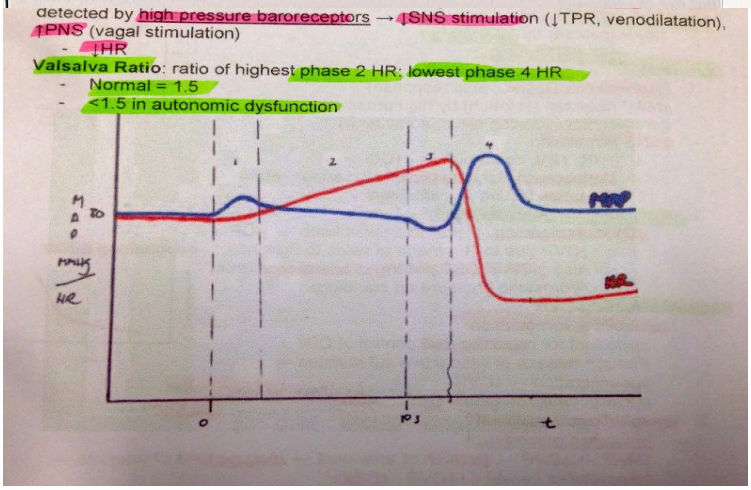
- = forced expiration against closed airway (glottis, mouth, nose, ETT – doesn't matter)
- standardised valsalva = blowing into mercury column & holding a pressure of 40mmHg for 10-15secs
- clinical use – testing baroreflex & autonomic ns:
  - autonomic function eg diabetes
  - reversal of SVT
  - Ax of cardiac murmurs:
    - ↑loudness in HOCM & MV prolapse
    - ↓loudness all other murmurs

Phases of Valsalva

- defining feature is ↑intrathoracic pressure (ITP)







- phase 1:
  - small brief ↑bp at start of straining:
    - 2 reasons:
      - ↑ITP squeezes intrapulmonary vessels ⇒ ↑VR to L heart ⇒ ↑SV & ↑CO ⇒ brief small ↑MAP
      - ↑ITP transmitted onto aorta
  - HR unchanged
- Phase 2:
  - Early phase:
    - Dropping bp: ↓VR due to ongoing ↑ITP & ↓ing CO
  - Middle phase:
    - ↑HR:
      - ↓bp is sensed by baroreceptors ⇒ ↓afferent activity ⇒ ↑SNS & ↓PNS ⇒ ↑HR & ↑contractility & ↑SVR

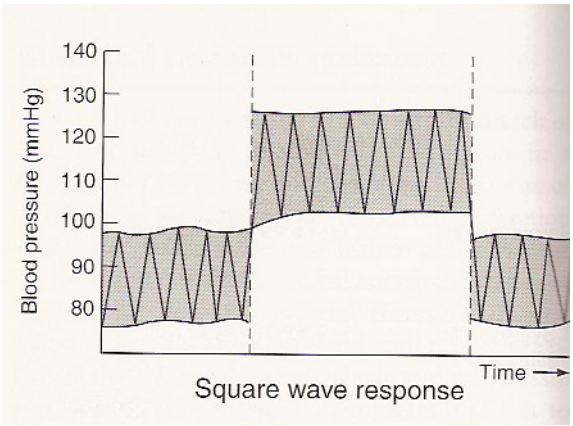
      ↳ ∴ ↑CO & ↑SVR help to counteract effect of ↓VR and defend bp
  - Late phase: In normal healthy: MAP usually rises > baseline due to alpha adrenergic activation
  - Pulse pressure narrows through phase– due to ↑SVR via SNS activity ⇒ ↑diastolic bp
- Phase 3:
  - Starts at cessation of strain
  - Small ↓bp immediately

  - = reverse of phase 1 mechanisms ie ↓squeeze on intrapulmonary vessels ⇒ ↓VR & ↓ITP on aorta
  - because of briefness of phase HR remains unchanged before starting to fall
- Phase 4:
  - Overshoot of bp:
    - Return of blood to L heart ⇒ restoration of CO
    - But now full CO pumping into vasculature still vasoC ⇒ ↑bp
  - ↓HR:
    - ↑bp sensed by baroreceptors ⇒ ↑afferent firing ⇒ ↑PNS & ↓SNS ⇒ ↓HR (to lower than baseline) & ↓SVR
- it is ↓HR of phase 4 which is exploited to attempt SVT termination

