THE CIRCUITRY

• two pumps in series, one servicing the pulmonary circulation, the other the systemic
• unidirectional flow is achieved by four flap valves,

a. tricuspid / pulmonary
b. mitral / aortic

• although the cardiac output is ***pulsatile***, the peripheral blood flow is continuous due to the compliance and elastic recoil of the major arterial vessels
• blood flows rapidly through the aorta (~ 50 cm/sec) and its arterial branches
• later branches become thinner and their walls contains less elastic and more smooth muscle, until the level of the ***arterioles***, where the muscular layer predominates
• the pressure drop from the aortic root to the arterioles is small and flow velocity remains high
• the arterioles are the major resistance vessels of the arterial circuit, there being a large drop in pressure from arterioles to capillaries and a proportionate drop in flow rate
• flow becomes less pulsatile and more continuous, proportional to the inductance of the circuit
• these characteristics of the arterioles allow control of distribution of blood flow and total resistance of the vascular tree
• many capillaries arise from any given arteriole, with enormous increase in area and drop in ***resistance*** $\rightarrow$ very slow rate of flow allowing conditions for diffusion of exchangeable substances
• moving from capillaries to larger veins, area again decreases and flow velocity increases
• distribution of circulating blood volume,

a. arterial bed ~ 11%
b. capillary bed ~ 5%
c. venous bed ~ 67%
d. pulmonary bed ~ 12%
e. heart ~ 5%

• in contrast to the systemic circulation, blood in the pulmonary circulation is more equally distributed
• mean pressure of the pulmonary circulation ~ $1/7^{th}$ of systemic
• mean PA pressure **~ 15 mmHg** (25/8 mmHg), therefore is ***more*** pulsatile than that of the systemic circulation, with a S:D ratio of 3:1 vs. 3:2
• vessel walls are much thinner, with less muscle than the systemic (~ 30%)
• required to accept the entire CO at any given moment and not concerned with diverting blood flow, except in ***hypoxia***
• PA pressure consistent with lifting blood to the apex only, thereby reducing ***RV work***
• resistance drop around pulmonary circuit relatively constant, c.f. the step-wise reduction in the systemic
• pulmonary capillary pressures are ***hydrostatically dependent***
• pericapillary pressure closely approximates alveolar pressure but may be slightly less (Nunn: P ~ Atm-10 mmHg)

Blood Vessel Proportions				
	Diameter	Thickness	Area X/S	Blood Vol.
Aorta	25 mm	2 mm	4.5 cm^2	2 %
Artery	4 mm	1 mm	20 cm^2	8 %
Arteriole	30 µm	20 µm	400 cm^2	1 %
Capillary	5-7 µm	1 µm	4500 cm^2	5 %
Venule	20 µm	2 µm	4000 cm^2	54 %
Vein	5 mm	0.5 mm	40 cm^2	
Vena Cavae	30 mm	1.5 mm	18 cm^2	

ELECTRICAL ACTIVITY OF THE HEART

Transmembrane Potentials

Phases of the Myocardial Action Potential		
Phase 4	• resting potential of myocyte interior	-90 mV
Phase 0	• rapid depolarisation	+20 mV
Phase 1	• rapid repolarisation	0 to +10 mV
Phase 2	• plateau	0 to +10 mV
Phase 3	• repolarisation	-95 to 90 mV

• ***phase 0*** precedes the development of fiber tension
• completion of ***repolarisation*** coincides approximately with ***peak tension***, and the duration of contraction tends to parallel the duration of the AP
• as the frequency of contraction increases, the duration of the AP and fiber contraction decrease
• two main types of AP are observed in the mammalian heart,

1. fast responses - seen in myocardial fibers & Purkinje fibers
2. slow responses - seen in the sinoatrial & atrioventricular nodes

• ***fast responses*** may be converted to slow responses either spontaneously, or in certain pathological conditions
• a gradual shift of the resting membrane potential (V_m) from its normal level to -60 mV will produce ***slow responses*** in (a) fibers above
• the amplitude and rate of rise (dV/dt) of the AP are the major determinants of the ***velocity*** of propagation

Ionic Basis of the Resting Potential V_m

Ion	ECF [mmol]	ICF [mmol][1]	E_m
Na^+	145	10	+ 70
K^+	4	135	- 94
Ca^{++}	2	10^{-4}	+ 132

[1] ICF concentrations are estimated ***free cytosolic***, not total intracellular

- resting membrane is relatively permeable to K^+, but not Ca^{++} and Na^+
- as a result there is net diffusion of K^+ from the cell along its ***chemical*** concentration gradient
- as K^+ diffuses from the cell protein anion A^- remains behind causing the interior to become (-)'ve
- the two resulting ***forces*** determining diffusion of K^+ are,

1. chemical energy $\ln[K^+]_i - \ln[K^+]_o$
2. electrical energy $E_m.(zF/RT)$

NB: at ***equilibrium*** these opposing energies must be ***equal***, therefore by rearrangement, viz.

$$E_m = \frac{RT}{zF} \ln \frac{[K^+]_i}{[K^+]_o}$$

which for ***potassium*** reduces to,

$$E_K = -61.5 \log \frac{[K^+]_i}{[K^+]_o}$$

The Nernst Equation

- where E_K is the potassium equilibrium potential
- the measured value for E_K (-90 to -100 mV) is close to, but slightly ***more negative*** than the true V_m of myocardial cells
- therefore, there is a net driving force for diffusion of potassium out of the cell

- the driving forces for Na^+ are quite different
- E_{Na} ~ 40 to 70 mV and the extracellular concentration is much higher, therefore ***both*** electrical and chemical gradients provide a driving force for ***entry*** of Na^+ into the cell
- little Na^+ enters due to the low resting permeability to sodium, however this ion flux is the main reason the V_m is more (+)'ve than E_K
- this steady inward current (i_{Na}) would result in depolarisation of the cell except for the activity of the membrane bound Na-K-ATP'ase pump which ***maintains*** the above concentration gradients

→ ***electrogenic pump***

• the dependence of the V_m on the equilibrium potentials and relative membrane conductances of the ion species is given by the ***chord conductance equation***,

$$V_m = \frac{g_{Na} \times E_{Na}}{g_{Na} + g_K} + \frac{g_K \times E_K}{g_{Na} + g_K}$$

• strictly chloride, and ***all*** ion species, should be included in the above equation
• thus, the ***relative conductances*** of the ion species determines V_m, not the absolute conductance
→ $g_K \sim 100 \times g_{Na}$

• and the ***conductance*** (**g**) for any ion:

$$g_x = i_x / (V_m - E_x) \qquad \text{(ie., I/V or 1/R)}$$

• as $[K^+]_o$ increases, so V_m approaches E_K; as $[K^+]_o$ decreases below 5 mmol/l the effect of the Na^+ gradient becomes increasingly more important and the value of V_m deviates further from E_K
• also from with the chord conductance equation, changes in the ***ratio*** of Na^+ have little effect on the value of V_m

Ionic Basis of the Fast Response

Phase 0 Depolarisation

• the rapid depolarisation of phase 0 is almost exclusively related to the rapid increase in g_{Na} due to the opening of ***voltage gated*** membrane channels
• the movement of sodium suggests that the flux is controlled by two "gates" related to the Na-channel,

a. the ***m-gate*** - opens the channel as V_m approaches threshold
→ ***activation gate***

b. the ***h-gate*** - tends to close the gate as V_m becomes less negative
→ ***inactivation gate***

• at normal resting V_m, the h-gate is completely open and depolarisation results in a large increase in g_{Na}, proportional to opening of the m-gates
• as sodium enters the cell V_m is further decreased favoring the opening of more m-gates with a further increase in g_{Na} → ***regenerative process***
• activation of the fast channels is therefore termed ***voltage dependent***
• the maximum rate of change of V_m

$\delta V \delta t$ = 100 to 200 V/s in myocardial cells
= 500 to 1000 V/s in Purkinje fibers

• although V_m changes by ≥ 100 mV each AP, the net movement of ions is too small to alter $[Na^+]_i$

NB: the chemical forces across the membrane remain essentially constant, only the ***electrostatic*** forces alter significantly

• the inward sodium current ceases when the h-gates close and the activity of these gates is also determined by V_m
• the opening of the m-gates is very rapid ~ 0.2 ms, whereas the h-gates are much slower requiring ~ 1.0 ms
• the closure of the h-gates soon after the opening of the m-gates accounts for the rapid repolarisation ***phase 1*** of the action potential and the return of g_{Na} to its resting value
• B&L states there is an additional K^+ current (i_{to}) at this stage
• the h-gates remain closed until the cell is partially repolarised during ***phase 3***
• during this period the cell is ***absolutely refractory*** to further excitation
• this mechanism prevents the sustained, tetanic contraction seen in skeletal muscle
• at less negative, but still sub-threshold levels of V_m, the h-gates are partially closed and the resultant increase in g_{Na} is less
• the overall change in ionic conductance of the membrane at any given moment reflects the number of channels open at that time
• each channel allowing ~ 1.5 pA of current to flow
• individual channels open and close in a ***quasirandom*** fashion, the overall membrane conductance being the statistical probability that a given number of channels will be open or closed
• the temporal characteristics of the AP represent the time course of the increasing probability that specific channels will be open or closed, rather than the kinetic characteristics of the activation/deactivation of single channels

▪ ***Phase 2 The Plateau***

• the generation of the plateau is due to the entry of Ca^{++}, but also Na^+, through slow channels

→ the ***slow inward current,*** i_{SI}

• the slow channels conducting Na^+ are totally separate from those of phase 0
• the fast channels may be blocked by tetrodotoxin, or saxitoxin, whereas the slow channels are blocked by manganese ions (Mn^{++}) or verapamil
• these later agents preventing the movement of Ca^{++} into the cell
• slow channels are activated when V_m reaches threshold of -30 to -40 mV
• opening of these channels increases g_{Ca} and begins shortly after the upstroke of the AP
• calcium enters the cell → ***excitation contraction coupling***
• thus, drugs that impede slow channel conductance decrease the strength of myocardial contraction

• during the plateau, the $[K^+]$ gradient is virtually the same as phase 4, however V_m ~ 0 mV and the chemical force is dominant driving K^+ out of the cell by diffusion
• this ion flux would tend to repolarise the cell, terminating the plateau
• however, during phase 2 the membrane g_K is ***decreased*** in the outward direction

NB: this unidirectional decrease in g_K is termed ***anomalous (inward) rectification***

• the decreased outward flux of K^+ tends to balance the i_{SI} and maintains the plateau with V_m at around 0 mV

NB: increasing concentrations of slow channel blockers thus lead to
a ***less*** (+)'ve plateau & a ***shorter*** duration of the AP

- ***Phase 3 Repolarisation***

• depends on two processes,

1. an increase in outward g_K
2. inactivation of i_{SI}

• the increase in g_K is mediated partly by the increased $[Ca^{++}]_i$
• following this the outward K^+ flux exceeds the i_{SI} and the cell interior becomes more negative, further increasing g_K accelerating the process
• hence, rapid repolarisation is a ***regenerative process***, as is the inward Na^+ current in phase 0

NB: the excess Na^+ that enters the cell during phases 0 and 2 is pumped in exchange for the K^+ that exits the cell during phases 2 and 3, by the membrane Na-K-ATPase

Ionic Basis of the Slow Response

• in the slow response,

1. ***phase 0*** rapid depolarisation is ***absent***
2. the ***plateau*** phase accounts for the entire AP

• if fast Na-channels are blocked (tetrodotoxin) then slow responses are generated
• slow responses are usually found in the SA and AV nodes
• there depolarisation is achieved by the entry of Ca^{++} and Na^+ through ***slow channels***
• in myocardial fibers a gradual shift of V_m to -60 mV will convert fast to slow responses
• the normal resting V_m of nodal cells is around this level, resulting in fast Na-channels being blocked by h-gates
• at less negative, but still sub-threshold V_m's, the h-gates are partially closed and the resultant increase in g_{Na} is less

Conduction in Cardiac Fibres

• fluids in contact with internal and external surfaces of the membrane are solutions of electrolytes which are good conductors
• as one region depolarises, current will flow from the adjacent region of the membrane resulting in its depolarisation, and so on
• current is actually carried by the movement of cations in one direction and the movement of anions in the other

■ *Conduction of the Fast Response*

• fast Na-channels are activated when the V_m is raised to **-70 mV**
• these depolarise the cell membrane rapidly, producing a ***current sink*** and a boundary of depolarisation, which advances along the membrane
• the ***conduction velocity*** along the fiber is determined by the following during ***phase 0***,

a. the absolute amplitude of the AP
b. the rate of change of V_m → $\delta V_m/\delta t$

• the amplitude between the fully depolarised and polarised portions of the cell membrane determines the size of local current flow and, hence, the distance at which membrane will be brought to threshold and the rate of advance of the depolarisation front
• the ***resting membrane potential*** is an important determinant of conduction velocity, as it determines both the amplitude of the AP and the rate of rise $\delta V/\delta t$
• this potential may be altered,

a. by variations in $[K^+]_o$
b. in cardiac fibers with automaticity, V_m decreases in phase 4
c. during premature contraction, repolarisation may be incomplete
   → the less negative the V_m, the lower the velocity of conduction

• this effect is due to the inactivation of Na-channels by the ***voltage dependent h-gates***
• when depolarisation is more gradual in onset, some Na-channels are blocked before depolarisation is complete
• the percent of fast channels inactivated is approximately,

1. ~ 50% at V_m = **-70 mV**
2. ~ 100% at V_m = **-50 mV**

- ***Conduction of the Slow Response***

• the threshold potential is ~ -45 to -35 mV, and the conduction velocity is correspondingly slower
• the fast response is conducted at ~ 0.3 to 1.0 m/s in myocardial cells and 1.0 to 4.0 m/s in Purkinje fibers
• the slow response is conducted at ~ 0.02 to 0.1 m/s for SA and AV nodal tissue
• fast responses are conducted easily in antegrade and retrograde directions

NB: the ***slow response*** may be conducted at a far greater velocity in one direction, or may be conducted only in one direction,

→ allows ***unidirectional block***, and therefore ***reentry***

Cardiac Excitability

- ***Fast Response***

• once the fast response has been initiated the cell will remain inexcitable until about the middle of phase 3 → ***effective refractory period***
• this lasts from the beginning of phase 0 until the point in phase3 when V_m reaches -50 mV
• ie. when many of the h and m-gates have been reset
• the cell is not fully excitable, however, until the normal resting potential has been reached
• when excited prior to this, the resulting AP is of lower amplitude, proportional to the V_m
→ ***relative refractory period***
• by the end of phase 3 all of the gates have been reset and no alteration of excitability occurs

- ***Slow Response***

• the ***effective refractory period*** of the slow response often extends ***beyond*** the end of phase 3
• during the ***relative refractory period***, excitability progressively increases despite a ***constant*** $\mathbf{V_m}$
• the time required for full recovery of excitability is much slower than the fast response and may involve several seconds, c.f., several tenths of a second for the fast response
• until full excitability is achieved, conduction velocity varies with excitability
• even when slow responses recur at relatively low repetition rates, the fiber may be able to conduct only a fraction of the incoming impulses

- ***Effects of Cycle Length***

• there is a direct relation between cycle length and action potential duration; ascribable to the relationship between $[Ca^{++}]_i$ and potassium conductance (g_K)

NB: as the cycle length is diminished with increasing frequency, the relative proportion of time spent in phase 2 increases → the mass of Ca^{++} entering the cell is increased and g_K increases, terminating phase 2 earlier ***decreasing*** the APD

Nature of Excitation of the Heart

• the properties of ***automaticity*** and ***rhythmicity*** are intrinsic to cardiac tissue
• at least some cells in the walls of all four cardiac chambers are capable of initiating AP's
• these probably reside in the nodal tissue or the specialised conducting tissue of the heart
• the sinoatrial node forms the natural pacemaker of the heart; actually 2 or 3 sites, within 1-2 cm of the SA node, serve along with the node to form an ***atrial pacemaker complex***
• ***ectopic*** pacemakers may arise when,

1. their own rhythmicity becomes enhanced
2. the rhythmicity of higher order pacemakers becomes depressed
3. the conduction pathways between the these two are blocked

• when the SA node and adjacent tissue is removed, the AV node usually displays the next highest order of activity
• the Purkinje fibers in the ventricles also posses automaticity but characteristically fire at very slow rates → ***idioventricular rhythms***
• frequently only at rates of 30-40 bpm

▪ *Sinoatrial Node*

• in humans is 15 x 5 x 2 mm and lies in the ***terminal sulcus*** on the posterior aspect of the heart, where the superior vena cava joins the right atrium
• contains two principal types of cells,

1. small, round cells which have few organelles and myofibrils
   - probably the pacemaking cells
2. slender, long cells, intermediate between the former and ordinary myocardial cells
   - form conducting paths to the nodal margins

• fast Na-channels do exist in nodal tissue, however they are far more sparse and ordinarily inactivated by the h-gates as V_m is around -65 mV

1. the resting V_m of nodal cells is less
2. the upstroke of the AP (phase 0) has a slower rise time
3. a plateau is absent
4. repolarisation is more gradual → ***slow response*** (B&L 2-17)

• under ordinary conditions, tetrodotoxin has ***no effect*** on the nodal AP
• the most distinctive feature, c.f. other fibers, is the slow depolarisation of the membrane during ***phase 4*** → ***pacemaker potential***
• the frequency of discharge may be varied by either,

1. the rate of the depolarisation during phase 4
2. the threshold potential
3. the resting potential, V_m

• normally the frequency of depolarisation is governed by activity of both arms of the autonomic nervous system, alterations in the frequency of discharge being produced by,

a. SNS (***NA***) → ↑ phase 4 depolarisation
   i. ↑ rate of decrease of g_K during phase 4
   ii. ↑ g_{Ca}

b. PNS (***ACh***) → ↓ phase 4 depolarisation
   ↑ negativity of V_m
   i. ↑ g_K via a special set of K-channels → membrane ***hyperpolarisation***
   ii. ↓ g_{Ca}

NB: strong vagal stimulation may abolish spontaneous discharge for some time

• vagal stimulation frequently evokes ***pacemaker shift***, where the true pacemaker cells are inhibited more than other regions and latent pacemakers within the node or pacemaker complex become dominant

■ ***Ionic Basis of Automaticity***

• in the pacemaker cells of the SA node, the rate of depolarisation during ***phase 4*** is ascribable to at least three separate currents

1. i_f → slow inward Na^+ current induced by hyperpolarisation
   • activated at the end of phase 3 & early phase 4, as V_m becomes < -50mV
   • the lower V_m becomes, the greater the activation

2. i_{SI} → slow inward current during phase 2, Ca^{++} & Na^+
   • activated toward the end of phase 4, as V_m > -55mV
   • accelerates depolarisation and → AP
   • a decrease in $[Ca^{++}]_{ECF}$, or the addition of a Ca-channel blocking drug will decrease both the amplitude of the AP and the rate of phase 4 depolarisation
   • the progressive diastolic depolarisation of the membrane mediated by these two currents is opposed by the third,

3. i_{K1} → slow outward current of K^+, variably active in all phases
   • tends to repolarise the cell but progressively ***decreases*** throughout phase 4, thereby leading to a dominance of i_{SI} and i_f depolarising the cell

• similar mechanisms apply in the ***AV node***, and probably in the automatic cells of the ***His-Purkinje system***, except that in the later the slow inward current i_{SI} is not involved → i_f and i_K determining depolarisation

• the adrenergic agonists increase all three currents in SA nodal automaticity, however the increased slope of phase 4 indicates i_f and i_{SI} must predominate
• the hyperpolarisation caused by ACh is achieved by an increase in g_K, mediated by specific ion channels that are controlled by cholinergic receptors, rather than those responsible for i_{K1}

▪ ***Overdrive Suppression***

• the automaticity of the pacemaker cells becomes depressed after a period of excitation at high frequency → ***overdrive suppression***
• the firing of the SA node tends to suppress the activity of lower order pacemakers
• if an ectopic focus in the atria established a rate of 150 bpm for several minutes, then suddenly stopped, the SA node would remain quiescent briefly due to overdrive suppression
• the interval from overdrive to recovery is termed the ***sinus node recovery time***, and in some patients is markedly prolonged and may lead to a period of asystole → ***sick sinus syndrome***
• the exact mechanism is uncertain
• postulated that under conditions of overdrive, the Na^+ pump becomes more active, extruding more Na^+ than K^+ entering the cell → ***hyperpolarisation***
• further, when overdrive ceases, the activity of the Na^+ pump remains elevated for some time
→ decreasing automaticity

▪ ***Atrial Conduction***

• depolarisation spreads radially from the edge of the SA node throughout the right atrium, with a conduction velocity of **~ 1 m/sec**
• the ***anterior interatrial myocardial band*** carries impulses directly from the SA node to the LA
• three internodal pathways have been described,

1. the anterior internodal tract of Bachman
2. the middle internodal tract of Wenckebach
3. the posterior internodal tract of Thorel

• these may be the principal routes of conduction from the SA node to the AV node

▪ ***Atrioventricular Conduction***

• the AV node is ~ 22 x 10 x 3 mm, situated posteriorly on the right side of the interatrial septum, near the ostium of the coronary sinus
• contains the two same cell types as the SA node, however the small round cells are more sparse and the elongated cells predominate
• the node may be divided into three functional regions,

a. A-N Region → transitional zone between the atrium and AV node proper
b. N Region → the midportion of the AV node
c. N-H Region → zone in which nodal fibers merge with the bundle of His

• normally, the AV node and His bundle are the only conduction pathways from the atria to the ventricles
• the ***A-N region*** is responsible for the principal delay in passage through the node

NB: the conduction velocity (v_c), is actually least in the N region,
however due to the greater path length of the A-N region, most delay occurs here
→ the ***P-R interval*** of the ECG

• in the ***N region***, AP's display many of the characteristics of the slow response,

1. V_m ~ -60 mV
2. $\delta V/\delta t$ ~ 5 V/sec
3. v_c ~ 0.05 m/sec
4. tetrodotoxin has no effect
5. the AP amplitude and duration are depressed by slow channel blockers