Valsalva Ratio
- = way to characterise/quantify Valsalva Response
- 2 way of calculation:
  - ECG – ratio between
    - Longest R-R interval in phase 4
    - Shortest R-R interval in phase 2
  - Ratio between max HR phase 2 & min HR phase 4
- HR changes are secondary response to valsalva via baroreflex
- Norm valsalva ratio = >1.5
- Causing of ↓ing ratio (ie baroreflex ↓responsive):
  - Ageing
  - Diabetes
  - disease

Abnormal Valsalva's

Square Wave Response
- see in heart failure
- chars:
  - elevated bp throughout phase 2
  - no reactive ↑bp in phase 4
  - HR remains constant
- Caused by ↑ed pulmon blood volume acts as reservoir that maintains LV filling during phase 2
  ↳ ie like an extension of ↑bp mechanism of phase 1



Beta Blocked Response
- HR remains constant in phase 2
- Phase 4:
  - Much smaller overshoot
  - Quicker recovery
  ↳ because of lack of HR changes

↳ if gave atropine (ie ↑HR) recovery time would lengthen

↳ ie ↑bp here solely due to ↑VR ⇒ ↑CO (without HR changes as well)

Alpha Blocked Response

- Chars:
  - Lower bp in late phase 2 – lack of ↑SVR due to no α receptor action
  - Larger early phase 2 bp drop ⇒ ↑ed cardiac, periph SNS & central SNS compensatory output which still present when come to phase 4 ⇒ ↑ed overshoot
  - ↑ed bp overshoot in phase 4
    - size of response depends on HR
  - HR responses intact
- Caused by lack of ↑SVR in phase 2: attempting to attenuate ↓bp from ↓CO

Labetalol Effect

- = mixed beta-alpha blocker
- see:
  - dramatic ↓size phase 4
    - compared with pure alpha blocker
    - by blocking ↑HR ie B blocking effects predominate over alpha effects
  - late phase 2 alpha blocking effects still occur (ie ↓bp) – but less so

↳ ∴ propranolol weak a antagonist

Autonomic Dysfunction Response

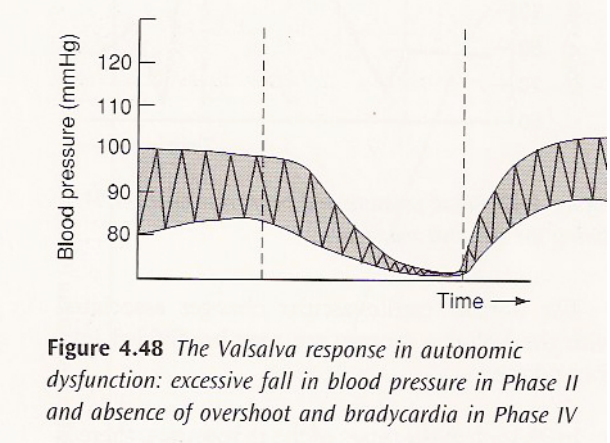


Figure 4.48 *The Valsalva response in autonomic dysfunction: excessive fall in blood pressure in Phase II and absence of overshoot and bradycardia in Phase IV*

- Excessive ↓bp in phase 2
- Absence of overshoot in phase 4
- Bradycardia in phase 4

Substances Released from Endothelium

Prostacyclin & Thromboxane A2

- prostacyclin:
  - from ECs
  - inhibit aggregation platelet
  - VD
- thromboxane :
  - from Platelets
  - ↑platelet aggregation
  - VC
- Balance thromboxane & prostacyclin shifted by aspirin
  - Aspirin irreversible inhibition of COX by acetylating a serine residue in active site
  - ECs can remake prostacyclin in hours
  - Platelets can never – thus need new platelets in circ before TxA2 rises again

↳half life ~4days

Nitric Oxide

- Aka Endothelium derived relaxation factor (EDRF)
- NO from arginine by NO synthase (NOS)
- 3 forms of NOS –
  - 1 – nervous system
  - 2 – MP & other immune cells
  - 3 – in ECs
- NOS is activated by agents which ⇒
  - ↑Ca [in] incl Ach & bradykinin
  - products of platelet activation on uninjured ECs
- NOS keeps patent vessels dilated
- if EC injured: platelet activation ⇒ marked VC
- NO formed in EC then diffuses into vasc smooth mm ⇒ activates guanylyl cyclase ⇒↑cGMP ⇒ VD
  ↳GTN acts in same way
- Other roles of NO:
  - tonic release important mediator of bp
  - vascular remodelling & angiogenesis
  - penile erection – Viagra slows breakdown of cGMP
  - impt in brain function
  - antimicrobial & cytotoxic effects in inflam cells
- NO inactivated by Hb
- VCs of vessels have there effect ↓ed by also causing NO release ⇒ less VC
  ↳eg bradykinin, VIP etc