• the characteristics in the other two regions are intermediate between the N region and the relative adjacent tissues, atrial and ventricular
• the relative refractory period of the N region extends well beyond phase 3 and is said to be ***time dependent***, in contrast to the normal ***voltage dependent*** process
• as the repetition rate of atrial depolarisations is increased , conduction through the AV junction is prolonged, predominantly in the N region
• if the atria are depolarised at a high frequency, then only a fraction of the impulses will be transmitted to the ventricles → ***concealed conduction***
• this protects the ventricles from an excessively rapid rate

NB: retrograde conduction can occur through the AV node, however the v_c is dramatically ***slower*** and impulses are blocked at lower repetition rates in the retrograde, c.f. the antegrade direction

→ the AV node is therefore a common site of ***reentry***

• moderate vagal activity usually prolongs the A-V conduction time
• stronger vagal stimulation may result in complete AV block
• the SNS on the other hand has a facilitatory action

Ventricular Conduction

• the bundle of His passes ***subendocardially*** down the ***right*** side of the interventricular septum for ~ 12 mm, then divides into the ***right*** and ***left bundle branches***, the later piercing the septum
• on the subendocardial surface of the left side of the interventricular septum, the left bundle branch → ***anterior*** and ***posterior divisions***
• these three divisions then give rise to the Purkinje fibers which are a complex, ramifying system of conduction pathways spreading throughout the myocardium
• Purkinje fibers are the broadest fibers of the heart, 70-80 µm in diameter, c.f. 10-15 µm for ventricular myocardium, this accounting for their high v_c
• they posses abundant, linearly arranged sarcomeres as do myocardial cells, however the T-tubular system is absent
• the rapid **v_c ~ 1-4 m/sec** allows rapid activation of the entire myocardium and coordinated contraction
• the configuration of the AP from Purkinje cells is very similar to that of myocardial cells, with phase 1 being more prominent and the duration of phase 2 being longer
• in certain regions of the Purkinje system there is a pronounced ***increase*** in APD, and hence effective refractory period → ***gate cells***
• because of their long refractory periods, these act as an additional safeguard against premature activation of the ventricles by the atria, or by ectopic ventricular foci
• this function is especially pronounced at slow heart rates, due to the inverse relationship between HR and AP duration
• similar changes in the refractory period with HR occur in other areas of the heart, however are ***not*** seen in the AV node

> ***NB:*** the refractory period of the AV node is relatively constant with varying HR and may actually ***increase*** at very rapid rates,
> therefore, at high rates, it is the AV node which protects the ventricles

• the first portions of the ventricles to depolarise are the interventricular septum (except the basal portion), and the papillary muscles
• activation then spreads into the substance of the septum from both left and right surfaces
• early contraction of the septum acts as an anchor point and the papillary muscles prevent eversion of the AV valves during systole
• the endocardial surfaces of both ventricles are activated rapidly, but the wave of excitation spreads from ***endocardium*** ® ***epicardium*** at a much slower rate, v_c = 0.3 to 0.4 m/sec
• as the right ventricle is thinner than the left, the epicardial aspect of the RV is activated earlier than the left
• also, apical and central epicardial regions of both ventricles are activated earlier than their respective basal portions
• the last areas to be activated are the posterior basal epicardial aspects of the ventricles and a small zone of the basal portion of the interventricular septum

▪ ***Reentry***

• under appropriate conditions, a cardiac impulse may excite some region of the myocardium through which it had previously passed → ***reentry***
• this reentry may be either,

a. random - as in fibrillation
b. ordered - where the impulses traverse a fixed path (SVT)

• the two requisite factors for ordered reentry are: (B&L 2-27)

1. a unidirectional block of conduction
2. the effective refractory period of the reentered region must be less than the propagation time around the loop

• therefore, the conditions that promote reentry are those which,

1. prolong the conduction time, or
2. shorten the effective refractory period

▪ ***Triggered Activity***

• this mechanism probably accounts for many of the dysrhythmias previously ascribed to reentry
• several characteristics are similar, notably, the depolarisations ascribable to triggered activity are always ***coupled*** to a preceding beat, as are those of reentry
• the hallmark of triggered activity is ***afterdepolarisation***, which may be either early or delayed (G&G 31-3)
• the afterdepolarisations responsible for triggered activity are associated with increased $[Ca^{++}]_i$
• the increased Ca^{++} within the cell is associated with the oscillatory release of Ca^{++} from the ***sarcoplasmic reticulum***
• therefore, in myocardial cells, these afterdepolarisations are accompanied by small changes in developed tension
• the high Ca^{++} also activates certain membrane channels allowing increased conductance of Na^+ and K^+
• factors which predispose to afterdepolarisations include,

1. digoxin
2. catecholamines
3. increased extracellular Ca^{++}
4. decreased extracellular K^+
5. decreased extracellular Na^+
6. shorter cycle lengths

CARDIAC PUMPING ACTIVITY

Structure & Function

▪ *Myocardial Cells*

• each skeletal and cardiac muscle cell is made up of ***sarcomeres*** (Z-Z), containing thick filaments made of ***myosin*** and thin filaments made of ***actin***
• thin filaments are anchored at the ***Z lines*** and extend across the I-bands, from where they interdigitate with the thick filaments of the A-band
• contraction of both cardiac and skeletal muscle occurs by the ***sliding filament mechanism***, actin filaments sliding along adjacent myosin filaments by cycling of the intervening cross bridges
• both show similar length-force relationships, the maximal developed force for cardiac muscle is observed at a resting sarcomere length of **2-2.4 µm**
• this relationship tends to hold for the intact heart as described by the ***Frank-Starling relationship***, of initial myocardial fiber length to force/pressure developed by the ventricle
• in the normal intact heart, maximal pressure development is attained at,

a. filling pressure ~ 12 mmHg
b. sarcomere length ~ 2.2 µm

• even with high filling pressures, up to 50 mmHg, the sarcomere length is not greater than 2.6 µm
• this is a function of the connective tissue component of the myocardium and protects the heart against diastolic overload
• usual ventricular diastolic pressure is ~ 0 to 7 mmHg
• this also corresponds with a sarcomere length ~ 2.2 µm (?? misprint in B&L)
• thus, the normal heart operates on the ascending portion of the Frank-Starling curve
• major difference with skeletal muscle is the appearance of a ***syncytium***
• this is not true anatomically, as the myocardial fibers are separated laterally from adjacent fibers by their respective ***sarcolemmas***, and at their ends by ***intercalated disks***, which are continuous with the sarcolemma
• cardiac muscle does, however, function as a syncytium, the spread of excitation occurring through gap junctions present within the intercalated disks
• conduction in myocardium progresses with a greater v_c in the direction ***parallel*** to the long axis of the fibers, gap junctions being present in far greater concentration at the ends of the fiber
• in contrast to fast skeletal muscle fibers, myocardial cells are very rich in ***mitochondria***, not being able to sustain any degree of oxygen debt
• the capillary supply is also rich and the intercapillary distance is small
• the ratio of capillaries to myocardial cells ~ 1:1, therefore diffusion distances are short
• deep sarcolemmal invaginations constitute the ***transverse-tubular system***, the lumens of which are continuous with the interstitial fluid, and play a key role in ***excitation-contraction coupling***

NB: in myocardial cells these occur at the Z-lines,
c.f. skeletal muscle where they occur between the A and I-bands

• a network of ***sarcoplasmic reticulum*** lies in close proximity to the T-tubules forming ***diads***

■ ***Excitation Contraction Coupling***

• earliest experiments indicated the need for optimum ECF concentration's of Na^+, K^+, and Ca^{++}

a. Na^+ - absence → heart inexcitable
- however, the resting V_m is independent of $[Na^+]$

b. K^+ - reductions cause little effect on excitation/contraction
- increases → depolarisation, then arrest in diastole

c. Ca^{++} - decreases lower contractility ± arrest in diastole
- increases raise contractility ± arrest in systole

• free intracellular Ca^{++} is the agent responsible for the contractile state of the myocardium
• excitation spreads rapidly along the myocardial sarcolemma
• from cell to cell via ***gap junctions*** and to the interior of the cells via the ***T-tubules***
• during phase 2, g_{Ca} increases as a part of i_{SI} and Ca^{++} enters the cell
• opening of the Ca^{++} channels is believed to be caused by phosphorylation of channel proteins by a ***cAMP-dependent protein kinase***; the later being accelerated by adrenergic β_1-agonists
• the mass of Ca^{++} entering the cell from the exterior is not sufficient to cause contraction
• rather this serves as ***trigger*** $\mathbf{Ca^{++}}$ causing release of calcium from intracellular storage sites, predominantly the ***sarcoplasmic reticulum***
• resting cytosolic free $Ca^{++} \sim 10^{-7}$M, and this increases by x10-100 with depolarisation
• Ca^{++} binds the ***troponin C*** portion of the tropomyosin protein complex, resulting in the unblocking of the active sites between actin and myosin
• cyclic crossbridging between the filaments
→ sliding filament mechanism of muscle contraction

• factors which affect the level of free cytosolic Ca^{++} alter the developed force of contraction,

a. catecholamines - increase inward i_{SI} phase 2

b. ACh/vagus

c. extracellular Ca^{++}

d. decreased $[Na^+]_o$ - decreased Ca^{++} leaves via antiport

e. Ca^{++} channel blockers

• at the end of systole the sarcoplasmic reticulum actively takes-up Ca^{++} via an ATP pump which is phosphorylation activated, the resulting decrease in calcium reversing the above events
• a sarcoplasmic reticular protein, ***phospholamban***, accelerates Ca^{++} sequestration and may help regulate the active pump of the SR
• contraction and relaxation are both accelerated by catecholamines and adenylate cyclase-cAMP activation, exact mechanisms unknown
• mitochondria are also involved in the uptake and release of Ca^{++} but the rate is too slow for E-C coupling ?? alterations of contractility
• removal of Ca^{++} in diastole occurs via,

a. ***electroneutral*** 2Na:Ca membrane ***antiport*** - major component

b. ***electrogenic*** 4Na:Ca membrane ***ATP'ase*** - ?? significance (see G&G)

Myocardial Contractility

• most simple models of myocardium include the following elements,

1. the contractile element
2. the series elastic element
3. the parallel elastic element

• with the exception of the first, these components have not been identified anatomically
• the parallel element is important in determining the resting length of the fiber for any given preload
• the force and velocity of contraction are related to the intracellular Ca^{++}, however the two are inversely related to each other

a. with no load → force is minimal and velocity maximal
b. isometric contraction → force is maximal and velocity zero

• the sequence of events in contraction of a preloaded and afterloaded muscle preparation are as follows: (B&L 3-8)

a. resting state - preload responsible for initial fiber length
b. isometric contraction - elongation of the series elastic element
c. isotonic contraction - muscle shortening with no increase in F

• the initial stretch of the series elastic element consumes some energy, therefore the energy of muscle shortening is actually less than the total energy expenditure in contraction
• the transition from isometric to isotonic contraction occurs when the extending force of the series elastic element is equal to the afterload
• the initial slope of the shortening curve depicts the initial rate of fiber shortening (dl/dt)
• since the initial velocity depends on the ***afterload***, a series of initial velocities v_0 can be obtained for any muscle preparation
• with increasing load the onset of shortening is delayed but the time interval from stimulation to maximal shortening in unaltered
• by plotting the v_0 against afterload, force velocity curves are obtained and the maximal velocity of shortening v_{max} may be obtained by extrapolation back to zero load
• representing the maximal rate of cycling of crossbridges

Def'n: ***contractility*** can be defined as a change of developed force at any given resting fiber length,
it may also be defined in terms of a change in v_{max}

• an increase in initial fiber length results in greater force of contraction, however the estimated v_{max} is unaltered and, therefore, contractility is unchanged
• this relies on the assumption of extrapolation of the force-velocity curves back to v_{max}
• this has recently been questioned as some workers have failed to show the hyperbolic relationship and have observed changes in v_{max} with changes in intial length (ie. v_{max} is length dependent)

• further, these experiments are carried out with isolated papillary muscles in a one dimensional fashion, c.f. the intact myocardium working in a 3 dimensional field
• for the left ventricle (LV), the ***preload*** is the end-diastolic pressure and the ***afterload*** aortic pressure
• due to the complex three dimensional arrangement of myocardial fibers, many are not oriented parallel to the line of developed force, and estimates of true contractility are difficult
• a reasonable index of contractility can be obtained from ***pressure-volume curves*** (B&L 3-11)
• the slope of the ascending limb representing the maximal rate of force developed by the LV (**dP/dt**); the slope being greatest during ***isovolumetric contraction***
• another indicator of the contractile state of the myocardium is the ***ejection fraction***, being the ratio of the stroke volume to the residual volume present in the LV at the end of diastole

NB: * there is no universally accepted index of contractility at present

• three factors permit more effective ventricular function at large diastolic volumes,

1. the Frank-Starling relationship
2. minimal myocardial viscosity as less shortening is required
3. minimal generation of elastic forces in connective tissue

   NB: these three are opposed by a fourth, which limits work at large volumes

4. the Laplace effect $\rightarrow$ $T = Pr/2h$
   - so tension is directly proportional to the product of radius and pressure

Cardiac Valves

Atrioventricular Valves

• the ***tricuspid*** valve between the RA and RV which has 3 leaflets
• the ***mitral*** valve between the LA and LV which has 2 leaflets
• the total area of the cusps of each valve in ~ twice the area of the respective A-V orifice, so there is considerable overlap in the closed position
• the free edges of these valves are continuous with the ***cordae tendineae*** which give rise to the powerful ***papillary muscles*** preventing eversion of the leaflets during diastole
• closure of the valves is achieved, in part, by the velocity of blood past the valve (Bernoulli principal) and by the formation of eddy currents behind the valve

Semilunar Valves

• consist of three cusps attached to the valve ring
• at the end of the reduced ejection phase of ventricular systole there is a period of ***reversal*** of flow toward the ventricles closing the valves
• during systole the cusps float midstream between the vessel walls and the closed position
• behind the cusps are the ***sinuses of Valsalva***, where eddy currents keep the valves away from the vessel walls, preventing closure of the ***ostia***
• the orifices of the right and left coronary arteries are located behind the right and left cusps respectively

The Pericardium

• is an epithelialised fibrous sac which closely invests the entire heart
• normally contains a small amount of fluid as lubricant
• the distensibility is small protecting the heart from overdistension, however heart functions within normal limits after its removal
• when intact, an increase in diastolic pressure in one ventricle increases the pressure and decreases the compliance of the other → ***ventricular interdependence***

THE CARDIAC CYCLE (Selkurt fig. 13-7)

1. Atrial Systole
2. Isovolumetric Contraction Phase
3. Rapid Ejection Phase
4. Reduced Ejection Phase
5. Isovolumetric Relaxation Phase
6. Rapid Filling Phase
7. Reduced Filling Phase

▪ *Atrial Systole*

• the sinoatrial pacemaker complex initiates excitation, which spreads across the atria and is recognised in the ECG as the ***P-wave***
• atrial contraction follows increasing the pressure within both atria
• this increase in the RA pressure gives the ***a-wave*** of the JVP, or CVP trace
• the increased pressure causes additional ventricular filling
• little blood is pumped in a retrograde direction due to the momentum of blood entering the atria and contraction of the venous orifices
• with reduced ventricular compliance, atrial contraction may give rise to a ***fourth heart sound***
• due to the additional filling, left ventricular end-diastolic pressure is increased slightly
• atrial contraction is normally not necessary for ventricular filling, however, at high heart rates diastasis is abbreviated and the atrial contribution may be important
• similarly, in disease states of the A-V valves, atrial contraction is important

• excitation of the ventricles occurs as the wave of excitation passes through the AV node, bundle of His and Purkinje system → the ***QRS-complex*** of the ECG
normal ***P-R interval*** **~ 0.12 - 0.2 sec**

• ventricular contraction starts within about 10 msec, the onset of ventricular contraction coinciding with the peak of the ***R-wave*** of the ECG an the initial vibration of the ***first heart sound***

▪ *Isovolumetric Contraction Phase*

• in response to contraction of the muscle, the ventricular pressure rises very rapidly
• this is not true isometric contraction, as some fibers lengthen and others shorten as the ventricle changes shape
• the maximal rate of dP/dt **~ 1600 mmHg/sec** and is an indicator of the contractile state of the myocardium
• this equates to a rise in pressure from near 0 to 80 mmHg in $1/20^{th}$ of a second
• the rapid rise in ventricular pressure is transmitted across the semilunar valves and appears as a small rise in the aortic pressure trace
• as the ventricular pressure exceeds aortic pressure the valves begin to open ending this phase

NB: the minimum aortic pressure (diastolic), actually occurs in ventricular systole

▪ ***Rapid Ejection Phase***

• associated with an abrupt rise in ventricular and aortic pressures and a rapid flow of blood
• flow velocity reaching 5-10 x the mean flow rate
• ventricular pressure ***exceeds*** aortic and reaches its maximum, due to the force required to accelerate the bolus of blood from the heart into the inductive load of the aorta
• because of the high ventricular pressure, unless the papillary muscles perfectly compensate, there is a tendency for the A-V valves to bulge into the atria → the ***av-wave*** of the JVP
• soon after this increase in atrial pressure comes a fall due to the descent of the base of the heart and stretching of the atria, the ***x descent***
• this reduced atrial pressure aids the return of blood from the periphery
• ventricular volume reduces slowly at first due to the inertial forces but the increases in rate until the end of this phase

• systolic arterial pressure may be used as an arbitrary demarcation point between the rapid and reduced ejection phases
• the peak in arterial pressure follows the peak in flow from the heart due to the distensibility of the aorta which accumulates some of the outflow
• this causes dampening and lagging of the pressure pattern

▪ ***Reduced Ejection Phase***

• both the contractile forces and the pressure within the ventricles are decreasing during this phase and are ***less*** than those within the aorta by several mmHg
• flow continues due to the ***momentum*** of the bolus of blood into the aorta
• peripheral aortic run-off, however, exceeds inflow from the heart and pressure declines
• ***repolarisation*** of the myocardium occurs during this phase → ***T-wave*** of the ECG

NB: the mechanical and electrical events of the myocardium are not synchronous and the fibers may be fully repolarised before the ventricles have reached a relaxed state

i.	stroke volume	~ 80 mls
ii.	LVEDV	~ 120 ml
iii.	ejection fraction	~ 2/3

• LVEF may increase to ~ 3/4 with massive SNS activity and is often less than 1/2 in disease
• the end of systole occurs at the beginning of the ***second heart sound***
• the ventricular pressure is decreasing very rapidly and there is reversal of flow toward the heart, closing the valves and generating the second HS
• the sudden increase in back-resistance to flow increases aortic pressure giving rise to the incisura, or ***dicrotic notch***

NB: this occurs only in the aortic pressure trace, not the LV pressure trace

- ***Isovolumetric Relaxation Phase***

• both valve sets are closed, so pressure drops very rapidly as there is "no" change in volume
• as this is occurring atrial pressure is increasing to its maximum, due to the,

1. movement of blood from the periphery
2. movement of the base of the heart back to its resting position → ***v-wave*** of the JVP

- ***Rapid Filling Phase***

• ventricular pressure decreases below atrial, the A-V valves open and filling occurs rapidly
• elastic recoil of the ventricle may aid in drawing blood into the ventricle when the residual volume is small, but is probably not important in normal circumstances
• as the ventricle fills intraventricular pressure increases slowing the rate of filling
• at large volumes, and with ventricles with low compliance, the rapid reduction of filling at the end of this phase may → ***third heart sound***

- ***Reduced Filling Phase***

• demarcation between these phases is arbitrary
• only significant if the diastolic period is abnormally long, when flow may actually cease
→ ***diastasis***

Synchrony of Contraction

• LV is first to start contraction and the last to start to fill, the differences between the ventricles being only a few sec/100
• the pattern follows the sequence,

1. excitation is initiated in the RA and rapidly conducted to the ventricles by the AV node
2. LV contraction starts first, with closure of the mitral valve occurring within ~ 30 ms of the start of the Q-wave of the ECG
3. RV contraction lags due to the anatomy of the conducting system by ~ 15 ms
4. the pulmonary valve opens first (~ 60 msec after Q-wave), and pulmonary flow begins around 10 ms before aortic due to the lower pressure in the pulmonary circuit
5. the isovolumetric period for the LV ~ 40 ms
RV ~ 15 ms
6. because of higher systemic pressure LV outflow ends first with the total LVET being shorter that the RVET
7. the mitral valve opens after the tricuspid due to the greater time for ventricular pressure to drop below atrial

NB: the isovolumetric phases of the RV, being shorter, occur within the time frame of the LV isovolumetric phases

Length of Systole & Diastole

- the duration of ***systole*** is rate dependant,
    a. at 70 bpm ~ 0.3 sec
    b. at 200 bpm ~ 0.16 sec → approximately ***halved***

- shortening is due mainly to a reduction in the duration of ***systolic ejection time***
- however, the duration of systole is far more fixed than ***diastole***, durations at
    a. at 70 bpm ~ 0.62 sec
    b. at 200 bpm ~ 0.14 sec → approximately a ***quarter***

- this is important because,
    a. LV ***subendocardial blood flow*** only occurs during diastole
    b. most of the ***ventricular filling*** occurs in diastole

- cardiac muscle cannot be tetanised like skeletal muscle, and the theoretical maximum rate of ventricular contraction is **~ 400 bpm**
- however, in normal adults the AV node will not conduct at > ~ 230 bpm

- the exact measurement of isometric ventricular contraction is difficult
- therefore, instead it is possible to measure;
    a. total ***electromechanical systole*** **QS_2**
        - from the onset of the QRS to the 2 nd heart sound
    b. left ventricular ejection time **LVET**
        - from the beginning of the carotid pressure rise to the dicrotic notch
    c. pre-ejection period **PEP** = QS_2 - LVET
        - represents the electrical and mechanical events preceding systolic ejection