Endothelin

- Endothlin 1 =
  - one of most potent VCs isolated
  - in ECs, brain & kidneys
- Also
  - ET-2
    - In kidney & intestine
  - ET-3
    - As ET-2 and also in blood & high amounts in brain
- endothelin-1 gene ⇒ big endothelin-1 (↳ECs create prohormone) ⇒ endothelin -1 (↳endothelin converting enzyme)
- products act mostly locally & paracrine
  ↳but some big endothelin & endothelin-1 released into blood
- receptors coupled to phospholipase C via G proteins:
  - ET_A – specific to ET-1 ⇒ VC
  - ET_B –
    - responds to all ET 1-3
    - may ⇒ VD
    - mediates developmental effects of endothelins

Regulation of Secretion

- ET-1 not stored
- Activators of gene:
  - Angiotensin II
  - Catecholamines
  - Hypoxia
  - Insulin
  - HDL
  - Shear stress

- Inhibitors of gene:
  - NO
  - ANP
  - PGE_2
  - Prostacyclin

Other Functions of Endothelins

- Brain:
  - Produced in early brain by neurons & astrocytes
  - Role in regulation of transport across bbb.
- Face – prevent severe craniofacial abnormalities
- Resp – prevent resp failure
- GI – prevent Hirchsprung megacolon
- Closure of ductus arteriosus

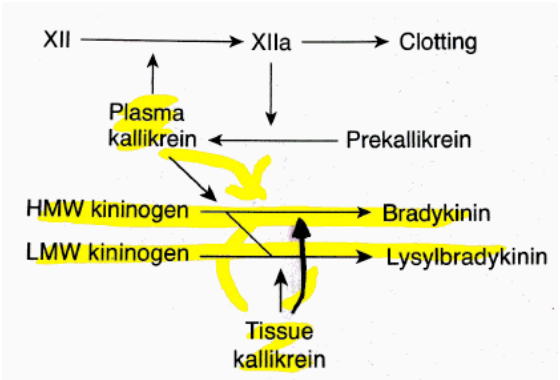
Systemic Regulation by Hormones

- Circulating VD hormones:
  - Kinins
  - VIP
  - ANP
- Circulating VC hormones:
  - Vasopressin
  - Adrenaline
  - NA
  - Angiotensin II

Kinins

- Actions resemble histamine:
  - VC of visceral smooth mm
  - VD of vasc smooth mm via NO ⇒ ↓bp
  - ↑cap permeability
  - pain
  - chemoattractant
- created during:
  - sweat & salivary secretion
  - exocrine pancreas

  ↳creates ↑blood flow to active tissue



- plasma kallikrein – circulates in inactive form
- tissue kallikrein – located on apical cells involved in across cell electrolyte cell transport
-
- bradykinin receptors – coupled to G proteins
  - B_1 – mediates pain
  - B_2 – found many tissues. Very similar to H_2 receptor

Natriuretic Hormones

- Family:
  - Atrial (ANP) - plasma
  - Brain (BNP) - plasma
  - C-type (CNP) – acts paracrine
- Hypervolaemia ⇒ release
- Action:
  - Antagonise various VC agents ⇒ ↓bp
  - ANP & BNP control fluid & electrolyte homeostasis via kidney

Circulating VCs

- Vasopressin:
  - Potent VC
  - Also causes ↓CO ∴ little change in bp
- NA & Adrenaline:
  - NA generalised VC action
  - Adrenaline – dilates vessels in skeletal mm & liver
- Angiotensin II:
  - Generalised VC
  - Created by:
    - Kidney releases renin ⇒ rennin acts on angiotensinogen ⇒ angiotensin I
    - ACE acts on angiotensin I ⇒ angiotensin II
  - Renin secretion ↑ed by
    - ↓bp
    - ↓volume of extracellular fluid
  - action of Angiotensin II:
    - ↑water intake
    - ↑aldosterone release
    - -ve feedback mech on renin