    NB: the normal ratio **PEP:LVET ~ 0.35**

    this increases, without a change in QS_2, in a number of pathological states

Typical Resting Cardiac Variables in the Adult[1]			
Variable[2]		Right	Left
Atrial mean pressures	mmHg	4.5 (3)	8.0 (3)
Ventricular pressures	mmHg		
• End-diastolic		4.5 (4)	9.5 (4)
• Max-systolic		26 (6)	125 (15)
• Max dP/dt (mmHg/sec)		250 (100)	1600 (500)
Arterial pressures	mmHg		
• Systolic		25 (7)	125 (15)
• Mean		14 (4)	95 (10)
• Diastolic		9 (4)	80 (10)
Heart Rate	bpm	70 (3)	
Cardiac output:			
• Sitting	l/min	5.5 (1.1)	
• Supine	l/min	6.8 (1.5)	
	ml/min/kg	90 (20)	
Cardiac index	$l/min/m^2$	3.5 (0.7)	

[1] Altman and Dittmer, 1971

[2] figures are mean +/- standard deviation (SD)

ECG Intervals			
	Average	Range	Events during interval
PR-interval	0.18[1]	0.12 - 0.20	atrial depolarisation AV node conduction
QRS duration	0.08	≤ 0.12	ventricular depolarisation
QT-interval	0.4	≤ 0.43	ventricular depolarisation & repolarisation
ST-interval	0.32		ventricular repolarisation

[1] shortens as HR increases, from 0.18 at 70 bpm, to 0.14 at 130 bpm

MEASUREMENT OF CARDIAC OUTPUT

▪ *Fick Principle*

• derived by Adolph Fick, a German physiologist, in 1870

→ O_2 consumed by any organ = the A-V [O_2] difference x blood-flow

• therefore, pulmonary blood-flow, or CO, is equal to the body O_2-uptake divided by the arterial/mixed venous [O_2] difference,

$$\dot{Q} = \frac{\dot{V}_{O_2}}{C_{aO_2} - C_{\bar{v}O_2}}$$

where CvO_2 = PA blood

• patient rebreathes O_2 into a Benedict-Roth spirometer through a soda-lime absorber and the rate of O_2-uptake, VO_2, is determined from the ***slope*** of the tracing
• alternatively CO_2 excretion could be used

NB: in general, the rate of arrival, or removal of any substance for an organ

= blood flow x the [a-v] difference

▪ *Indicator Dilution Stewart-Hamilton Method*

• based on the law of ***conservation of mass***
• requirements

1. mass of indicator known and given as bolus
2. not metabolised or synthesised
3. adequate mixing must occur
4. no indicator lost from system

• using indocyanine green or radioactive isotope injected into arm vein
• the concentration of indicator in serial arterial samples is used to derive a concentration-time curve, from which the average $[I]_{art}$ after one circulation through heart is calculated
• solving for CO,

$$CO = \text{mass injected} / \text{average } [I]_{art}$$

Thermodilution

• same as above but cold saline injected into RA and δT measured in PA using thermistor on flow-directed catheter
• avantages of

a. negligible recirculation
b. repeated measurements can be made
c. arterial puncture not required
d. errors of extrapolation are avoided

• disadvantages of,

a. low signal to noise ratio
b. unable to inject as "bolus"
c. heat exchange with surroundings → oscillations

Body Plethysmograph

• used to measure instantaneous pulmonary blood flow by measuring **N_2O *uptake***
• gas mixture 21% O_2 / 79% N_2O from a rubber bag inside the box
• as N_2O highly soluble, it is taken-up in series of steps coinciding with heart rate

→ N_2O uptake is ***flow limited***,

∴instantaneous flow can be measured

REGULATION OF THE HEART BEAT

Nervous Control of Heart Rate

• local factors such as temperature and tissue stretch can affect the discharge rate of the SA node, however, under normal conditions the principal control of heart rate is via the autonomic nervous system (ANS)
• normal adults at rest HR ~ 70 bpm
• during sleep the rate reduces by ~ 10-20 bpm
• in well trained athletes the resting HR may be 50-60 bpm

• the SA node is usually under tonic influence of both divisions of the ANS
• changes in rate being effected by reciprocal changes of tone in both
• in normal adult at rest PNS tone is dominant over SNS
• with both divisions blocked by drugs the ***intrinsic heart rate*** **~ 100 bpm**

▪ *Parasympathetic Pathways*

• fibers originate from cells in the dorsal motor nucleus or the nucleus ambiguus and travel in the ***vagus nerve*** (X) through the neck and mediastinum to the postganglionic cells within the heart
• most of the cardiac ganglion cells are located near the ***SA & AV nodes***
• the two branches of the vagus are distributed differently, according to the embryological origin of the SA & AV nodes;

1. (R) vagus → predominantly the SA node
2. (L) vagus → predominantly the AV nodal conducting tissue

• there is, however, reasonable functional overlap
• both the SA and AV nodes are rich in cholinesterase, hence the effects of released ACh are ephemeral due to rapid hydrolysis
• at the SA node, PNS effects preponderate over SNS effects, such that in the presence of moderate vagal tone the SNS has little effect in increasing the HR

- ***Sympathetic Pathways***

• fibers originate in the intermediolateral columns from around C_7 to T_7
• then emerge from the spinal cord through the white rami and enter the paravertebral ganglion chain
• preganglionic and postganglionic fibers synapse mainly in the ***stellate ganglion***, or in the caudal cervical ganglion
• these later ganglia lie close to the vagus nerve and postganglionic fibers travel in a common plexus to the heart
• SNS fibers reaching the base of the heart along the adventitial surface of the great vessels
• fibers are then distributed to the cardiac chambers as an extensive epicardial plexus, penetrating the myocardium with the coronary vessels
• adrenergic receptors in the myocardium and nodal tissue are β_1 receptors
• as with the vagi, distribution is asymmetrical,

1. (L) sympathetic fibers $\rightarrow$ more pronounced effects on ***contractility***
2. (R) sympathetic fibers $\rightarrow$ more pronounced effects on ***heart rate***

• also, like the PNS, there is some functional overlap
• effects of SNS stimulation decay very gradually, in contrast to the rapid decay of vagal effects
• most noradrenaline (NA) released is taken-up again by the nerve terminals, and much of the remainder is carried away by the circulation
• relatively little NA is degraded in the tissues

Control by Higher Centres

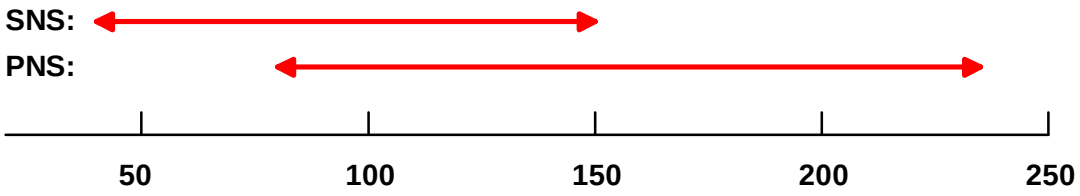
• in the cerebral cortex the centers regulating cardiac function include,

a. frontal lobe
b. orbital lobe
c. anterior region of the temporal lobe
d. the motor and premotor cortex
e. the insula and cingulate gyrus

• in the thalamus the ventral, midline & medial groups of nuclei induce tachycardia on stimulation
• variations in HR may also be evoked from the posterior and posterolateral regions of the hypothalamus
• undoubtedly the cortical and diencephalic centers are responsible for the variations in cardiac function with excitement, anxiety, and other emotional states
• the hypothalamic centers are also involved in the responses to temperature
• in certain dorsal regions of the medulla, distinct cardioaccelerator and augmentation sites have been found in animals with transected vagi
• the accelerator regions were more abundant on the right and the augmentation sites more abundant on the left
• therefore, it would appear that most SNS fibers descend the brainstem ***ipsilaterally***

- ***Baroreceptor Reflex***

• the inverse relationship between HR and BP was first described in 1859, and subsequently referred to as ***Marey's law*** of the heart
• the reflex originates from ***baroreceptors*** (stretch) located in the arch of the aorta and in the carotid sinus
• these two sets of receptors being approximately ***equipotent***
• the response to alterations of blood pressure around the normal range are mediated by reciprocal changes in SNS/PNS tone
• outside of the normal range one or other division acts in solitude



Bainbridge Reflex

• in 1915 Bainbridge reported that infusions of blood or saline ***increased*** HR
• this increase in rate occurred irrespective of whether the infusion altered arterial BP
• acceleration was observed whenever the CVP was increased sufficiently to distend the RA, and the effect was abolished by transection of the ***vagi***
• this effect has been confirmed, however the resultant effect is dependent upon the prevailing HR,

a. low HR + infusion → acceleration of HR
b. high HR + infusion → usually slows the HR

• increases in blood volume not only activate the Bainbridge reflex, but also others, including the ***baroreceptor reflex*** which has the opposite effects on HR
• the Bainbridge reflex is prepotent over the baroreceptor reflex when the blood volume is raised
• conversely, the baroreceptor reflex is prepotent in hypovolaemia
• receptors influencing HR are located in both atria, principally in the ***veno-atrial junctions***
• response is highly selective, there being a negligible effect on contractility or peripheral SNS activity
• stimulation of these receptors also increases the ***urine volume*** via,

a. neurally mediated inhibition of ADH secretion
b. release of atrial natriuretic factor

▪ ***Respiratory Cardiac Arrhythmia***

• variations in HR with respiration are more pronounced in children, typically HR increasing with inspiration and decreasing with expiration
• recordings of the ANS during respiration,

a. expiration → increases in vagal tone

b. inspiration → increases in sympathetic tone

NB: ACh is rapidly removed, therefore the vagal effects are transitory

• the effects of cyclic increases in NA are dampened due to the slow removal and reuptake
• therefore, the cyclic variations in HR with respiration are almost completely ascribable to oscillations in ***vagal tone***
• sinus arrhythmia is therefore exaggerated whenever vagal tone is enhanced
• both reflex and central factors contribute to the genesis of sinus arrhythmia,

1. inspiration → decreased intrathoracic pressure
   → increased venous return
   → Bainbridge reflex
2. increased venous return + time delay → increased LV output
   → baroreceptor reflex
3. fluctuations in SNS activity to the arterioles alters TPR and BP with respiration
   → baroreceptor reflex
4. stretch receptors in the lung may also affect HR, inflation → increases HR
5. the respiratory center in the medulla influences the autonomic cardiac centers

▪ ***Chemoreceptor Reflex***

• in intact animals, stimulation of the ***carotid chemoreceptors*** consistently increases ventilatory rate and depth but ordinarily evokes only slight increases or decreases in HR,

a. when respiratory stimulation is mild → decreases in HR

b. with more pronounced stimulation → HR usually accelerates

• the cardiac response is the sum of primary and secondary reflex effects
• the primary effect of carotid chemoreceptor stimulation on the SA node is ***inhibitory***
• the secondary effects are facilitatory and vary with the level of respiratory stimulation
• these are,

a. enhanced pulmonary inflation reflexes

b. hypocapnia

• both of which antagonise the primary response of the SA node

- ***Ventricular Receptor Reflexes***

• receptors are located near the ***endocardial*** surfaces of the ventricular walls and elicit responses similar to those of the arterial baroreceptors
• excitation of these receptors ***decreases*** the HR and TPR
• the frequency of discharge parallels the changes in ventricular pressure
• impulses are carried in myelinated vagal fibers to the medulla

INTRINSIC REGULATION OF MYOCARDIAL PERFORMANCE

• the heart is partially or completely ***denervated*** in a number of clinical situations,

1. the surgically transplanted heart
2. pharmacologically blocked by atropine/propranolol
3. certain drugs deplete cardiac NA stores (reserpine)
4. chronic CCF cardiac NA stores are often severely depleted

Heterometric Autoregulation

▪ ***Studies on Isolated Hearts***

• in 1895 Frank described the response on the isolated heart to alterations of load on the myocardial fiber prior to contraction → ***preload***
• he observed that with increasing preload the heart responded with a more forceful contraction
• in 1914 Starling described the intrinsic response of the heart to changes in ***right atrial*** and ***aortic pressure***
• he observed that increasing the right atrial pressure, holding aortic pressure constant, resulted in a progressive increase in ventricular volume to a new equilibrium point
• the increase in diastolic fiber length facilitating ventricular contraction and increasing stroke volume (SV)
• at equilibrium the augmented cardiac output matching the increase in venous return
• he also showed that there is an optimum fiber length, beyond which excessively high filling pressures may ***depress*** rather than enhance myocardial performance
• changes in diastolic fiber length also permit compensation for increased ***afterload***
• with venous return held constant, increasing aortic pressure decreases stroke volume, with a subsequent increase in ventricular end-diastolic volume and resting fiber length
• this increase in fiber length enabling the heart to pump a given SV against a greater peripheral resistance
• as cardiac work is proportional to the ***product*** of SV and arterial pressure, increases in resting fiber length enable the LV to increase work output
• however, increases in TPR may reduce SV proportionately greater and decrease LV work
• changes in ventricular volume are also involved in cardiac adaptation to alterations in HR
• with reduced rates, filling time is increased and the increased SV may fully compensate for the reduced rate, CO remaining ~ constant
• in the intact animal, the relatively rigid pericardium limits the pressure-volume relationship at high filling pressures

NB: with ventricular dilation, the force generated by each myocardial fiber must be substantially greater for a given pressure;
thus the dilated heart requires considerably more oxygen to perform a given amount of external work (Laplace, for spheres, **T = Pr/2**)

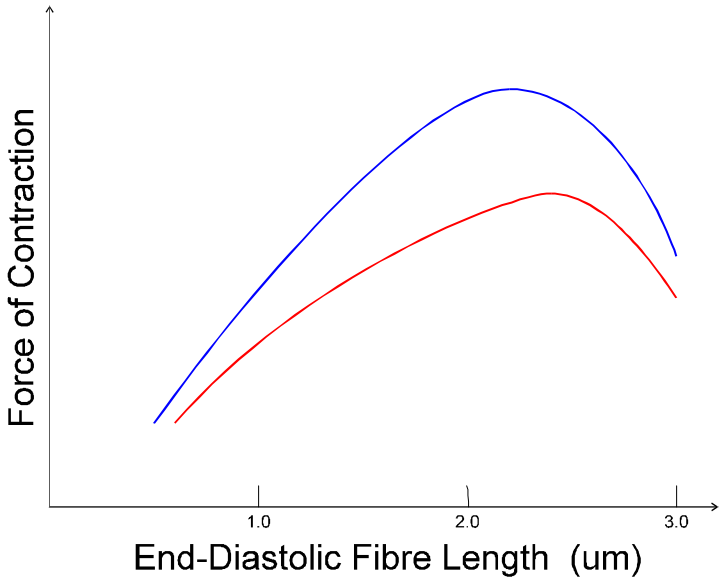
Studies on More Intact Preparations

• the main problem with assessing the Frank-Starling mechanism is the inability to measure end diastolic fiber length
• the most commonly used indices of ***ventricular performance*** are,

a. cardiac output
b. stroke work
c. stroke volume

• the commonly used indices of ***resting fiber length*** are,

a. LV end diastolic volume
b. LV end diastolic pressure
c. ventricular circumference
d. mean LA pressure



• the F-S mechanism is best represented by a family of ventricular function curves, (cf. B&L fig. 4-16)

• a shift of the curve to the right usually signifies a reduction in contractility, a shift to the left increased contractility

NB: a shift in the ventricular function curve ***does not*** uniformly indicate a change in ***contractility***; as this is a measure of myocardial performance at a given level of preload and afterload, therefore to assess contractility afterload would have to be held constant as end diastolic pressure was varied

• it is very difficult to assess the contribution of the F-S mechanism in the intact animal
• where blood volume is reduced, the EDV is diminished and the F-S mechanism undoubtedly helps regulate cardiac output
• conversely, when blood volume is increased, the EDV cannot increase appreciably due to the constraints of the pericardium, hence ***extrinsic*** mechanisms are probably more important
• the F-S mechanism is ideally well suited to matching CO to venous return and, therefore, is important in maintaining the precise balance in the outputs of the RV and LV

• the curves relating CO to mean atrial pressure for the two ventricles are not coincident
• the curve for the left ventricle usually lies below that of the right (B&L 4-17)
• under these conditions, for the output of the two ventricles to be equal, LA pressure must be greater the RA pressure, as is the case

Homeometric Autoregulation

▪ *Afterload-Induced Regulation*

• the mammalian ventricle has the intrinsic capability of adapting to changes in the filling pressure and arterial resistance, ***without*** a continued increase in resting fiber length
• for the heart to pump blood against a higher pressure, the fiber tension must be greater in accordance with Laplace, (T=Pr/2h)
• an increase in afterload may evoke a type of homeometric autoregulation called the ***Anrep effect***
• ie. the same stroke volume is ejected in the face of increased aortic pressure, thus the ***work*** output in increased
• this response requires several beats to develop, however is ***independent*** of fiber length or hormonal influences
• the systolic ***fiber tension*** may be the principal determinant of not only homeometric autoregulation but also oxygen consumption

▪ *Rate-Induced Regulation*

• the progressive increase in developed force induced by an increase in contraction frequency is called the staircase, or ***treppe phenomenon***
• this is ascribable to a gradual rise in ***intracellular calcium***
• calcium enters the cell during phase 2 of the AP
• as frequency increases, AP shortens and less Ca^{++} enters per AP
• however, the net influx per unit time is increased due to the greater number of bpm
• similar effects are seen with postextrasystolic potentiation, where the extra beat itself is feeble and the beat after the compensatory pause is very strong
• two mechanisms appear to operate,

a. the F-S mechanism, the longer pause causing greater filling
b. accumulation of Ca^{++} in the "release compartment" of the SR

• intracellular Ca^{++} being recirculated from,

a. "release compartment" $\rightarrow$ cytosol + contraction $\rightarrow$
b. "uptake compartment" in sarcotubular network $\rightarrow$
c. translocation to "release compartment" in sarcoplasmic reticulum

• this translocation requires ~ 500 to 800 ms
• therefore, the postextrasystolic beat has available the Ca^{++} for one beat plus the portion of the Ca^{++} not translocated at the time of the extrasystole

EXTRINSIC REGULATION OF MYOCARDIAL PERFORMANCE

Nervous Control of Myocardial Performance

- ***Sympathetic Nervous System Influences***

1. significantly increases,
   i. both atrial and ventricular contraction
   ii. peak LV pressure and $\delta P/\delta t$
   iii. the rate of ventricular relaxation
2. the proportion of systole:diastole is reduced
3. increase in discharge rate of SA node
4. increased automaticity and conduction velocity

• normally, the concentration of ***noradrenaline*** in the atria is ~ 3 times that in the ventricles
• the [NA] in the SA and AV node is about the same as that of the surrounding atrial tissue
• the SNS nerves on the left side of the body generally have a far greater influence on myocardial performance than do those on the right
• the shortening of systole and more rapid relaxation in diastole aid ventricular filling, especially at fast heart rates where SNS activity is likely to be increased
• neurally released NA interacts with b_1***-receptors*** activating adenylate cyclase, increasing intracellular cAMP with subsequent activation of cAMP dependent protein kinase, etc.
• the phosphorylation of specific sarcolemmal proteins augments the conductance of Ca^{++} channels in myocardial cell membranes
• as a result the influx of Ca^{++} with each AP is increased and more Ca^{++} is released from the SR

→ the contractile force of the cell is increased

• assessing myocardial performance by ventricular function curves, the increase in performance following SNS stimulation is usually accompanied by a ***reduction*** in LV end-diastolic pressure (see - coupling of heart/circulation)

- ***Parasympathetic Nervous System Influences***

1. inhibits the cardiac pacemaker
2. reduces atrial myocardial performance
3. inhibits AV conduction tissue
4. depresses ventricular myocardium - less pronounced
5. decreases both the maximal pressure and $\delta P/\delta t$
6. reduces the rate of ventricular relaxation in diastole

• the effects of vagal stimulation are mediated by at least four mechanisms
• one of which is ***direct***, the others indirect via the SNS, (B&L 4-24),

1. ACh $\rightarrow$ $\uparrow$ cGMP $\rightarrow$ $\downarrow$ contractility ??how
2. ACh $\rightarrow$ $\downarrow$ cAMP
3. cGMP $\rightarrow$ $\uparrow$ hydrolysis of cAMP by phosphodiesterase
4. postganglionic vagal fibers $\rightarrow$ presynaptic SNS inhibition

• these effects are minimal when the existing level of SNS activity is low, however are quite marked when the SNS level is greater

- ***Baroreceptor Reflex***

• just as carotid sinus and aortic arch stimulation affect HR, so they may also affect contractility
• with successive rises in mean arterial pressure the ventricular function curves are displaced progressively to the ***right***, denoting depression of myocardial performance
• in normal resting individuals, basal SNS activity is very low and reflex alterations have little effect on performance
• conversely, in states of enhanced SNS activity, reflex alterations may have a marked effect on myocardial performance
• this acts as a compensatory mechanism in hypovolaemia, where reduced BP increases both the heart rate and myocardial contractility

- ***Chemoreceptor Reflex***

• when pulmonary ventilation is controlled, carotid chemoreceptor stimulation results in profound ***bradycardia***, often with some degree of AV block
• this increased vagal activity may also depress contractility
• the atria are far more susceptible to vagal tone than the ventricles

Chemical Control

■ *Adrenomedullary Hormones*

• principally ***adrenaline*** (AD), with some NA, largely controlled by the same factors as the SNS
• CVS effects of circulating catecholamines are probably ***minimal*** under normal conditions
• changes in contractility, $\delta P/\delta t$, are directly proportional to the [NA] in the blood
• however, under exercise or stress conditions the increases are almost completely ascribable to neurally released NA, not the blood [NA]

■ *Adrenocortical Hormones*

• these are involved in the control of circulating ***blood volume*** and, therefore, mean circulatory pressure
• further, cortisol is ***permissive*** for the effects of the catecholamines
• this may be effected by inhibition of neuronal uptake of CAs
• however there is likely an intracellular mechanism also (? G-protein coupling)

■ *Thyroid Hormones*

• increased levels enhance cardiac performance
• the rate of $\mathbf{Ca^{++}}$ ***uptake*** and ***ATP hydrolysis*** by the sarcoplasmic reticulum are increased
• increased protein synthesis with subsequent myocardial hypertrophy alter ***isoenzyme pattern*** toward those which have the greatest ATPase activity, thereby enhancing contractility
• indirect effects result from the increased metabolic rate with arteriolar vasodilation
→ decreased TPR and increased cardiac output
• either the level of SNS activity is increased, or there is increased sensitivity of the tissues to NA
• it is generally agreed that the density of β_1-receptors in cardiac tissues increases

■ *Insulin*

• insulin has a prominent, direct, ***positive inotropic*** effect which is not abolished by beta blockade, or prevention of hypoglycaemia by glucose infusion
• actually, this effect is enhanced by beta blockade
• this may be mediated by prevention of intracellular Ca^{++} binding, thereby increasing the free levels

■ *Glucagon*

• also has potent ***positive inotropic*** and chronotropic effects
• the endogenous hormone probably plays no role in normal regulation of the CVS
• the effects of glucagon closely resemble those of the CA's and certain metabolic effects are similar
• both activate adenylate cyclase and cAMP but the mechanisms differ, glucagon having no effect on β_1-receptors
• therefore it may be useful in the R_X of β-blocker overdosage

Anterior Pituitary Hormones

- the derangements of CVS function mediated by the pituitary relate to the target organ hormones
  → adrenocortical and thyroid especially
- GH also has some effect on the myocardium, mainly in concert with thyroxine

Oxygen

- the P_{aO2} affects the heart by indirect reflex mechanisms via the central and peripheral chemoreceptors
- moderate degrees of hypoxia usually increase the HR, CO and contractility
- these effects are abolished by β-blockade
- more severe degrees of hypoxia have a direct depressant effect, which usually become evident at O_2 saturations < 50%

Carbon Dioxide

- the P_{aCO2} also has indirect and direct effects on the heart
- the indirect, neurally mediated effects produced by increased P_{aCO2} are similar to those of hypoxia
- in intact animals, the direct depressant effect of CO_2 on the myocardium are compensated for by the increased sympathoadrenal activity
- neither the P_{aCO2}, nor the blood $[H^+]$ are primary determinants of myocardial behavior

→ the change in ***intracellular pH*** is the critical factor

NB: lowering the intracellular pH →

i. ↓ release of Ca^{++} from the SR in response to excitation
ii. depresses myofilament function directly

In Summary

- there are ***five*** main classes of influence over the vigor of myocardial contraction
    1. ***Metabolic*** condition of the cells
        - which in turn depends on an adequate coronary blood flow, oxygen supply, nutrient supply, and absence of toxins
    2. ***Heterometric*** Autoregulation
        - the Frank-Starling relationship, or the influence of resting fiber length on contraction
    3. ***Homeometric*** Autoregulation
        - the increased contractility of the heart in response to an increased pressure load without changes in end-diastolic fiber length
    4. ***Interval*** between beats
        - the increase in contractility seen with moderate increases in heart rate
    5. ***Central nervous system*** action
        - including the effects of circulating catecholamines and the release of autonomic mediators at the heart

HAEMODYNAMICS

Factors Influencing Flow

• the rate of fluid flow is proportional to the driving pressure, expressed mathematically as:

$$Q = G.\delta P$$
$$= (1/R).\delta P$$

• where G is the ***conductance***, or proportionality constant of the equation and is equal to flow divided by driving pressure
• as for electrical circuits, the reciprocal of conductance is ***resistance***
• for the systemic system, venous pressure is so comparatively low to arterial pressure that is may be ignored in calculations of overall tissue vascular resistance
• this does not apply for the lower pressure pulmonary circuit, where differences are smaller and the pressure drop is more uniform
• the pressure, in dynes/cm^2 (N/m^2), at a distance h cms below the surface of a liquid is,

P = phg

where, p is the ***density*** in gm/cm^3, and
g is the acceleration due to ***gravity*** (cm/s^2)

▪ *Poiseuille's Equation*

• steady laminar flow of a newtonian fluid through a cylindrical tube (Q) is given by,

$$\dot{Q} = \frac{\pi r^4.\delta P}{8\eta l}$$

where p/**8** is the ***constant of proportionality***

• the primary assumption of this equation, courtesy of Newton, is that fluid flow is ***laminar***,

a. the velocity profile is ***parabolic***
b. velocity is greatest at the center of the stream → ~ 2x mean flow
c. the velocity ***gradient*** is greatest near the wall
   • the force per unit area, ***shear stress*** t, tending to impede this sliding is directly proportional to the relative velocity between adjacent layers, ***shear rate***
   • the ratio of shear stress to shear rate being the ***viscosity*** h, of the fluid

• if the viscosity is ***independent*** of shear rate, the fluid is ***Newtonian***
• blood any many colloidal solutions are non-newtonian, for at low shear rates, less than 100 sec-1 (10 cm/sec/mm thickness), viscosity becomes sensitive to shear rate
• since flow is proportional to the fourth power of the radius, changes in vessel caliber have a marked influence on flow
• physiologically, resistance to blood flow is determined primarily by the caliber of small arteries, arterioles and precapillary sphincters, which are in turn dependent on ***vasomotor tone***

Total Peripheral Resistance

Def'n: total peripheral resistance is the resistance to blood flow through the systemic circuit as a whole;
ie. mean arterial pressure minus venous pressure divided by cardiac output

• as, in most vascular beds, arterioles and capillaries are ***parallel*** elements, the ***reciprocal*** of the total resistance = the sum of the reciprocals of the individual resistances,

$$1/R_T = 1/R_1 + 1/R_2 + ... + 1/R_n$$

• stated another way, as hydraulic conductance is defined as the reciprocal of resistance, the total ***conductance*** is the sum of the individual conductances

NB: thus the resistance of any individual vascular bed must be ***greater*** than the TPR

• for an individual with a cardiac output of 5 l/min and a mean arterial pressure of 100 mmHg

→ **TPR ~ 0.02 mmHg/ml/min** (PRU)

• for one kidney with a blood flow of 600 ml/min, $R_K \sim 0.17$ (PRU)

• despite the fact that the arterioles have a greater X-sectional area than the main arteries, they are the main site of systemic resistance
• as resistance varies with the 4^{th} power of the radius but area only with the 2^{nd}, so resistance is ***inversely proportional*** to the area squared,

$$R = k/A^2$$

• so for any number of small tubes, equal in area to one large tube, the total resistance of the small tubes will be greater than the single large tube
• eg., if there are y small tubes such that $y.A_y = A_l$, then the total resistance of the small system will be $y.R_l$ (see B&L, p115)

Viscosity of Blood

• ***plasma*** is ***~ 1.8 times*** as viscous as water (B+L → 1.2 to 1.3)
• ***whole blood*** has a variable viscosity → 2-15 times water
• the haematocrit ratio has a marked effect upon the viscosity of blood
• above the normal haematocrit of 0.45, blood viscosity increases markedly
• temperature has an inverse effect upon viscosity; at 0°C, both blood and water are about 2.5 times more viscous than at 40°C
• at body temperature, there is a 2% increase in viscosity for each 1°C decrease in temperature
• fluid velocity may influence blood viscosity, for although blood is newtonian under normal physiological conditions; in certain pathological conditions, where flow becomes stagnant, viscosity increases

> ***NB:*** because the calculated viscosity of blood is different depending upon the shear rate or the diameter of the flow channel, the ratios of shear stress to shear rate are called ***apparent viscosities***

• as the minute vessel structure is so complicated and pressure/flow data are unavailable, the viscosity of blood is compared to that of a standard solution (normal saline), giving the relative viscosity
• the apparent viscosity of blood diminishes as the shear rate is increased, a phenomenon called ***shear thinning***
• the ***axial streaming*** of RBCs at high flow rates is partly responsible for this behavior
• a more important cause of the increased viscosity at low shear rates is the tendency of erythrocytes to ***rouleaux formation***
• blood possesses a small but finite ***yield stress***, such that blood will not flow at < 0.1 dyne/cm^2
• as the shear rate increases the apparent viscosity decreases toward an asymptote (B+L fig. 5-17)
• ***fibrinogen*** is necessary for this anomalous rheological behavior of whole blood and the changes in viscosity are more pronounced when its concentration is high
• the ability of RBCs, diameter ~ 8 µm, to pass through vessels of diameter 3-4 µm is dependent upon their flexibility and this is enhanced as the concentration fibrinogen increases
• also, at low flow rates leukocytes tend to ***marginate***, thereby increasing the apparent viscosity
• although normal blood does not undergo rapid aggregation, this tendency is markedly increased in burns or traumatic shock

■ ***Shear Stress on Vessel Walls***

• from the definition of viscosity, it becomes evident that the ***shear stress***

$$t = h \times \text{shear rate}$$

• where shear rate is the ***velocity difference***, du, between layers y distance apart →

$$\text{shear rate} = du/dy$$

• hence, the greater the rate of flow and the more viscous the fluid, the greater the shear stress exerted on the vessel wall → ***viscous drag***

• for a flow regimen that obeys Poiseuille's law,

$$\tau = 4\eta Q / \pi r^3$$

• the greater the rate of flow, the greater will be du/dy near the vessel wall, and the greater will be the viscous drag

▪ *Flow in Minute Vessels*

• when blood is pumped through small caliber vessels, the apparent viscosity ***decreases***, blood behaving more like plasma
• this phenomenon is termed the ***Fahraeus-Lindqvist effect***
• in large tubes the flow in independent of diameter (> 0.3-0.5 mm)
• however as the diameter is decreased viscosity decreases until diameter reaches around 4-5 µm when viscosity again increases due to the restriction to passage of RBCs
• the diameter of the highest resistance vessels is less than this critical value
• therefore, this phenomenon reduces the resistance to flow where blood vessels posses the greatest resistance
• another aspect of this effect is axial streaming of RBCs, which leaves a cell-free marginal zone against the vessel wall, where the velocity gradient is greatest (du/dy)
• this phenomenon also reduces the relative haematocrit of blood as it flows through vessels of < 500 µm diameter
• this results from the disparity in the velocities of RBCs and plasma
• since the axial stream contains more RBCs and travels at a greater velocity, RBCs traverse the vessel in a shorter period of time, effectively lowering the haematocrit
• for a vessel of 30 µm the relative haematocrit is ~ 0.6
• the reduction in apparent viscosity in small tube is particularly prominent at high haematocrit

> ***NB:*** axial streaming, by permitting ***plasma skimming*** into side branches, is a factor in the distribution of RBCs and plasma in capillary beds

▪ *The Continuity Equation*

• states that the product of flow velocity and X-sectional area is constant,

$$v_1 \times A_1 = v_2 \times A_2$$

• thus, in the aorta, where the area is ~ 4.5 cm^2 & flow is ~ 50 cm/sec
→ the 4 µm capillaries where area is ~ 4500 cm^2 & flow is ~ 0.1cm/sec

The Equation of Motion

• derived from Newton's laws of motion, when applied to flowing fluid,

$$P = M.Q'' + R.Q' + S.Q,$$ where,

M	= the ***mass*** of the fluid	x	Q"	= the ***acceleration***
R	= the ***resistance*** to flow	x	Q'	= the rate of ***flow***
S	= the ***stiffness*** of the vessel	x	Q	= the distending ***volume***

• at the peak of ventricular pressure, the ***inertial*** and ***viscous*** terms normally represent < 5% each of the total driving force
• most of the driving pressure is acting to distend the aorta and move blood through the periphery
• energy is lost to the environment only by the ***frictional*** term
• the energy stored as momentum on acceleration and that used to distend the aorta are later available to drive blood through the periphery

Bernoulli's Equation

• based upon the principle of ***conservation of energy***, where the total energy of a laminal streamline flow, is given by,

$$E = P_V + mgh + \tfrac{1}{2}mv^2$$

where, P_V = the potential energy of ***pressure***
mgh = potential energy due to ***gravity***
$\tfrac{1}{2}mv^2$ = the kinetic energy of ***motion***

• this gives the effective pressure gradient, or driving force between two points as it gives the true total difference in energy
• when the rate of flow changes, as in arteries, the resistance to flow, more correctly termed ***impedance*** includes this inertial term
• where inertance/compliance are significant factors in a systems behavior, the flow pattern does not coincide with that of pressure change,

a. lags behind where the inertial component dominates
b. leads where the compliance arterial compliance dominates

• another consequence of this equation is, that where flow velocity is high because of a constriction in the vessel, more of the total energy is in the form of kinetic energy of motion, ie., the lateral static pressure is reduced
• this is important in closure of the valves of the heart and the patency of the coronary ostia, especially as the orifices of the later are at right angles to the direction of flow
• with stenotic valves, or high ejection rates, angiographic studies have shown flow may reverse in the large coronary arteries at the peak of the rapid ejection phase
• this defines the differences in measured pressure with pitot tubes, where they are directed into, or at right angles to, the direction of flow
• the ***kinetic energy*** component has the units dynes/cm^2, or mmHg, where 1330 dynes/cm^2 = 1 mmHg

- ***Transmural Pressure***

• by definition, is the difference between the intraluminal pressure and the pressure outside the vessel
• most often the outside pressure is atmospheric and can be considered as zero
• also a major determinant of flow, as vessels passively distend their resistance decreases

→ ***non-linear*** pressure/flow curves of living tissue

Compliance

Def'n: compliance (C), is a general term relating the change in dimension, ***strain***, to the distending pressure, ***stress***

$$C = \delta V/\delta P$$

• the coefficient of ***stiffness***, S, is the reciprocal of compliance in the above equation
• the structure of most blood vessels and other living tissues is such that with increasing distention, the compliance ***decreases***, ie., they become stiffer
• as blood vessels have a ***resting volume*** when distending pressure = 0, the volume/pressure must be specified when measuring compliance
• ***capacitance*** is an electrical term which implies storage, used by some as the ratio of total volume to transmural pressure, equating it to compliance
• because a long vessel will have a greater δV for a given δP, the coefficient of ***volume distensibility*** (k) is defined as the fractional change in volume per unit δP,

$$k = \delta V / V.\delta P$$

NB: the combination of resistance, compliance and inertance of the blood in the arterial system determines the arterial input ***impedance***, the ratio of δP to flow at a specified ***frequency***

• because of its compliance, the aortic input impedance for ***pulsatile flow*** at frequencies of 1 to 15 Hz is only ~ 10% of that for steady flow
• this greatly reduces myocardial work, in addition to maintaining peripheral flow during diastole

Laplace's Equation

• due to the profound influence of vessel diameter on flow, factors determining vascular dimensions, ***transmural pressure*** and ***wall tension***, are important contributors to vascular resistance
• for a vessel of constant diameter, the ***wall tension*** is given by

$$T = Pr$$

• where P is the transmural pressure and r the radius
• therefore, for a given pressure, the forces in the wall of a larger vessel must be higher than in a small vessel
• similarly, in a large heart the wall forces required to eject blood into a given aortic pressure must be greater at higher EDV's
• for vessels with ***thicker walls*** (h), the tension is reduced, so

$$T = Pr/h$$

• for ***spheres***, where distending pressure acts through 2 radii of curvature,

$\rightarrow$ $P = T.h.(1/R_1 + 1/R_2)$, so

$$T = Pr/2h$$

Turbulence

• blood flow through vascular channels is normally streamline, or laminar, however under various conditions turbulent flow may develop
• in this event the flow through the vessel will become approximately proportional to the ***square root*** of the pressure drop
• therefore, an increase in driving pressure results in a less than proportionate increase in flow,

$$Q \propto k.\sqrt{\delta P}$$

• the potential driving energy become dissipated in the swirls and eddies as heat & sound
• if the ratio of ***inertial*** to ***viscous*** forces exceeds a given value, a slight disturbance to laminar flow will result in randomly oriented turbulent flow
• turbulence becomes likely when this ratio, the ***Reynold's number***, exceeds a value of 1000 for blood, or 2000 for fluids (liquid or gas) not containing suspended particles,

$$Re = \rho v D / \eta$$

where, ρ is the ***density*** of fluid in gms/cm^3 x g (9.8m/sec^2)
v is the average ***velocity***, in cms/sec
D is the vessel ***diameter***, in cms, and
η is the ***viscosity***, in gm.sec/cm^2

• therefore, other factors remaining constant, turbulent flow is likely to result from,

a. increases in velocity
b. decreases in viscosity
c. increases in vessel diameter

• streamline flow may also be disrupted by the generation of organised swirls, or ***vortex shedding***, the downstream wake fluctuating from side to side
• the studies of Bruns (1959) showed that the frequency and location of cardiovascular sounds under physiological conditions could be explained by this process
• the wake has a maximal component of fluctuation at right angles to the flow stream
• when the lateral fluctuations are of sufficient magnitude and frequency audible sound is produced
• in this type of turbulence, the level of audible energy is greater for a given driving pressure than for classical turbulent flow, and this source probably accounts for most of the murmurs heard in the CVS and can occur when ***Re*** is much less than 2000

THE ARTERIAL SYSTEM

Hydraulic Filtering

• the arterial system, systemic > pulmonary, being a circuit possessing compliance, inductance and resistance, acts as a hydraulic filter in the same manner as resistance/capacitance filters of electrical circuits
• this filtering has several functions,

a. converts the intermittent output of the heart into a continuous flow through the peripheries

b. reduces the work of the heart

• the entire stroke volume is discharged into the arterial system during systole, which usually comprises ~ 1/3 of the cardiac cycle
• most of the SV is expelled in the rapid ejection phase which is 1/2 of systole
• the determinants of external cardiac work are pressure x volume
• therefore, for a given cardiac output, the compliance of the system by reducing the peak systolic pressure, reduces cardiac work (B+L fig. 6-2)
• under average conditions, the additional work imposed by the intermittent cardiac pumping, above that required for steady flow, is

a. ~ 35% for the RV, and

b. ~ 10% for the LV

• these figure are highly dependent on compliance, TPR, HR, and CO

Arterial Elasticity

• most commonly represented by static pressure-volume curves of the aorta
• curves for younger individuals are ***sigmoidal*** in shape and accommodate far greater volumes than do those of older subjects (B+L fig. 6-3)
• in the most compliant curve of the young, the curve is quite linear over most of its range, however the compliance ($\delta V/\delta P$), decreases at both high and low volumes
• this pattern is due to the elastic properties of the arterial wall
• the changes in the shape of the curve with age, representing decreased compliance, are due to progressive changes in the elastin and collagen content of arterial walls
• as compliance decreases and vessels become stiffer, the heart is unable to eject a given stroke volume into the arterial system as rapidly as for the compliant system of youth
• the peak arterial pressure occurs progressively later in systole, and reaches a higher value, as compliance decreases

NB: such static curves are only an approximation, as the dynamic behavior of the system differs considerably → arterial pressure is a function not only of the volume change (δV), but also of the ***rate*** of change of volume ($\delta V/\delta t$)

→ therefore the arterial system is ***viscoelastic*** in function

Mean Arterial Pressure

• the P_{MA} can usually be approximated from the systolic and diastolic pressure as follows,

$$P_{MA} \sim P_D + (P_S - P_D)/3$$

• the mean pressure is a function of the ***mean volume*** of blood is the arterial system, and the ***compliance*** of the arterial circuit,

$$\delta Pa = \delta V_A / C_A$$

• the volume of blood in the arterial circuit, in turn, is a function of the rate of inflow, or ***cardiac output***, and ***peripheral runoff***
• the rate of peripheral runoff is determined by the arterial pressure and peripheral resistance,

$$Q_O \sim P_{MA}/R$$

• combined with the above, the pressure change with time,

$$\delta P_A/\delta t = (Q_I - Q_O)/C_A$$

• where the new mean arterial pressure will not be attained until $Q_O = Q_I$
• with changes in inflow, or outflow, the arterial compliance determines the ***rate*** at which the new mean arterial pressure will be reached, ***not*** the magnitude of the pressure rise

> ***NB:*** therefore, the level of the mean arterial pressure is determined only by the ***cardiac output*** and ***peripheral resistance***

Pulse Pressure

• assuming that P_{MA} is dependent upon V_{MA} and C_A, it can be shown that the pulse pressure is principally a function of ***stroke volume*** and ***arterial compliance***

▪ *Stroke Volume*

• during the rapid ejection phase of systole the aortic inflow exceeds outflow and the arterial pressure rises
• the maximum arterial volume corresponds with the end of the rapid ejection phase and with the maximum pressure, giving the systolic pressure
• conversely during diastole the peripheral runoff exceeds inflow and the arterial pressure continues to fall until the beginning of the next period of ejection, giving the diastolic pressure
• the pulse pressure being the difference between these two
• a normal heart ejects **~ 80%** of its SV during the ***rapid ejection phase*** and this volume increment corresponds with the pulse pressure increment
• during the remainder of the cardiac cycle, Q_O will greatly exceed Q_I
• a rise in SV will result in an increase in ***both*** mean and pulse pressures
• the hyperdynamic heart will tend to eject the same fraction of its SV in the same time period
• hence the volume and pressure increments in the rapid ejection phase will increase proportionately to the increase in SV and the rise in systolic pressure will ***exceed*** that of the diastolic (assuming the arterial system has ~ linear compliance curve)

▪ *Arterial Compliance*

• for a given SV, the less compliant vessels of the elderly will result in a greater change in pressure during the rapid ejection phase, however the mean pressure will remain the same, so long as V_A and R are constant
• increases in SV will be accompanied by commensurately greater rises in pulse pressure, again systolic >> diastolic

> ***NB:*** these effects will increase the external workload of the LV, for any given values of SV, P_{MA}, and TPR

▪ *Total Peripheral Resistance & Arterial Diastolic Pressure*

• often stated that TPR affects primarily the level of diastolic pressure
• not entirely true, as the elevated TPR seen in hypertensive patients is associated with an "old" arterial compliance curve, ie., as volume and pressure increase, the compliance decreases
• therefore, elevations of Pá into the less compliant regions of the curve are associated with greater elevations of systolic pressure (B+L fig. 6-9)

Peripheral Arterial Pressure Curves

• the rapid ejection phase of systole and distention of the aorta → pressure wave which travels through the vascular circuit with a finite velocity, in accordance with ***wave theory***
• the forward velocity of the wave in considerably faster than the actual flow of blood

→ propagated ***pressure wave*** of peripheral arteries

• the ***velocity*** of transmission,

1. varies inversely to the arterial compliance
2. increases with age, confirming the reduction of compliance with age
3. increases progressively as the wave travels down the aorta and into narrower main arteries, indicating the lower compliance of the more peripheral portions of the vascular circuit
   - this is also due to narrowing of the vessels and conservation of energy

• the ***waveform*** is distorted as it travels toward the periphery,

1. high frequency elements are lost, eg. incisura
2. systolic hump is elevated and narrowed, "peaking"
3. additional hump may appear in diastolic plateau

• these changes in contour are more pronounced in the young subject and decrease with age
• the damping of the high frequency components is essentially a function of the viscoelastic properties of the vessels
• the mechanism for the ***peaking*** of the systolic wave is controversial, however probably results from several factors,

1. ***reflection*** from higher impedance peripheral branches
2. ***resonance*** in the columns of blood
3. ***tapering*** of the column → increasing pressure front
4. changes in the ***velocity*** of transmission with pressure level

NB: at any point the waveform is the algebraic sum of the antegrade incident wave and retrograde reflected waves

• ~ 80% of the antegrade wave is reflected back from the periphery at normal levels of TPR
• as velocity varies inversely with compliance, and compliance inversely with pressure → the higher pressure points travel at greater velocity and tend to "catch-up" on the later segments of the waveform

MICROCIRCULATION AND LYMPHATICS

Anatomical Organisation

• the microcirculation is composed of serially and parallel arrangements of blood vessels including,

i. arterioles
ii. metarterioles
iii. precapillary sphincters
iv. capillaries
v. arteriovenous anastomoses
vi. venules
vii. collecting venules

• the precise positioning of these vessels differs in different tissues
• generally there are multiple collateral channels
• the ***arterioles*** range in diameter from 5 to 100 µm, have a thick smooth muscle layer, a thin adventitial layer and endothelial lining
• these give rise directly to ***capillaries***, 5 to 10 µm, or in some vascular beds to ***metarterioles***, 10 to 20 µm in diameter which then give rise to capillaries
• these metarterioles may serve either as conduits to capillaries or as ***virtual shunts***
• at the points of origin of capillaries in some tissues there is a small cuff of muscular tissue, the precapillary sphincter, which controls flow through cognate capillaries
• some tissues organize the arteriolar system into an arcade to provide an isoperfusion source for all microcirculatory units

Functional Organisation

• the series and parallel coupled components of the microcirculation may be classified as either,

a. resistance vessels
b. exchange vessels
c. shunt vessels
d. capacitance vessels

■ ***Resistance Vessels***

• resistance to flow is manifest by all blood vessels, which may be essentially classified as either,

a. precapillary, or
b. postcapillary resistance elements

• the precapillary resistance elements include small arteries, arterioles and precapillary sphincters
• the muscular arterioles are the major resistance vessels of the systemic circulation

• the ***precapillary sphincters*** determine,

a. the number of open capillaries
b. regulate regional flow to capillary beds
c. the extent of capillary flow velocity
d. capillary surface area
e. the mean extravascular diffusion distances

• the postcapillary resistance vessels include the muscular venules and small veins
• although they manifest only small changes in resistance, their position enables them to markedly influence capillary pressure
• it is the ratio of pre/post-capillary resistance which determines ***hydrostatic pressure***

▪ ***Exchange Vessels***

• exchange between the vascular and extravascular compartments occurs primarily across capillaries and venules
• these vessels have very high surface area to volume ratios
• the capillaries form a network of channels of varying length → 0.5-1 mm
• the number of, and distance between, capillaries varies in tissues depending upon their respective metabolic activity → ***capillary density***
• as some of the smaller capillaries have diameters less than RBCs, it becomes necessary for RBCs to be capable of considerable distortion and flexibility
• exchange vessels are normally situated within 20-50 μm of tissue cells, so diffusion distances are small
• within a single tissue the venous end of the circuit is more permeable to water and solute than is the arterial end
• different tissues have marked variation of capillary structure resulting in different permeabilities

▪ ***Shunt Vessels***

• all vessels that bypass the effective exchange circulation of the tissue serve as shunt vessels
• these include arteriovenous anastomoses, metarterioles, preferential channels, and capillaries when flow greatly exceeds metabolic requirements

▪ ***Capacitance Vessels***

• by virtue of their great distensibility, the veins are the major capacitance vessels of the vascular circuit
• the venular and small venous division constitutes the major functional capacity of the vascular system, containing ~ 70% of blood volume

Functional Activity of The Microcirculation

▪ *Normal Blood Flow*

• in contrast to the laminar flow seen in small arterioles and venules, laminar flow characteristics are ***less*** evident in the microcirculation
• the blood flow to capillaries is not uniform and is determined by the contractile state of the arterioles and the metabolic activity of the tissue
• velocity has been estimated at,

a. arteriolar ~ 4.5 mm/sec
b. venular ~ 2.5 mm/sec
c. capillaries ~ 1.0 mm/sec

• capillary flow may vary from 0 to several mm/sec within the same vessel within a short period of time, and may actually reverses direction so the transit time of RBCs is even greater
• RBCs flow in single file at varying rates and are distorted due to the restricted vessel lumen

▪ *Intermittency Of Blood Flow*

• these changes in capillary blood flow may be ***random***, or of a rhythmical nature due to ***vasomotion*** of the precapillary vessels
• changes in the transmural pressure affect the contractile state of the precapillary vessels

→ ? the myogenic mechanism of ***autoregulation***

• metarteriolar vasomotion is concerned with main channel flow, never being intense enough to completely arrest flow
• precapillary sphincter vasomotion, on the other hand, may completely arrest capillary flow
• as flow through capillaries is directed toward the metabolic needs of the tissues, it has been termed ***nutritional*** flow, c.f. flow bypassing the capillary bed termed ***nonnutritional***, or ***shunt*** flow
• anatomical evidence for the existence of shunts is lacking in some tissue, e.g. skeletal muscle, however shunt flow can still be demonstrated and is termed ***physiological shunt***
• in tissues that have metarterioles, shunt flow may be continuous from arteriole to venule during periods of low metabolic activity, when many precapillary vessels are closed
• this provides a ready source of blood flow when required
• true capillaries are devoid of smooth muscle, however endothelial cells which form the vessel walls contain actin and myosin and are capable of changing their shape in response to a number of chemical stimuli
• there is ***no*** direct evidence that these alterations in shape are involved in the regulation of capillary blood flow

Transcapillary Exchange

▪ *Capillary Structure*

• the capillaries are small diameter vessels consisting of a single layer of endothelial cells
• endothelial cells are involved in a number of physiological functions, eg. the release of ***endothelial derived relaxing factor*** in response to stimulation with ACh
• at the outer surface is an amorphous mucopolysaccharide matrix called the ***basement membrane***
• inner surface is covered by mucoprotein, "snot", which determines plasma, RBC and WBC flow through capillaries
• also involved in contents of vesicles transported across membrane
• this forms a barrier ~ 500 Å thick (1A° = 10^{-10}m), which contributes to the permeability characteristics of the capillary
• capillaries are classified on the basis of their endothelial perforations, or ***fenestrations***, and the extent of the basement membrane and perivascular investment, thus

a. capillaries of muscle, skin heart and lung →
   i. prominent, continuous BM
   ii. prominent pericapillary investment
b. capillaries of the liver →
   i. faint, discontinuous BM
   ii. large endothelial perforations
   iii. no significant pericapillary investment
c. capillaries of the intestine →
   i. thin, fenestrated endothelial walls
   ii. continuous but indistinct BM
   iii. only slight perivascular investment

▪ *Capillary Pores*

• exchange of lipid-insoluble molecules such as glucose, electrolytes, AA's etc. are believed to take place through aqueous filled "pores", which are associated with the intercellular spaces
• these spaces are ~ 200 Å wide with several foci of narrowing where adjacent cells fuse
• fusion is, however, incomplete and openings ~ 40 Å (4 nm) are present
• these provide for rapid exchange of small solutes (MW < 10,000) by diffusion
• these clefts, or pores, are sparse and represent only ~ 0.02% of the capillary surface area
• in addition to these small pores, there are larger ones (radius ~ 250 Å) which are associated with the venous end of the exchange system
• these do not contribute significantly to the exchange of small molecules due to their low density
→ ratio, large:small ~ 1:30,000
• they are, however, one of the routes by which large molecules such as ***albumin*** leave the circulation
• fenestrations may be considered as giant pores, being 20 to 100 nm wide, and contribute markedly to the permeability of the capillary bed
• the relative permeabilities of the above groups following the size of their fenestrations
• liver being the most permeable, the endothelium actually being discontinuous

▪ ***Diffusion***

• under normal conditions, movement of ***water*** across the capillary wall is due to,

a. filtration and absorption ~ 0.06 ml / 100 g tissue / min

b. diffusion ~ 300 ml / 100 g tissue / min

• transcapillary exchange of ***solute*** is also primarily governed by ***diffusion***
• according to ***Fick's law*** of diffusion, the quantity of material diffusing per unit time (Q) is directly proportional to the concentration gradient, viz

$$\dot{Q} = \frac{A.D}{t} \times (C_1 - C_2)$$

where D = the free diffusion coefficient
A = the cross sectional area
C = the concentration gradient
t = the thickness/distance of diffusion

• the ***capillary permeability*** $\mathbf{P_s}$, may be defined as the degree to which the capillary permits the passage of molecules, and Fick's law may be stated as,

$$Q = P_S.A.(C_O - C_I)$$

• the major determinants of diffusibility being ***molecular size*** and ***lipid solubility***
• most ionic and molecular constituents are not lipid soluble and must pass through aqueous channels in, or between cells
• the size of these channels can be calculated by measuring the diffusion rate of an uncharged molecule whose free diffusion coefficient is known
• this measurement is not straight forward and requires corrections for,

a. attractions between solvent and solute molecules → ***solvent drag***

b. interactions between solute molecules → ***interionic forces***

c. pore configuration

d. ***electrostatic*** interactions between ions and pore surface

• small molecules, such as urea, glucose, water and NaCl, the capillary pores offer little restriction

→ low ***reflection coefficient***

• diffusion becomes minimal for molecules whose **MW > 60,000**
• thus, for small molecules the only limitation to continued diffusion is the rate of blood flow,

a. small molecules → ***perfusion limited***

b. larger molecules → ***diffusion limited***

• the rate of diffusion is uninfluenced by ***filtration*** in the opposite direction
• in fact, filtration ***or*** absorption, increases the removal of tracer ions from the interstitial fluid
• lipid soluble molecules pass directly through the membranes of the entire capillary endothelium
• lipid solubility, measured as the oil:blood partition coefficient giving a good index of the rate at which a particular species will diffuse
• both ***oxygen*** and ***carbon dioxide*** are lipid soluble and pass readily through endothelial cells
• the O_2 supply of normal tissues is not limited by diffusion, or by the number of open capillaries
• in many tissues the O_2-saturation has dropped to 80% by the entrance to the capillary due to diffusion of O_2 from arterioles
• this diffusion reflects not only the movement to respiring tissues, but also direct flux of both O_2 and CO_2 with adjacent venules in a ***countercurrent*** fashion
• this effective shunt of gas bypassing the tissues may limit O_2 supply at low flow rates

Capillary Filtration

NB: represents the algebraic sum of ***hydrostatic*** and ***osmotic*** forces

Hydrostatic Forces

• capillary hydrostatic pressure (P_C) depends on arterial pressure, venous pressure, precapillary and postcapillary resistances such that,

$$P_C = \frac{(R_V/R_A).P_A + P_V}{1 + (R_V/R_A)}$$

NB: a given increment in ***venous*** pressure produces a ***greater*** effect on P_C than the same increment in arterial pressure

• ~ 80% of an increment in venous pressure is transmitted back to the capillaries
• the important factor is the resistance ratio, R_V/R_A, which under normal circumstances is ~ 1/4
• hence an increase in one resistance may be offset by a commensurate change in the other
• figures vary considerably between tissues, but average values at the level of the heart are,

a. 32 mmHg → arterial end
b. 15 mmHg → venous end

• the hydrostatic pressure, minus the interstitial fluid hydrostatic pressure, is the principal force in filtration across the capillary wall
• the true value of P_I is debatable and was thought to be zero for years
• however, recent studies indicate it may in fact be -1 to -2 mmHg

■ *Osmotic Forces*

• the main factor retarding the loss of water from the capillaries is the colloid osmotic pressure, or ***oncotic pressure***, p_P
• the total osmotic pressure of plasma is ~ 6000 mmHg, whereas the oncotic pressure is only ~ 25 mmHg
• this pressure is important as the plasma proteins are essentially confined to the intravascular space, c.f. the electrolytes which distribute almost equally by diffusion
• the relative permeability of the membrane to solute and water influence the magnitude of the osmotic pressure
• the ***reflection coefficient*** being the relative impediment to the passage of a substance through the capillary membrane,

a. water which diffuses freely $\sigma \sim 0$
b. albumin which is essentially impermeable $\sigma \sim 1.0$

• the true oncotic pressure is defined as,

$$\pi = \sigma RT.(C_I - C_O)$$

where, σ = the reflection coefficient
R = the gas constant
T = the absolute temperature

• of the plasma proteins, ***albumin*** is preponderate in determining the oncotic pressure

Protein	MW	Concentration	π
Albumin	69,000	3.5-5.0 gm/dl	65 %
Globulin	80,000-200,000	1.5-2.5 gm/dl	15 %
Fibrinogen	350,000-400,000	0.2-0.4 gm/dl	
	TOTAL	6.0-8.0 gm/dl	~ 25 mmHg

NB: ***albumen*** exerts a ***greater*** osmotic force than can be accounted for solely on the basis of the number of molecules; this effect being greater at higher concentrations of albumin and almost absent at low concentrations, due to,

i. polyanion at pH = 7.4 - therefore retains cations (Gibbs-Donnan)
ii. albumen binds a small number of Cl^- ions increasing (i.)

• the net effect of these is that albumin behaves as if it had a **MW ~ 37,000**
• if this were the case, then it would not be retained within the intravascular compartment and could not function as a counterforce to P_C
• further, if albumin didn't have an enhanced osmotic force, ~ 12 g/dl would be required to achieve the oncotic pressure of 25 mmHg and this would increase the viscosity of blood significantly
• small amounts of albumin leak from the circulation and exert a small oncotic force in the interstitial fluid $\rightarrow$ p_I **~ 0.1 to 5 mmHg**

The Balance of Hydrostatic and Osmotic Forces, Starling's Hypothesis

NB: Fluid Movement, $Q = k[(P_C + \pi_I) - (P_I + \pi_P)]$

where, k = the filtration constant for the capillary membrane

→ ***filtration*** occurs when the value is positive
absorption occurs when the value is negative

- some capillaries show filtration for their entire length, such as in the glomerulus
- others may show absorption for their entire length, as for the gastric mucosa
- in the normal steady state, most other factors remain fairly constant and pre/postcapillary ***resistance*** is the chief determinant of fluid movement across the wall of any capillary
- since water moves freely, the hydrostatic and osmotic forces are nearly in equilibrium along the entire length of the capillary and normal filtration and absorption occur with very small driving pressures
- only a small fraction of the plasma flowing through the vascular circuit is filtered, ~ 2%
- of this ~ 85% is reabsorbed by the capillaries and venules

- in the ***pulmonary*** circuit,
  a. mean P_C ~ 8 mmHg
  b. π_P ~ 25 mmHg

NB: the balance of forces → ***absorption*** along the entire capillary length
pulmonary ***lymph*** is formed due to the osmotic action of the small amount of plasma protein which leaks across the endothelium

▪ ***Capillary Filtration Coefficient***

- the rate of movement of fluid (Q_f), depends not only on Starling's forces (δP), but also on,
  a. the ***area*** of capillary wall available for filtration (A_m)
  b. the ***distance*** across the capillary wall (δx)
  c. the ***viscosity*** of the filtrate (η), and
  d. the ***filtration constant*** for the membrane (k),

$$Q_f = \frac{k.A_m.\delta P}{\eta.\delta x}$$

NB: this is essentially equivalent to ***Poiseuille's law*** for laminar flow

• since the thickness of the capillary wall and the viscosity of the filtrate are relatively constant they can be included with the filtration constant
• and, since the area of membrane is unknown, the rate of filtration can be expressed per unit weight of tissue,

$$Q_f = k_t.\delta P$$

where, k_t = the capillary filtration coefficient, and
Q_f is expressed in ml/min/100g tissue/mmHg

NB: in any given tissue, k_t is not altered by physiological changes in arteriolar or venous pressure, pH, P_{aO2}, or P_{aCO2}

however, capillary injury such as occurs in burns, septicaemia etc. results in a marked increase in permeability and leakage of significant amounts of fluid and protein into the interstitium

• since k_t doesn't change physiologically, it may be used to calculate the fraction of open capillaries in a vascular bed under different conditions
• increases in filtration resulting from ***capillary recruitment***

• if the plasma proteins are replaced by an equi-oncotic, nonprotein substitute

→ k_t increases markedly and oedema occurs

• normal permeability is restored by as little as 0.2% albumin
• ?? albumin binds to endothelial pores and determines function

■ ***Disturbances in Hydrostatic-Osmotic Balance***

a. hypovolaemia → net ECF reabsorption
b. orthostatic pressure → myogenic arteriolar constriction
c. vomiting, dehydration, etc. → increased π_p
d. burns, septic shock, nephrosis → protein loss, decreased π_p

■ ***Pinocytosis - Vesicular Transport***

• EM studies show the presence of abundant vesicles 500 to 800 Å diameter in the endothelial membrane
• many of these are attached to the surface by "necks" which can be as large as 400 Å
• number varies between different tissues → muscle > lung > brain
• these are believed to be important in the exchange of large (> 30 nm), lipid insoluble molecules, such as ***albumin*** and ***fibrinogen***
• contents of vesicles are partly determined by the mucoprotein coating of the endothelial cells
→ "***endothelial snot***"
• transport of small molecules by this route is inefficient, since these rapidly diffuse across the capillary wall

Lymphatics

• widely distributed, closed-end network of highly permeable lymph capillaries
• lack tight junctions between endothelial cells and possess fine filaments which anchor them to surrounding connective tissue
• ultimately drain into main lymph channels, which join the systemic circulation at the junctions of the subclavian and internal jugular veins
• the only tissues devoid of lymphatic drainage are,

a. cartilage
b. bone
c. epithelium
d. central nervous system

• circulation is maintained by skeletal muscular activity and an extensive system of valves
• volume of lymph flow per 24 hours ~ total plasma volume (3.5l)
~ 1/4 total circulating plasma protein

• since back diffusion of albumin cannot occur against the high concentration gradient, failure of lymphatic drainage would $\rightarrow$ massive oedema

• in addition to returning filtered fluid and extravasated protein, lymphatic system filters particles at lymph nodes, eg. bacteria
• the largest lymph channel, the ***thoracic duct***, not only drains the lower extremities but returns protein and chylomicrons lost from the highly permeable hepatic capillaries

THE PERIPHERAL CIRCULATION AND ITS CONTROL

• the peripheral circulation is essentially under the dual control of the CNS and local tissue factors
• the relative importance of these two varies between tissues
• the resistance vessels, the arterioles, are chiefly concerned with the regulation of tissue blood flow and ultimately TPR

Vascular Smooth Muscle

• smooth muscle cells are small, ***mononucleate*** and spindle shaped
• generally arranged in helical or circular layers in the walls of the larger blood vessels, and in a single circular layer in the arterioles
• parts of the endothelial cells project into the vascular smooth layer, suggesting a functional interaction → ***myoendothelial junctions***
• in general, the close association between AP's and cell contraction seen in skeletal and cardiac muscle is absent in smooth muscle
• smooth muscle also lacks the transverse tubule system of the former
• graded changes in membrane potential are associated with changes in the cell's contractile state
• contractile activity can be elicited by either ***neural*** or ***humoral*** activity
• the behavior of smooth m. varies between tissues, eg. portal and mesenteric circulation has longitudinal smooth m. which shows spontaneous activity
• cells contain large numbers of thin, ***actin*** filaments and comparatively small numbers of thick ***myosin*** filaments
• the filaments are aligned along the long axis of the cell but ***do not*** form visible sarcomeres
• however, the contractile process → ***sliding filament mechanism***, as for skeletal muscle, and phosphorylation of crossbridges regulates the rate of contraction
• compared to skeletal m., smooth m.

a. contracts at a very slow rate
b. develops high forces
c. maintains force for prolonged periods with low ATP usage
d. operates over considerable range of lengths physiologically
e. lacks fast Na^+ channels and troponin

• actin/myosin interaction is controlled by intracellular $\mathbf{Ca}^{++}$ as in other muscle, however the mechanism differs
• increased myoplasmic Ca^{++} may originate from,

a. intracellular stores - the sarcoplasmic reticulum
b. displaced from the plasma membrane
c. result from increase membrane g_{Ca}

• Ca^{++} is extruded from the cell by an active membrane pump

• most of the arteries of the body are supplied, to different degrees, soley by fibres of the SNS which exert a basal tonic activity
• in contrast to the SNS, the PNS tends to decrease vascular resistance, however it innervates only a small fraction of the blood vessels in the body, mainly of the viscera and pelvic organs
• smooth m. also undergoes contraction in response to humoral stimuli, without evidence of electrical excitation → ***pharmacomechanical coupling*** and is mediated by increased Ca^{++}
• ***humoral*** substances affecting vascular smooth m. include,

a. catecholamines
b. histamine
c. ACh
d. serotonin
e. angiotensin
f. adenosine
g. ADH
h. prostaglandins
i. nitric oxide

• ***local*** influences on the contractile state of vascular smooth m. include,

a. temperature
b. pH
c. P_{CO2}
d. K^+

Intrinsic Control of Local Tissue Blood Flow

• in a number of different tissues, blood flow appears to be closely regulated to the ***metabolic rate*** of the tissues
• further, changes in arterial pressure at a constant metabolic rate are met by reflex changes maintaining constancy of flow → ***autoregulation***
• the mechanism for autoregulation is unknown, however three theories have been advanced,

1. ***tissue pressure*** hypothesis
2. ***myogenic*** hypothesis
3. ***metabolic*** hypothesis

▪ *Tissue Pressure Hypothesis*

• increased perfusion pressure → increased extravasation of fluid and increased tissue hydrostatic pressure → small vessel compression
• this can only operate in an encapsulated organ and, even in the kidney, convincing evidence is lacking

▪ ***Myogenic Hypothesis***

• that smooth m. contracts in response to stretch and relaxes with a reduction in tension
• for this theory to hold true the stimulus must be ***wall tension***, not stretch, as with increased pressure vessels must constrict to ***less*** than their resting state
• this follows for tension in accordance with ***Laplace's law*** (T=Pr)
• the myogenic mechanism has been demonstrated in certain tissue and in isolated arterioles
• since blood pressure is reflexly controlled under physiological conditions, operation of this mechanism would be expected to be minimal
• however, orthostatic pressure changes in the extremities are controlled by arteriolar constriction and its absence would result in the extravasation of an enormous amount of fluid

▪ ***Metabolic Hypothesis***

• blood flow is governed by the metabolic activity of the tissue and any intervention which decreases O_2 supply will result in the formation of vasodilator metabolites
• attractive, in that in most tissues blood flow closely parallels metabolic activity, however a specific mediator of vasodilation is still absent
• early suggestions were lactic acid, CO_2 and H^+, however the dilation produced by increased concentration's of these metabolites is considerably less than that observed *in vivo*
• local P_{O2} can also affect arteriolar tone, however following arterial occlusion the reactive hyperaemia persists well after normal P_{O2} has returned
• K^+, inorganic phosphate and interstitial fluid osmolality can also incite arteriolar dilation, and all of these are increased with increased tissue metabolism
• however, significant increases in the later two are not observed in contracting muscle and they only produce transient increases in flow
• K^+ release coincides with muscle activity or increased cardiac activity and could be responsible for the initial increase in blood flow, however K^+ release is not sustained, despite continued arteriolar dilation
• reoxygenated venous blood from active muscles does ***not*** cause vasodilation when infused into resting vascular beds
• recent evidence indicates that ***adenosine*** is involved in the regulation of coronary blood flow and may well be important for skeletal m.
• also, ***prostaglandins*** may be important in some vascular beds, eg. renal
• the metabolic control of vascular tone is superimposed upon the resting basal tone, and is independent of the CNS and may result from either,

a. a myogenic response to the arteriolar pressure
b. the high P_{aO2}
c. the presence of Ca^{++}
d. some unknown factor

NB: the unknown factor may well involve ***nitric oxide***, which being a gas would not have been measured in many of the early experiments

Extrinsic Control of Local Tissue Blood Flow

▪ *Innervation of Blood Vessels*

• SNS-NA vasoconstrictor fibres end on vessels in all parts of the body
• however, postganglionic sympathetic fibres to cerebral vessels are of little fucntional importance
• in addition to this, the resistance vessels of skeletal muscle receive SNS-ACh vasodilator fibres, which travel with the sympathetic nerves
• bundles of smooth NA & ACh fibres form a plexus in the adventitia of the arterioles
• fibres do not extend through the muscular layer
• neurotransmitter reaches the deeper layers by diffusion, and current spreads inward via tight junctions
• nerves containing other peptides are also found on blood vessels
• SNS nerves also contain neuropeptide Y, a vasoconstrictor
• PNS nerves also contain VIP which is a vasodilator
• sensory nerves near blood vessels contain calcitonin gene related peptide, CGRP and substance P

▪ *Neural Sympathetic Vasoconstriction*

• a number of regions in the medulla affect CVS activity,

a. the ***cardioinhibitory area***
   - predominantly the nucleus ambiguus in the medulla
   - also parts of the dorsal motor nucleus of the vagus & NTS
     → PNS mediated, (-) chronotrope & inotrope
   - also has inhibitory fibres to (b) & inhibits SNS

b. the ***vasomotor area***
   - groups of neurons in the ventrolateral medulla
   - excitatory neurons, including the C_1 area
     → increase activity in descending SNS pathways

• fibres descend in the spinal cord in the ***intermediolateral grey columns***, then emerge with the ***ventral roots*** to join the paravertebral sympathetic chains through the ***white rami***
• the preganglionic, myelinated fibres synapse with the unmyelinated postganglionic fibres, which then join the segmental ***spinal nerves*** which accompany the major vessels to the periphery and various target organs
• noradrenaline is the vasoactive transmitter and acts at α_1-adrenergic receptors
• the vasoconstrictor regions of the medulla are tonically active (1-3 Hz) and vasodilation is achieved by inhibition of these pressor regions

• these regions show rhythmic variations of tonic activity,

a. with respiration → Traube-Hering waves

b. lower frequency, respiration independent → Mayer waves

- factors affecting the activity of the ***vasomotor area***,
    a. direct stimulation
        - hypercapnia
        - hypoxia
    b. excitatory inputs from,
        - the cortex via the hypothalamus
        - the pain pathways
        - the carotid & aortic chemoreceptors
    c. inhibitory inputs from,
        - the cortex via the hypothalamus
        - the lungs
        - the carotid sinus, aortic & venous baroreceptors

Sympathetic Constrictor Influence on Resistance and Capacitance Vessels

• vasoconstrictor fibres supply the arteries, arterioles and veins; however, the neural influence on the larger vessels is of far less importance than the microcirculation
• capacitance vessels are apparently more responsive to SNS activity than are the resistance vessels, since they reach maximum constriction at a lower frequency of discharge
• the capacitance vessels ***do not*** posses β_2-adrenergic receptors, nor do they respond to vasodilator metabolites
• in addition to active changes in vessel caliber, passive changes also occur with alterations in transmural pressure; however, these changes are small in comparison to active changes
• at basal tone ~ 1/3 of the blood volume can be mobilised by physiological SNS activity
• basal tone is low in capacitance vessels and denervation produces only small increases in volume, therefore the resting blood volume of the tissue is close to its maximum
• tissues vary and a greater amount of blood can be mobilised from skin, c.f. skeletal muscle
• this represents the greater sensitivity of skin vessels to SNS activity and the lower basal tone

Active Sympathetic Vasodilation

• sympathetic ***cholinergic*** fibres innervate the resistance vessels of skeletal muscle and skin
• there is ***no*** evidence that these fibres innervate the capacitance vessels
• stimulation of SNS nerves usually results in vasoconstriction; if the effects of NA are blocked with an α-blocker, stimulation results in vasodilation which can be blocked with atropine
• fibres of the sympathetic cholinergic system arise in the motor cortex, pass through the hypothalamus and the ventral medulla before joining the main sympathetic outflow in the intermediolateral grey columns
• activation of these pathways results in a relatively large, transient initial increase in blood flow, followed by a smaller prolonged increase
• there is ***no*** evidence of any tonic activity in these fibres
• these pathways are believed to be operative in the initial increase in muscle blood flow seen with exercise, excitement, apprehension etc.

• in addition to the cholinergic vasodilator system, there are β_2-adrenergic receptors on the resistance vessels which produce the vasodilation observed with low levels of adrenaline secretion

Parasympathetic Neural Influence

• efferent fibres of the,

a. cranial division supply the blood vessels of the head and viscera
b. sacral division supply the genitalia, bladder and large bowel

NB: skeletal muscle and skin ***do not*** receive parasympathetic supply

• as only a small proportion of blood vessels receive PNS supply, the effect on TPR is ***negligible***
• stimulation of PNS fibres to glands $\rightarrow$ marked vasodilation
• unsettled whether this is the result of the release of a cholinergic neurohumor, or the local formation and release of bradykinin, or both

Humoral Vasoactive Factors

Adrenaline

- in low concentration → dilation of resistance vessels (β_2)
- higher concentrations → vasoconstriction (α_1)
- in the skin → only vasoconstriction

Noradrenaline

- → vasoconstriction in ***all*** vascular beds (α_1)
- however, under physiological conditions, NA released from nerve terminals is of far greater importance than NA/A released from the adrenal medulla

Kinins

- three related vasodilator peptides, the kinins, are found in the body,

1. bradykinin - a nonapeptide, is formed in the ***plasma***
2. lysylbradykinin - a decapeptide, formed in the ***tissues***
3. methionyllysylbradykinin - found in the urine

- these are formed from substrates called ***kininogens***
- both high & low MW kininogens are found, predominantly,

a. high MW kininogens → plasma
b. low MW kininogens → tissues

- the kinins are formed by the action of proteolytic enzymes, the ***kallikriens***
- plasma kallikrien is formed from ***prekallikrien***, by the action of prekallikrien activators, which are fragments of the activated ***factor*** $\mathbf{XII}_a$
- the later are formed by the action of plasmin on factor XII
- however, a (+)'ve feedback exists, as plasma kallikrien also cleaves factor XII

- tissue kallikrien does, and plasma kallikrien may, convert prorenin to ***renin***
- the kinins are predominantly inactivated by ***kinase II***
- this is actually ***ACE*** in the lung and this is the major site of inactivation
- kinin release is inhibited by adrenal glucocorticoids
- the actions of the kinins are similar to histamine,

a. vasodilation
b. contraction of visceral smooth muscle
c. increase capillary permeability
d. attract leukocytes
e. result in local pain on s.c. injection

Atrial Natriuretic Peptide

- antagonises the effects of a number of vasoconstrictors & lowers BP

Angiotensin II

- octapeptide formed from the action of ACE on angiotensin I $\rightarrow$

1. adrenal cortex - increased secretion of ***aldosterone***
2. kidneys
   i. arteriolar constriction decreasing GFR but increasing GRF:RPF ratio
   ii. direct tubular effect increasing Na^+ reabsorption
3. vascular smooth muscle - increased tone
4. CNS/PNS - facilitation of sympathetic activity
   - stimulates secretion of ADH
   - stimulates thirst

NB: all of which favour ***retention*** of salt and water and elevation of BP

Vasopressin

- is a potent vasoconstrictor, however not in normal physiological concentrations

Vascular Reflexes

▪ ***Baroreceptors***

• these are ***stretch*** receptors located in the,

a. carotid sinus → sinus nerve (of Hering)
glossopharyngeal nerve
nucleus of the tractus solitarius (NTS)

b. aortic arch → vagus nerve
nucleus of the tractus solitarius

NB: input from a.&b. → buffer nerve activity

• the NTS is the site of central projection of the chemoreceptors and baroreceptors,

a. ***stimulation*** → ***inhibition*** of SNS activity

b. lesions of the NTS produce vasoconstriction and a pressor response

• this is in contrast to the ***dorso-lateral medulla***, which is pressor to stimulation
• increased impulse frequency from the stretch receptors, in response to raised BP, inhibits the vasoconstrictor regions, resulting in vasodilation and lowering of BP
• stimulation of the vagal, cardioinhibitory regions, simultaneously lowers HR
• the sensitivity of the two groups of receptors varies with δBP,

a. ***nonpulsatile*** alterations → carotid sinus >> aortic arch

b. ***pulsatile*** changes in BP → responses are ~ equipotent

NB: the receptors in the carotid sinus show adaptation, therefore are more responsive to constantly changing pressures than sustained ones

• the threshold for firing of the carotid sinus is ~ 50 mmHg and a maximum sustained firing rate in achieved at ~ 200 mmHg
• since the receptors show adaptation, the rate of firing is greater at any mean BP where the pulse pressure is higher
• the increased vascular resistance in response to reduced arterial pressure is different in various vascular beds, therefore results in a ***redistribution*** of flow
• also, the ***sensitivity*** of the carotid sinus can be increased by local application of NA, or SNS stimulation
• a decrease in baroreceptor sensitivity occurs with hypertension, as the sinus becomes stiffer and less deformable as a result of the high arterial pressures

• the baroreceptors play a key role in the short-term management of arterial pressure in response to abrupt changes in CO, BP, TPR, and blood volume
• long term control, and far more important, is the responsibility of the kidneys

▪ ***Cardiopulmonary Baroreceptors***

• in addition to the above, receptors are located in the atria, ventricles and pulmonary vessels
• these have vagal afferent and SNS efferent nerves and are tonically active
• when stimulated, they reflexly inhibit SNS vasoconstrictor tone to resistance vessels, thereby lowering blood pressure
• the ***atrial receptors*** are of two types,

1. A receptors - stimulated by atrial contraction (δP)
2. B receptors - stimulated by filling, distension (δV)

• these also play a role in,

a. the regulation of ***ADH secretion***
   • release of this hormone being tonically ***inhibited*** by afferent B-receptor activity
b. regulation of ***atrial natriuretic hormone***
c. modulation of the renin-angiotensin-aldosterone system

▪ ***Peripheral Chemoreceptors***

• consist of small, highly vascular bodies in the region of the aortic arch, just medial to the carotid sinuses
• sensitive to changes in P_{aO2}, P_{aCO2}, and arterial pH
• although primarily concerned with the regulation of ***respiration***, they reflexly influence the vasomotor regions of the medulla

a. $\downarrow P_{aO2}$ $\rightarrow$ vasoconstriction
b. $\uparrow P_{aCO2}$ & $\downarrow$ pH $\rightarrow$ effects far less than those of the central chemoreceptors

• when hypoxia and hypercapnia occur together, the stimulatory effect is synergistic
• also, when combined with ***hypotension*** they potentiate the effects of the baroreceptors
• however, when both receptor types are stimulated in opposite directions, eg. hypertension and hypoxia, the effects of the baroreceptors are prepotent
• there are also chemoreceptors with sympathetic afferent fibres in the heart which are activated by ischaemia and transmit pain

▪ ***Hypothalamus***

• stimulation of the ***anterior*** hypothalamus $\rightarrow$ $\downarrow$ HR & BP
• stimulation of the ***posterolateral*** region $\rightarrow$ $\uparrow$ HR & BP *(posterior = pressor)*
• also controls the ***temperature*** related changes in skin vessel tone

▪ ***Cerebrum***

• stimulation of the motor and premotor areas usually $\rightarrow$ pressor response
• responsible for emotional changes and sympathetic cholinergic effects

- ***Skin And Viscera***

• painful stimuli can elicit either pressor or depressor responses, depending upon the location and magnitude of the stimulus
• distension of the viscera usually → depressor response
• painful stimulation of the body surface usually → pressor response
• in the anaesthetised subject, strong stimulation of any sensory nerve will elicit a pressor response

Pulmonary Reflexes

• lung ***inflation*** → systemic vasodilation and decreased BP
• lung ***deflation*** → opposite
• stimulation of pulmonary stretch receptors → vagus n. to NTS
→ inhibition of the vasomotor areas

Medullary Chemoreceptors

• ↑ P_{aCO2} stimulates the vasoconstrictor regions → ↑ SNS outflow
• this is opposed by the local dilator effects of CO_2
• similar effects are seen for arterial pH
• both effects are mediated by by alterations in **CSF pH**, as for the respiratory centres
• oxygen tension has little direct effect on the vasomotor regions of the medulla, its effects being mediated peripherally
• cerebral ischaemia results in marked vasoconstriction, probably as a result of local accumulation of CO_2 and hypoxia
• prolonged, severe ischaemia → brainstem depression and hypotension

Intrinsic vs. Extrinsic Control of Local Tissue Blood Flow

• in both brain and heart the intrinsic flow-regulating mechanisms are dominant, maintaining flow under adverse conditions
• in the skin, the extrinsic mechanisms are dominant, mainly due to the temperature regulating function of skin blood flow
• in skeletal muscle control varies depending upon the circumstances

a. at rest neural control is dominant
b. prior to exercise SNS-ACh activity increases flow,
after the onset of exercise local factors determine control of blood flow

• under these conditions, vasoconstriction occurs in inactive vascular beds as a result of the general SNS outflow, thus diverting blood flow to the active muscles
• normally under exercise conditions, the P_{aCO2} remains near normal levels
• were P_{aCO2} to increase, a generalised vasoconstriction would follow due to SNS activity, however in active muscles, where CO_2 levels are highest the local dilatory effects would predominate

CONTROL OF CARDIAC OUTPUT
HYDRAULIC COUPLING

- the following ***four*** factors are usually considered to control cardiac output,
    1. myocardial contractility
    2. heart rate
    3. preload
    4. afterload

- the first two are strictly cardiac factors, the later two depend on both the characteristics of the heart and vascular circuit

    → preload and afterload are effectively ***coupling*** factors

- analysis of these interactions can be achieved by two curves (Guyton),
    a. vascular function curve
    b. cardiac function curve

Vascular Function Curve (VFC)

- defines the change in central venous pressure (CVP), which occurs as a consequence of changes in cardiac output (CO)
- ie., CVP is the ***dependent*** variable and CO the stimulus

- the characteristics of this curve depend upon the,
    1. vascular resistance
    2. arterial and venous compliances, and
    3. blood volume

- therefore, is entirely ***independent*** of the heart and may be studied with a mechanical pump

- for ease of assessment, the circulation is subdivided into four components,
    1. "pump-oxygenator" = heart plus pulmonary circuit
    2. peripheral resistance = high resistance microcirculation
    3. total arterial compliance, C_A
    4. total venous compliance, C_V

- where compliance, $C = \delta V/\delta P$ and, $C_V \sim 20 \times C_A$

• the system pressure at rest, ie. no flow, is a function of the ***blood volume*** and total system ***compliance***, as pressure will be equal at all points
• this is called the ***mean circulatory pressure***, $\mathbf{P_{MC} \sim 7\ mmHg}$
• as the pump begins, P_A will rise and P_V fall, until the pressure gradient P_A-P_V is such that the flow through the peripheral resistance is equal to the output of the pump

> ***NB:*** thus, the pressure gradient across the peripheral resistance is the single most important factor determining ***venous return***, and is directly ascribable to the action of the pump itself

• at "normal" peripheral resistances of 20 mmHg/l/min, a pressure gradient of 20 mmHg is required to establish a flow of 1 l/min
• if C_V:C_A is assumed to be 19:1, then a CO of 1 l/min would,

1. $\uparrow P_A$ 19 mmHg $\rightarrow$ 26 mmHg
2. $\downarrow P_V$ 1 mmHg $\rightarrow$ 6 mmHg (mean ~ 7 mmHg)

■ ***Venous Pressure Dependence on Cardiac Output***

• *in vivo* observations confirm that changes in CO ***do*** in fact alter arterial and venous pressures
• eg., the acute fall in CO in AMI results in lowered P_A and elevated P_V
• in animals, if the heart is replaced by a mechanical pump, a series values of P_V can be obtained at various CO's $\rightarrow$ VFC (B+L Fig. 9-5)
• the curve is plotted with the dependent variable, CVP, on the abscissa and the linear portion of the curve is described by,

$$P_V = - \frac{R.C_A.Q + P_{MC}}{C_A + C_V}$$

• thus, the ***slope*** of the curve depends only on R, C_A and C_V
• when Q = 0, so $P_V = P_{MC}$ and the reduction in P_V which can be achieved by increasing CO is limited by ***venous collapse***
• *in vivo* this collapse occurs as the great veins enter the thoracic cavity, due to the lower than atmospheric intrathoracic pressure
• this will limit the CO irrespective of the capabilities of the pump
• this simplified analysis assumes there is no venous resistance which is false, there being a constant pressure gradient from periphery to RA

■ ***Blood Volume***

• at zero flow conditions, P_{MC} is determined only by vascular compliance and blood volume
• for a given vascular compliance, P_{MC} will be increased by hypervolaemia and decreased by hypovolaemia
• thus, shifting the VFC to either the right or left (B+L Fig. 9-6)
• this assumes C_A and C_V are ***constant*** and not volume dependent, which they are!
• the slope of the VFC remains constant, where R, C_A and C_V are constant
• from this analysis it becomes apparent that the maximum CO is reduced as blood volume is reduced, however the P_V at which this occurs is unaltered, collapse being determined by ambient pressure

- ***Venomotor Tone***

• the effects of changes in venomotor tone closely resemble those of alterations in blood volume
• at Q = 0, an increased venomotor tone will raise P_{MC}, shifting the VFC to the right
• increased venomotor tone will decrease C_V, however the change in compliance is small and the effect of C_V on the slope of the VFC is also small
• therefore, shifts of the curve will be ~ ***parallel***

- ***Blood Reservoirs***

• in effect, vascular beds which undergo appreciable venoconstriction act as reservoirs of blood,

a. the skin
b. pulmonary circuit (arterial and venous)
c. liver
d. spleen

• in humans the spleen is less important than for lower animals

- ***Peripheral Resistance***

• arterioles contain ~ 3% of the circulating blood volume, therefore changes in tone ***do not*** significantly alter P_{MC}
• at any given CO, P_V varies inversely with arteriolar tone, other factors being constant (see B+L Fig. 9-7)
• increases in TPR effectively increasing the arterial blood volume at the expense of the venous side, assuming compliances remain constant
• the overall effect is a greater CO is attainable with vasodilation, than with normal or increased arteriolar tone

Coupling Between the Heart and Vessels

• since the circulation is a closed circuit, clearly the amount of blood returning to the heart must equal the output over any period of time
• therefore, ***cardiac output*** and ***venous return*** are simply two terms for the flow around the circuit
• acute changes in peripheral vascular resistance, myocardial contractility, or blood volume, may transiently exert disparate effects on CO and VR

NB: however, equilibrium is soon established and CO and VR are ***identical***

• in accordance with Starling's law, CO is dependent upon P_V, as RA and RV end-diastolic pressures are almost identical
• graphs of CO versus P_V → ***cardiac function curves*** (CFC)
• other intrinsic regulatory mechanisms will significantly affect such curves, however for simplified analysis these may be ignored
• extrinsic regulatory mechanisms can be considered as shifts of the CFC to the right or left, as appropriate

→ combined ***cardiac*** and ***vascular function curves***
see B+L Fig. 9-8, also following diagrams

• so long as the given cardiac and vascular function curves accurately describe the system, only transient deviations from the equilibrium point, where the two curves intersect, are possible

■ *Enhanced Myocardial Contractility*

• increases in contractility may be represented as a shift of the CFC to the left, thereby increasing the CO and decreasing the P_V for a given blood volume
• this may be achieved *in vivo* by stimulation of the cardiac SNS nerves, since effects of such stimulation are restricted to the heart (B+L Fig. 9-9)

■ *Blood Volume*

• changes in blood volume ***do not*** directly affect myocardial contractility, rather they shift the VFC to the right, thereby raising P_V which, in turn, raises CO by Starling's law
• thus, transfusion increases both P_V and CO, haemorrhage having the opposite effect

• pure increases in ***venomotor tone*** have very similar effects on the VFC, therefore also raise both P_V and CO

■ *Heart Failure*

• in acute heart failure, the CFC is shifted down & to the right, resulting in an increase in P_V with a lowering of CO
• as failure becomes chronic, fluid retention ensues and the VFC is shifted to the right, tending to compensate for the lowered CO, however P_V remains elevated
• as failure becomes more severe, the elevated blood volume cannot compensate for the reduced contractility, CO falls and P_V rises further (B+L Fig. 9-12)

Mean Circulatory Pressure
Venous Pressure
Cardiac Output

Cardiac Output
Venous Pressure

Cardiac Output
Venous Pressure

↑ Blood Volume
δ Contractility
Cardiac Output
Venous Pressure

- ***Peripheral Resistance***

• predictions of the effects of altered TPR are difficult, as this affects ***both*** curves, an increase in TPR causing the,

a. VFC → downward & to the ***left*** *but same x-intercept (P_{MC})

b. CFC → downward & to the ***right***

• the net effect being a reduction in CO at approximately the same P_V, the effect upon the later being determined by the relative effects on each curve
• under these conditions P_A will increase, assuming other factors constant

Role of Heart Rate

• CO is the product of stroke volume and heart rate
• in the preceding analysis, control of CO was restricted to SV as alterations of HR also alter preload, afterload and contractility
• an increase in HR over the range 60 to 160 does not alter CO appreciably as the increased rate is accompanied by a concomitant decrease in ventricular filling and SV
• below 60 bpm, SV is little enhanced by the increased time for diastolic filling and CO decreases with HR
• above 160 bpm, SV is greater than proportionately decreased due to the greatly reduced time for filling, CO again falling
• another factor is tissue autoregulation, which tends to hold tissue blood flow constant by alterations in preload and afterload which tends to hold CO constant
• during exercise, for example, the major factor in the increased CO is the fall in TPR, alterations in HR playing only a secondary, permissive role
• the mechanisms responsible for raising the HR in proportion to the increased CO are of neural origin

Ancillary Factors Affecting Cardiac Output

- ***Gravity***

• effects of $\pm g_x$ profoundly influence CO, eg. fainting and GLOC in pilots
• usual explanation that (+)'ve g_x impedes venous return, therefore reduces CO is incomplete as this ignores the facilitative counterforce on the arterial side of the same circuit
• additional ***hydrostatic pressure*** = r**hg** for the column of blood and, if blood vessels were rigid tubes would have no effect upon flow, merely alter the pressure at the extremities
• as vessels are distensible, and diameter is determined by the transmural pressure, vessel diameter is increased by the hydrostatic effect in dependent regions and vica-versa
• because flow is directly related to vessel diameter (Poiseuille), flow is likewise increased in the dependent regions
• however, as $C_V >> C_A$, the distension will be ***greater*** on the venous side with subsequent pooling of blood, the haemodynamic effects of which are similar to haemorrhage
• standing from the supine position results in the pooling of 300-800 ml of blood in the legs and can reduce CO by up to 2 l/min
• the baroreceptor reflex is activated increasing HR, SV and TPR by increased vasomotor tone

• SNS vasoconstriction is greater on the arterial side and factors which interfere with normal venous function, eg. standing stationary, warm ambient temperatures, reduce the compensatory mechanisms
• other factors which interfere with the normal orthostatic response include,

a. weightlessness - ie. space
b. prolonged supine position - bed rest
c. antihypertensives, and some other drugs
d. reduced blood volume - shock, adrenal insufficiency, etc

• elevation of a periphery, such that hydrostatic pressure was subatmospheric, would result in cessation, then fluttering of flow except that the deep venous system is prevented from collapse by supportive tissue

■ ***Muscular Activity and Venous Valves***

• adopting the standing posture the venous pressure increases, reaching equilibrium in ~ 1 min
• the gradual rise is due to the action of valves supporting the column at various levels from periphery toward the heart
• at equilibrium, pressure measurements reveal that peripheral P_V is only slightly greater than that due to ρhg, due to the very low venous resistance
• this low resistance is the justification for lumping the veins as a common compliance in the vascular circuit
• muscular contraction, by forcing blood centrally through valves, lowers P_V and serves as an auxiliary pump
• it reduces venous pooling and lowers capillary hydrostatic pressure, hence reducing the transudation of fluid in the periphery

■ ***Respiratory Activity***

• the normal activity of the respiratory muscles $\rightarrow$ ***thoracoabdominal pump***, inspiration reducing intrathoracic pressure & increasing venous return
• this may be exaggerated by a ***Müller's manoeuvre***, a strong inspiratory effort against a closed glottis, but is not increased proportionately due to collapse of the great veins where they enter the thorax
• during expiration, flow into the central veins decreases, however the mean venous flow is ***greater*** with rhythmic respiration than in its absence
• this is partly due to the action of valves reducing flow away from the thorax
• sustained expiratory efforts increase the intrathoracic pressure and impede venous return
• straining against a closed glottis, ***Valsalva's manoeuver***, regularly occurs during coughing, defecation and heavy lifting

- ***Artificial Respiration***

• in most forms of artificial respiration, inflation is achieved by positive airways pressure, with ensuing increased intrathoracic pressure and impeded venous return, and expiration by passive recoil of the chest wall
• the net effect is a considerable ***decrease*** in vena caval flow
• if negative endotracheal pressure is used to achieved lung deflation the reduction is flow is greatly reduced (according to Berne & Levy - not supported by *in vitro* clinical studies)

CORONARY CIRCULATION

Anatomy

1. right coronary artery → right ventricle and atrium
   dominant in ~ 50% of subjects
2. left coronary artery → anterior descendens and circumflex branches
   left ventricle and atrium
   dominant in ~ 20% of subjects

NB: ***dominance*** is determined by supply to the AV-node & PDA,
there is some overlap, the two main arteries are ~ equal in 30% of subjects

- these large ***epicardial arteries*** are functionally distinct from the intramyocardial arterioles,
  a. predominantly elastic walls → little influence on flow regulation
  b. perfusion pressure is progressively decreased → ~ 50% at subendocardium

- ∴the vascularity of the subendocardium is increased and the small coronary arterioles are in a chronic state of ***dilation***
- thus, in situations where vasodilation may be necessary to increase oxygen supply, these vessels are unable to dilate and this area is more susceptible to ***ischaemia***
- flow is most commonly measured in humans by thermodilution, however the catheter/thermistor is inserted into the coronary sinus (Ganz *et al*.)
- this does not measure total coronary blood flow, as only ~ 2/3 of the arterial inflow returns to the venous circulation via the ***coronary sinus***
- however, almost all of the blood flow that enters the sinus drains from the left ventricle
  → good measure of ***LV blood flow***
- other methods include,
  a. injecting ^{133}Xe into a coronary artery via a cardiac catheter and monitoring myocardial clearance of the tracer
  b. total coronary flow by the nitrous oxide method
     - originally used by Kety-Schmidt for cerebral blood flow
  c. radionuclide studies → regional perfusion & ischaemic areas
     i. ^{201}Th → "cold spots"
     ii. ^{99m}Tc-PYP → "hot spots"
  d. injection of radioactive microshperes

NB: b. & c. are commonly used for assessment of anaesthetic agents on CVR

normal CBF ~ **250 ml/min**
~ 5% of CO at rest

• ***venous drainage*** enters the RA via,

a. the coronary sinus - majority

b. the anterior coronary veins - great cardiac vein (≡ LAD)

c. vascular connections between the myocardium and the cardiac chambers,

i. arterio-sinusoidal

ii. arterio-luminal

iii. thesbian vessels

• intercommunication appears to exist between all of the minute vessels of the myocardium, in the form of an extensive ***subendocardial plexus***
• some suggest that some perfusion is derived directly from the chambers via these channels, however radioactive studies ***do not*** support sufficient perfusion to contribute to myocardial oxygen supply
• right coronary artery drainage is primarily via the anterior coronary veins to the RA

Factors Affecting CBF

Determinants of Myocardial Oxygen Supply & Demand	
Decreased O_2 Supply	Increased O_2 Demand
Coronary Blood Flow • tachycardia - diastolic perfusion • hypotension - especially diastolic • increased preload • hypocapnia • coronary artery spasm • ↑ wall thickness • ↓ capillary density	Wall Tension • LV volume ↑ preload • LV pressure ↑ afterload • 1/wall thickness ***NB:*** Laplace's Law
Decreased O_2 content • anaemia • hypoxaemia	Heart Rate • tachycardia
Decreased tissue O_2 uptake • left shift HbO_2 curve • metabolic poisons, CN^- • sepsis syndrome • myocardial depressant factor(s)	Contractility • ↑ myocardial contractile force

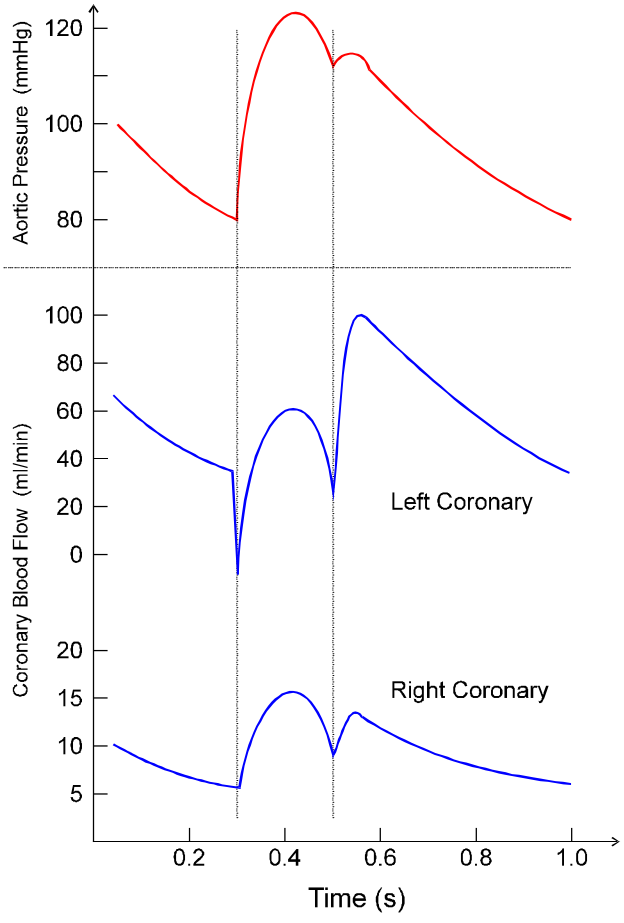
Physical Factors

▪ *Aortic Pressure*

• the primary driving force for coronary perfusion is ***mean*** aortic pressure, and changes in mean pressure usually evoke parallel changes in coronary perfusion
• however, alterations in cardiac work, as a result of altered afterload, have considerable effects on coronary resistance

> ***NB:*** any factor which increases the metabolic demands of the myocardium will reduce coronary vascular resistance (CVR), precise mechanism unknown

• under normal conditions the arterial pressure is maintained within narrow limits, so alterations of coronary perfusion are primarily the result of alterations in CVR in response to the metabolic demands of the myocardium



▪ *Intramural Pressure*

• the myocardium influences its own perfusion by a second mechanism, the ***extravascular resistance*** imposed during contraction
• this resistance is so great during the rapid ejection phase of ventricular systole that flow in the large coronary arteries may be reversed
• maximum left coronary inflow occurs during early diastole, when the myocardium is lengthening and extravascular compression of the coronary vessels is virtually absent (see diag.)
• this ***phasic coronary perfusion***, being out of synchronisation with myocardial work, is the theoretical basis of ***aortic counterpulsation***
• LV intramyocardial pressure is greatest near the endocardium, decreasing toward the epicardium
• this pressure gradient is compensated for by the greater supply of blood to the endocardium during diastole; studies show distribution of blood flow to the two areas are ~ equal, possibly greater to the endocardium
• since extravascular pressure is greater in the endocardium and flow is ~ equal, vascular tone in the endocardial vessels must be less

• under pathological conditions of reduced coronary perfusion, the ratio of endo:epicardial blood flow falls below 1, thus ischaemic damage is usually greater in the ***endocardial*** aspect of the wall
• flow in the right coronary artery shows a similar pattern to the left
• however, due to the lower mural pressures flow is ***not*** reversed and systolic flow contributes a greater proportion of total coronary flow

- ***Heart Rate***

• changes in heart rate, being achieved principally by alterations in the duration of ***diastole***, would have considerable effects on myocardial blood flow, except that the potential reduction is overridden by decreased CVR associated with the increased metabolic activity

- ***Neurohumoral Factors***

• the increase in CBF seen with SNS activity is the algebraic sum of,

a. ↑ HR and ventricular pressure → ↓ CBF
b. ↑ extravascular CVR → ↓ CBF
c. ↑ metabolic activity → ↑↑↑ CBF

→ the net effect being a marked ***increase*** in CBF

• when the physical aspects of (a+b) are removed by induced VF, the initial effect of increased SNS activity is ***vasoconstriction***
• in contrast to skeletal muscle, sympathetic-ACh innervation of the coronary ***does not*** exist
• use of α & β blockers confirms the presence of both on coronary vessels
• innervation of the β-receptors is questionable
• coronary vessels participate in the baroreceptor reflex via α-receptors and there is SNS tone to the vessels which can be reflexly modulated
• stimulation of the vagus nerve has little direct effect on the caliber of the coronary vessels, though, in the VF state some dilation can be achieved and activation of the chemoreceptors can elicit a decrease in CVR
• this lack of effect is not due to the absence of ACh-receptors as infusions of ACh evoke marked vasodilation
• these effects aside, in the normal subject, PNS activity has a negligible direct effect due to the dominance of local mechanisms
• the bradycardia and reduced contractility following vagal stimulation markedly reduce myocardial O_2 demand with ensuing vasoconstriction

• other ***hormones*** acting on the coronary vessels include,

a. ADH - not significant at physiological concentration
b. angiotensin - may be important in severe stress
c. prostaglandins - unlikely to play a significant role
d. thromboxane - involved with cascade → coronary thrombosis

Metabolic Factors

- the major factor in determining CBF is the level of myocardial MRO_2
- this holds true for the denervated heart and under conditions of VF
- asphyxia, hypoxia & infusions of cyanide are all able to increase CBF ≤ 300% in both innervated and denervated hearts
- substances investigated as possible mediators of the metabolic control include,

1. O_2, CO_2
2. lactate, H^+ ions, K^+ ions
3. increased osmolality
4. histamine, prostaglandins, polypeptides, and
5. adenine nucleotides

- none of these accounts for all of the effects observed *in vivo*, though, K^+ can account for ~ 1/2 of the initial increase in CBF
- most recent evidence indicates ***adenosine*** acts as a vasodilator at specific adenosine receptors
- this is probably the primary mediator, and is formed in the myocardium under conditions of relative hypoxia → breakdown of high-energy phosphate nucleotides
- a number of investigators have demonstrated changes in myocardial tissue adenosine levels which mirror changes seen in coronary vascular resistance & CBF (Merin 1989)

Factors Influencing CVR[1]

Factor	Increased CVR	Decreased CVR
O_2, CO_2	• hyperoxia • hypocarbia	• hypoxia • hypercarbia
ANS	• α-adrenergic activity	• β-adrenergic activity • cholinergic activity
Hormones	• vasopressin (ADH) • angiotensin II • thromboxane	• prostacycline • adenosine • adenine nucleotides
Blood Viscosity	• increased [Hb] • polycythaemia • hyper-globulinaemias	• decreased [Hb]

[1] modified from R.G. Merin, 1989, Anesthesia & the Coronary Circulation

Myocardial Oxygen Consumption & Work

a. resting 300g heart → CBF ~ 225 ml/min

b. basal O_2 consumption → MRO_2 ~ 8 to 10 ml/min/100g

c. oxygen extraction ratio → ER ~ 60%
~ 8 ml% O_2 in venous blood

NB: therefore, increases in **O_2 *supply*** are met primarily by increases in ***CBF***

- when the heart is arrested in ***diastole*** → MRO_2 ≤ 2 ml/min/100g
- this is ~ 6-8 times that for resting skeletal muscle
- LV work per beat, ***stroke work*** = SV x mean aortic pressure (MAP)

- at resting CO, the ***kinetic energy*** component is negligible
- however at high levels of CO, up to 50% of cardiac work may be kinetic
- for any given V.P product, myocardial O_2 demand will be higher as the ***pressure*** is increased
- ie., increases in volume work require only small increases in O_2 supply, whereas increases in pressure require large increases in O_2
- the area under the systolic portion of the LV pressure curve is termed the ***tension-time index***, and correlates well with myocardial O_2 consumption
- since this index does not account for the velocity of LV ejection, under conditions where the kinetic component is high, the index is inaccurate
- the main determinants of O_2 demand are,

1. wall tension
2. HR
3. contractility / velocity of shortening

NB: since the mean pulmonary pressure is $1/7^{th}$ of the systemic and the output of the two ventricles is equal, RV work is $1/7^{th}$ that of the LV

Cardiac Efficiency

- assuming a mean O_2 consumption of 9 ml/min/100g,

a. a 300g heart will use 27 ml of O_2/min

b. which equates to ~ 130 calories at a respiratory quotient of 0.82

- the work of the two ventricles ~ 8 kg.m/min, which is ~ 19 small calories
- therefore, the gross ***efficiency*** → 19/130 x 100 **~ 15%**
- the net efficiency is slightly higher, ~ 18%, if the O_2 consumption of the non-beating heart is subtracted
- with exercise the efficiency improves as P_{ma} remains constant, CO increases dramatically, however the O_2 consumption does not increase proportionately

Substrate Utilisation

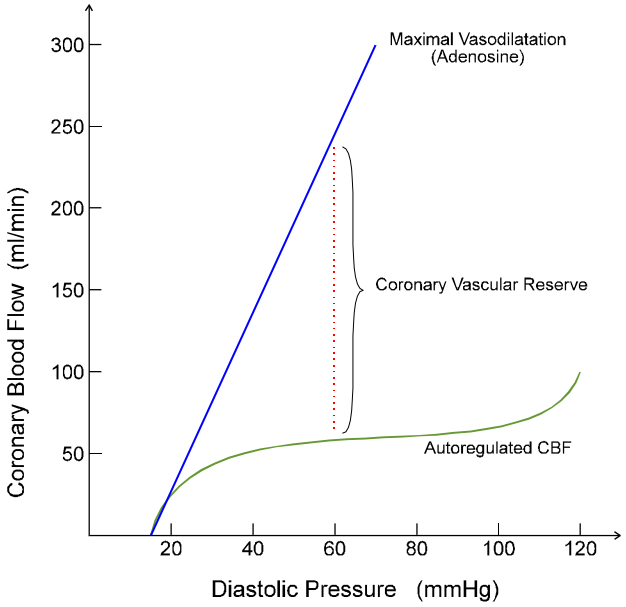
• the heart will essentially use whatever is presented to it in abundance
• at normal blood levels, ***lactate*** and ***glucose*** are consumed at about equal rates, whereas pyruvate utilisation is low, as is its blood concentration
• the threshold for glucose is ~ 4 mmol/l, below which myocardial uptake is virtually absent
• ***insulin*** reduces this threshold and increases glucose utilisation
• the threshold for lactate utilisation is very low and uninfluenced by insulin
• with hypoxia, glucose uptake is facilitated, whereas lactate cannot be metabolised and is actually produced by the hypoxic myocardium
• associated with this production of lactate is the breakdown of cardiac glycogen
• of the total O_2 consumption, only ~ 40% is due to the metabolism of CHO
• therefore, the heart derives the majority of its energy need by the oxidation of esterified and nonesterified ***fatty acids***
• these show different thresholds for uptake but are generally utilised in direct proportion to their blood concentration
• ***ketone bodies***, especially acetoacetate, are readily oxidised by the heart and are a major source of energy during ketoacidosis
• the contribution of amino acid oxidation is small
• normal oxidative phosphorylation of 1 mole of glucose yields 36 moles of ATP
• during hypoxia, glycolysis supervenes and 2 moles of ATP are provided
• during ischaemia lactic acid accumulates, due to lack of washout, and intracellular pH decreases inhibiting glycolysis, β-oxidation of fatty acids and protein synthesis
• these eventually lead to membrane dysfunction, cellular damage and necrosis

Effects of Anaesthesia on CBF

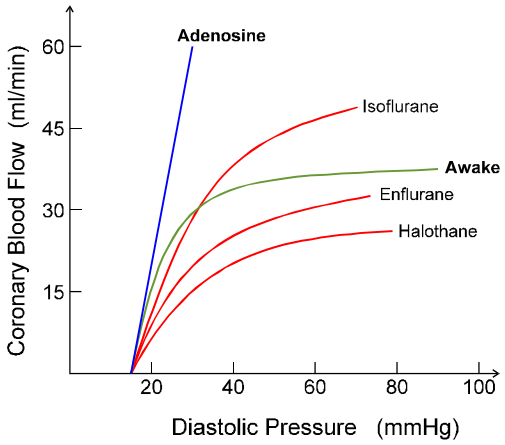
• all three inhalational anaesthetics interfere with normal coronary autoregulation
• halothane and enflurane have less effect and preserve autoregulation reasonably well, particularly within physiologic BP ranges
• ***isoflurane*** is certainly the most potent but is still well short of the dilation produced by ***adenosine*** (see fig. 3, Merin, 1989 - next page)
• multiple studies with other anaesthetic agents reveal that there is ***no*** uncoupling of the normal relationship between myocardial O_2 balance and CBF
• agents studied include,

i. thiopental
ii. propanidid
iii. droperidol/fentanyl
iv. Althesin
v. ketamine
vi. sufentanyl

• there is minimal evidence that N_2O may worsen myocardial ischaemia
• however most studies indicate that N_2O produces its effect on CBF in relationship to its effect on oxygen supply-demand balance



From Hickey, Sybert, Verier et al., Anesthesiology 1988
Effects of halothane, enflurane and isoflurane on coronary blood flow, autoregulation and coronary vascular reserve in the canine heart.



Coronary Collateral Circulation and Vasodilators

• in the normal human heart there are virtually no functional intercoronary channels, however if occlusion of a vessel occurs gradually then significant collateral circulation may develop
• collaterals develop from small preexisting vessels that undergo proliferation and hypertrophy, possibly in relation to wall stress or to chemical mediators released by ischaemic tissue
• however, in humans these vessels lie ***subendocardially*** and are subject to the normal compressive forces of the ventricular cavity
• also, they contain little smooth muscle and are thin walled, hence are unable to dilate effectively
• a number of drugs produce coronary vasodilation, these include,

a. sodium nitroprusside (arteriolar $\equiv^{t}$ venous)
b. nitroglycerin (arteriolar << venous)

• however, the clinical usefulness of these agents is not their ability to affect the CVR, but to reduce ***preload & afterload***, thereby reducing myocardial work and O_2 demand
• under certain circumstances vasodilators may, in fact, reduce flow to ischaemic areas by reducing the perfusion pressure to nonischaemic regions, from where collateral circulation arises

→ "***coronary steal***" (see over)

- ***Slogoff et al.*** ***(A&A.1991)***

• in a blinded retrospective review failed to show any difference in the occurrence of ischaemia between any of the volatile agents, or sufentanyl
• in a preceding randomised study of the effect of maintenance agent on the outcome after CABG surgery, they failed to find an increased incidence of ischaemia in the isoflurane group
• they then blindly reviewed the angiograms of these 1012 patients, selecting those with ***"steal-prone" coronary anatomy***, ie.

NB: complete occlusion of one vessel,
supply by collateral vessels,
plus > 50% stenosis in the vessel supplying the collateral flow
→ ~ 34% of the study group

• this percentage is comparable to the CASS (coronary artery surgery study) group ~ 23%
• a review of this group, > 16,000 patients, also failed to show any increase in ischaemia associated with isoflurane

• Slogoff's group also point out that human data supporting isoflurane steal is limited to a total 64 patients described in 5 studies, 27 of whom developed ischaemia
• however, the majority of these patients were subject to ***profound hypotension*** (35-45% ↓MAP)
• they conclude, "these data, when considered together ***do not*** document a steal mechanism as a cause of ischaemia during isoflurane anaesthesia"
• additionally they point out that,

1. ECG ischaemia unrelated to any haemodynamic alteration is common in patients with CAD and occurs spontaneously in,
   i. the ambulatory state
   ii. during hospitalisation
   iii. intraoperatively
2. ***more than*** **85%** of intraoperative ischaemia is random and occurs ***unrelated*** to any haemodynamic abnormality, or to the anaesthetic agent administered

NB: "our data....fail to support any recommendation for the withholding of isoflurane from any patients with any anatomic variant of coronary artery occlusive disease"

CEREBRAL CIRCULATION

Anatomic Considerations

▪ *Vessels*

• the principal arterial inflow is via 4 arteries, - 2 internal carotids
- 2 vertebrals
• the vertebral arteries unite to form the ***basilar artery***
• the basilar artery and the internal carotids unite to form the ***circle of Willis***, which gives rise to the 6 main arteries supplying the cerebral cortex
• in humans only a small fraction of the total arterial flow is carried by the vertebrals
• each carotid essentially supplies only that side of the cortex
• flow through anastomotic channels is minimal due to their small diameter and equal pressures on each side
• there are also precapillary anastomoses between arterioles, however these also carry little flow and are insufficient to prevent infarction
• venous drainage via the deep veins and ***dural sinuses*** enters principally the internal jugular veins
• in the ***choroid plexuses*** there are gaps between the endothelial cells of the capillary wall, however the choroid epithelial cells are densely intermeshed and interlocking
• the capillaries in the brain substance resemble ***nonfenestrated*** capillaries in muscle and other parts of the body
• however there are ***tight junctions*** between the cells which prevent the passage of substances
• also, there are relatively few vesicles in the endothelial cytoplasm and little vesicular transport
• the cerebral capillaries are surrounded by the end-feet of ***astrocytes***, which are closely applied to the basement lamina of the capillary, these form gaps ~ 20 nm wide

▪ *Innervation*

• three systems of nerves supply the cerebral vessels,

1. postganglionic sympathetic from the ***superior cervical ganglion***

   → NA and neuropeptide-Y

2. cholinergic neurones from the ***sphenopalatine ganglion***

   → ACh, VIP, and PHM?

3. sensory nerves with cell bodies in the ***trigeminal ganglion***

   → substance P

NB: the actions of these neurotransmitters are,

i. vasodilators - substance P, VIP, PHM, CGRP
ii. vasoconstrictors - NA, neuropeptide Y

Cerebrospinal Fluid

Formation & Absorption

- there is ~ 150 ml of CSF in the adult, ½ within the cranium
- about 50% of the CSF is formed by the ***choroid plexuses***
- the remaining 50% by the cerebral vessels lining the ***ventricular walls***
- in humans the CSF turns over ~ 4 times/day
- the composition depends on filtration and diffusion from the cerebral vessels, plus facilitated diffusion and active transport, predominantly from the choroid plexus
- the composition is essentially the same as brain ECF, and there appears to be free communication between the brain extracellular space, the ventricles and the subarachnoid space
- CSF flows out through the foramina of ***Magendie*** and ***Luschka*** and is absorbed through the ***arachnoid villi*** into the cerebral venous sinuses
- in addition, there is facilitated diffusion of glucose, and active transport of cations and organic acids out of the CSF
- bulk flow via the villi is **~ 500 ml/d**

i. ***formation*** is ***independent*** of ventricular pressure

ii. ***absorption***, being largely by bulk flow, is ***proportional*** to ventricular pressure

- at ***normal pressure*** **~ 7.0-18.0 cmH_2O** (mean ~ 11), filtration = absorption
- when pressure falls below ~ 7 cmH_2O absorption ceases
- brain extracellular space normally occupies ~ 15% of brain volume

CSF	Secretion	Absorption	Volume
Halothane	-	-	**0**
Enflurane	+	-	++
Isoflurane	**0**	+	-
Fentanyl	**0**	+	-
N_2O	**0**	**0**	**0**
Ketamine	**0**	-	+

NB: the time course of these effects is ***slow***, and their significance in the setting of raised ICP is lesser in comparison to other factors

The Blood-Brain Barrier

NB: the only substances entering the CNS with ease are **water, CO_2, & O_2**
the exchange of all other substances is slow

▪ *Penetration of Substances into the Brain*

• there is a $[H^+]$ gradient between blood and brain ECF → **pH ~ 7.33**
• the rate of entry of substances into the brain is inversely related to their molecular size and proportional to their lipid solubility
• ***no*** substance is completely denied access to the brain, the consideration is the ***rate*** of transfer
• eg., the amines dopamine and serotonin have limited penetration, c.f. their corresponding acids, L-dopa and 5-hydroxytryptophan, which enter with relative ease

▪ *Development of the Blood Brain Barrier*

• cerebral capillaries are far more permeable at birth than in the adult and the BBB effectively develops in the first few years

a. staining of the infant brain with bile pigments → ***kernicterus***
b. increased sensitivity of the neonate to ***morphine***

▪ *Circumventricular Organs*

• 4 small areas in or near the brainstem lie outside the BBB, these are the,

1. posterior pituitary & ventral median eminence
2. area postrema (CTZ)
3. organum vasculosum of the lamina terminalis (OVLT)
4. subfornical organ (SFO)

• these are referred to collectively as the ***circumventricular organs***
• all have ***fenestrated*** capillaries and are highly permeable
• the median eminence and posterior pituitary are ***neurohemal*** organs, areas where neurones secrete substances directly into the circulation
• the ***area postrema*** acts as the ***chemoreceptor trigger zone***, initiating vomiting in response to chemical changes in plasma
• ***angiotensin II*** acts on the SFO ± the OVLT to increase water intake

NB: the pineal and ***anterior pituitary*** have fenestrated capillaries and are outside the BBB, however they are endocrine glands, not part of the brain

- ***Function of the Blood-Brain Barrier***

• essentially to maintain the constancy of the CNS environment
• CNS neurones are extremely sensitive to changes in Mg^{++}, K^{+}, Ca^{++}, H^{+} and other ions
• also functions to protect the brain from endogenous and exogenous toxic substances; when these are lipid insoluble
• the effectiveness of the BBB is greatly reduced by irradiation, infections, and tumours
• can also be temporarily disrupted by sudden marked increases in BP, or the injection of hypotonic IV fluids

Cerebral Blood Flow

Normal Values		
CBF	• Global • Cortical • Subcortical • 1400g brain	~ 45-55 ml/100g/min ~ 75-80 ml/100g/min ~ 20 ml/100g/min ~ 700 ml/min ~ 12-15% CO
$CMRO_2$		~ 3-3.5 ml/100g/min ~ 50 ml/min ~ 20% basal MRO_2
Cerebral P_{vO2}		~ 35-40 mmHg
ICP (supine)		~ 8-12 mmHg ~ 10-16 cmH_2O

NB: a large proportion of the brains energy consumption (~ 60%) is used to support electrophysiological function & the maintenance of ***ion gradients***

local CBF & $CMRO_2$ are heterogeneous throughout the brain,
both are ~ 4x greater in ***grey matter***

Regulation of Cerebral Circulation

- the determinants of total cerebral blood flow are,
    1. the arterial pressure at brain level
    2. the venous pressure at brain level
    3. the intracranial pressure
    4. the viscosity of blood
    5. the tone of the cerebral arterioles

- factors which influence these, and therefore determine CBF include,
    a. chemical / metabolic / humoral factors
        i. $CMRO_2$ - arousal, seizures
- temperature
- anaesthetic agents
        ii. $PaCO_2$
        iii. PaO_2
        iv. drugs - vasodilators/vasopressors
- anaesthetic agents
    b. myogenic mechanisms - ***autoregulation*** & MAP
    c. rheologic factors - blood viscosity
- temperature
    d. neurogenic mechanisms - extracranial sympathetic pathways
- intracranial pathways

- although other intrinsic factors play a role, the most ***important factors*** are,
    1. $CMRO_2$/CBF coupling
    2. $PaCO_2$
    3. autoregulation
    4. neurogenic regulation

Coupling of $CMRO_2$ & CBF

• in the normal state there is tight coupling between *l*-$CMRO_2$ and *l*-CBF
• while it is clear that local metabolic factors play a role, the precise mechanism of flow/metabolism coupling is uncertain
• factors proported, but not proven, to contribute to this include,

a. H^+
b. extracellular K^+ and/or Ca^{++}
c. thromboxane & prostaglandins
d. adenosine

• $CMRO_2$ is influenced by a number of factors during neurosurgery,

a. functional state - sleep versus arousal
   - sensory stimuli
   - epileptiform activity
b. anaesthetic agents
c. temperature

• this is the mechanism of ***barbiturate*** & etomidate induced vasoconstriction
• studies *in vitro* devoid of metabolic influences show a direct vasodilatory effect, which is outweighed *in vivo* by the metabolic influences
• once the EEG is ***isoelectric***, there is no further reduction in $CMRO_2$, none of the anaesthetic agents appears to influence the basal "housekeeping" O_2 requirement

• ***lignocaine*** may be a possible exception to this, data suggesting that large doses (160 mg/kg in dogs) further reduces the $CMRO_2$, probably by its membrane stabilising effects
• this would predict that once the EEG is isoelectric, further doses of barbiturate would result in direct vasodilatation
• this ***has not*** been observed clinically
• further, the inference that isoelectricity represents a single physiological state does not hold true
• SSEP's can still be recorded at barbiturate levels far greater than those required for isoelectricity, whereas they are difficult to elicit following burst suppression doses of isoflurane
• there is a progressive decrease in CBF and $CMRO_2$ with ***age***
• this reduction in flow is probably not due to atherosclerotic vascular disease, but to the progressive neuronal loss with ageing

• temperature reduction decreases $CMRO_2$ ~ 6-7% per °C
• the EEG becomes ***isoelectric* ~ 20°C**, however, in contrast to anaesthetic agents, further reduction in temperature ***does*** result in further reduction in $CMRO_2$
• at 18°C the $CMRO_2$ ~ 10% of the basal rate and accounts for the profound protective effect during hypothermic arrest

• hyperthermia has the opposite effect, with marked increases in $CMRO_2$ up to 42°C, beyond which there is a reduction in $CMRO_2$, possibly due to inhibition of enzymatic function

▪ ***Carbon Dioxide***

• CBF is ***linearly*** related to $PaCO_2$ over the range **~ 18-80 mmHg**

$\rightarrow$ $\uparrow PaCO_2$ ~ 1 mmHg $\rightarrow$ $\uparrow$ CBF ~ 1-2 ml/100g/min

• these changes are so predictable that reactivity to $PaCO_2$ is often used for validation of methods of measurement of CBF
• under normal circumstances, CO_2 sensitivity appears positively correlated with basal $CMRO_2$
• accordingly, agents which alter basal $CMRO_2$, also alter ***slope*** of the $\delta CBF/\delta PaCO_2$ curve

• reduction of CBF & CBV by hyperventilation is useful for both ***brain decompression*** and ***brain relaxation***
• the brain actively compensates for this respiratory alkalosis and CBF gradually returns to baseline
• loss of **$PaCO_2$ *reactivity*** is a good predictor of ***outcome*** after severe head injury
• H^+ ions also have a vasodilator effect, changes in local and CSF pH being the mechanism of action of $PaCO_2$
• the action of H^+ appears to be direct on blood vessels
• however, due to the impermeability of the BBB, metabolic acidosis has little immediate effect upon CBF, in contrast to respiratory acidosis
• the effects of $PaCO_2$ occur rapidly but are not sustained, CBF returning to normal over **~ 6-8 hrs**
• the act of causing cerebral vasoconstriction by hyperventilation may actually decrease CBF to marginally perfused areas and augment ischaemia
• studies looking at global O_2 extraction show cases exist where hyperventilation results in an increased A-VO_2 difference
• this is probably a better guide to the ideal minute ventilation than measurement of ICP
• in normal subjects, ischaemia will not occur at a **$PaCO_2$ ^{3} 20 mmHg**
• this appears to apply even during induced hypotension and there is little to be gained in terms of CBF reduction below this level
• therefore, it is generally recommended to limit hypocarbia to 20-25 mmHg in previously normocarbic individuals
• the patient who has chronically adapted to a high $PaCO_2$ requires different consideration
• CSF bicarbonate adaptation occurs with a $T_{½}$ ~ 6 hours and CSF pH gradually returns to normal despite the sustained alteration of arterial pH
• thereafter, acute normalisation of arterial pH will result in significant CSF acidosis and induced "hypocapnia" may carry a theoretical risk of ischaemia

▪ ***Oxygen***

• changes in PaO_2 also affect cerebral vessels
• hyperoxia causes minimal vasoconstriction, from the range 60-300 mmHg CBF remains approximately constant and at 1 atm, CBF is decreased ~ 15%

NB: **PaO_2 < 60 mmHg** $\rightarrow$ CBF begins to increase rapidly

• the mechanisms mediating this vasodilatation are not fully understood

Autoregulation

- maintenance of a near constant CBF over a range of **MAP ~ 50-150 mmHg**
- beyond these limits, perfusion is ***pressure passive***
- this assures a constant metabolic supply in states of hypotension and prevents hyperaemia (which changes BBB permeability & elevates ICP) with hypertension
- there are a number of points relevant to anaesthesia,

1. hypertensive patients may have a ***right shift*** of the lower limit of autoregulation, and thus be less tolerant of hypotension
2. autoregulation is not an instantaneous process, ie. there are ***dynamic*** changes in CBF with changes in MAP ~ 3-4 minutes
3. induced hypotension should be achieved over a period of several minutes
4. volatile anaesthetics obtund autoregulation in a dose dependent manner

NB: therefore the use of high dose volatile should be avoided if autoregulation is being relied upon to maintain CBF during induced hypotension

- the precise mechanism is uncertain but appears to be ***myogenic*** in origin

Neurogenic Regulation

- there is extensive innervation, the density of which declines with decreasing vessel size
- there are three types of nervous supply to cerebral vessels,

1. cholinergic
2. adrenergic - sympathetic and non-sympathetic
3. serotonergic

NB: $\rightarrow$ extracranial and intracranial origins

- the role of these in regulation of CBF is debated
- the effects are generally ***mild*** and not believed to be of significance in normal regulation of CBF

- animals definitely have an extracranial sympathetic influence via the superior cervical ganglion
- the clearest evidence of functional significance comes from work with autoregulation, alterations in sympathetic tone altering the limits of the autoregulatory curve
- the increase in ICP associated with the administration of ***succinylcholine*** is thought to be due to a direct neurogenic mechanism, rather than an uncoupling of $CBF/CMRO_2$

▪ ***Viscosity***

• ***haematocrit*** is the single most important determinant of blood viscosity
• variations within the range 33-45%, result in ***clinically insignificant*** alterations of CBF
• in polycythaemia vera, raised viscosity may reduce CBF to ½ normal values
• in anaemia, CVR decreases and CBF increases, though this may represent a response to the decreased CaO_2 and O_2 delivery
• the effects of viscosity are more obvious during focal ischaemia, when vasodilatation is already maximal, where a reduction in Hct. results in an increase in flow to the ischaemic territory
• pooled data for DO_2 in the setting of ***focal ischaemia*** suggests the ***optimal Hct. ~ 30-34%***

▪ ***Vasoactive Agents***

1. ***systemic vasodilators***
   - the majority of agents (SNP, GTN, hydrallazine, adenosine, CEB's) also cause cerebral vasodilatation
   - therefore, CBF is maintained at lower MAPs during induced hypotension than during hypotension 2° to,

   i. haemorrhage/hypovolaemia
   ii. a non-cerebral vasodilator - trimethaphan

   - the ICP effects of vasodilators are less when hypotension is induced ***slowly***

2. ***catecholamine agonists & antagonists***
   - the data regarding the effects of these agents is unclear, in part due to,

   i. species differences
   ii. differences in receptor populations in different vessels
   - intraparenchymal vs. extraparenchymal
   iii. experimental model differences
   iv. the degree of MAP change which occurs with each agent
   v. the status of autoregulatory mechanisms - anaesthetic effects
   - damage during preparation
   vi. the integrity of the BBB

   - many studies assess the effects on CVR, however these changes may reflect either intrinsic vessel effects or 2° effects to altered MAP
   - the following results from Miller are predominantly human *in vivo* & higher primate

Agonist	CBF	$CMRO_2$
α_1-adrenergic	-	0
α_2-adrenergic	--	0
β	0	0
β (BBB open)	+++	+++
DA	++	-
DA (high dose)	?-	?0
Noradrenaline	-	0
NA (BBB open)	++	++
Adrenaline	-	0
AD (BBB open)	+++	+++

1. the effects of adrenaline & noradrenaline where the BBB has been damaged are 2° to β-induced increases in $CMRO_2$
2. the effects of high dose dopamine are α mediated, and occur at concentrations producing significant peripheral α-agonist activity

• there has been recent interest in α_2-agonists, due to their sedative and analgesic effects
• ***dexmedetomidine*** decreases CBF with ***no*** decrease in $CMRO_2$ (dogs)
• the α_2-antagonist ***yohimbine*** maintains CBF at lower MAPs in cats during haemorrhagic hypotension

• studies with ***clonidine*** have shown decreased CBF in humans and decreased SCBF with intrathecal injection in animal models
• these results are opposite to what might be expected from the reduction in noradrenaline release mediated by presynaptic α_2 receptors
• possible causes include activation of postsynaptic α_2-receptors or a central action (? locus ceruleus) mediating neurogenic vasoconstriction

Effects of Anaesthetics on CBF

a. delivery of energy substrate is dependent upon CBF, and in the setting of ischaemia, modest alterations of CBF can influence neuronal outcome

b. the control and manipulation of CBF is central to the management of ICP due to its effect upon CBV,

δ**CBV** ~ 0.04 ml/100g per $\delta PaCO_2$ = 1 mmHg (20-80 mmHg)
~ 17 ml $\delta PaCO_2$ = 25-55 mmHg

▪ ***Barbiturates***

• dose dependent reduction in $CMRO_2$ and CBF ~ 30% with the induction of anaesthesia
• larger doses result in an ***isoelectric*** EEG and $CMRO_2$ & CBF ~ 50% of normal
• further dose increases have little effect
• tolerance to these effects appears to develop quickly, and increasing doses are required following 24 hours of therapy
• during deep pentobarbital anaesthesia, ***autoregulation*** is preserved to pressures ~ 60 mmHg, and CO_2 responsiveness is also maintained

▪ ***Benzodiazepines***

• result in parallel reductions in CBF/$CMRO_2$ in both humans and monkeys
• the reduction appears intermediate between the opioids and the barbiturates
• the effect is probably metabolically coupled and CO_2 responsiveness is maintained
• they are therefore safe in the presence of raised ICP, providing the dose is not sufficient increase the $PaCO_2$

• ***flumazenil*** causes no effect when given to unanaesthetised human volunteers
• following midazolam induced depression, it results in reversal to baseline, however,

NB: this follows a brief period of "***overshoot***" → CBF ≤ 45-56%
ICP ≤ 180-217%

• $CMRO_2$ does not rise, indicating the effect is ***not*** metabolically mediated
• pending further studies, flumazenil should be used with caution in patients with raised ICP

▪ ***Ketamine***

• results in a marked increase in $CMRO_2$ and CBF, both 2° to the metabolic effects and due to direct vasodilatation
• the changes in $CMRO_2$ are regionally variable, with predominant activation of the thalamic and limbic structures
• autoregulation during ketamine anaesthesia has not been directly tested
• CO_2 responsiveness is preserved, as hyperventilation reduces the elevation of ICP following ketamine administration

- ***Propofol***

• reduces both CBF and $CMRO_2$, up to 51% and 36% respectively
• it may however may result in a precipitous fall in ***CPP*** in patients with raised ICP (~ 50%)

- ***Opioids***

• the available data is contradictory, but it is likely opioids have little effect upon CBF & $CMRO_2$ in the normal, unstimulated animal
• generally they produce mild decreases in both variables, with autoregulation remaining intact
• only 1 study has administered morphine (1 mg/kg) alone to humans, Moyer observed no change in global CBF but a 41% decrease in $CMRO_2$
• other studies, using N_2O in addition to morphine have shown a small decrease
• fentanyl will likewise cause a moderate reduction in $CMRO_2$/CBF in the quiescent brain but much larger decreases during arousal
• there is minimal data available for alfentanyl and the studies of sufentanyl suggest similar changes in CBF/$CMRO_2$ cf. fentanyl
• however, Marx (1989) looked at CPP (MAP - lumbar CSFP) following administration of these three opioids → all three caused a reduction in MAP and the net changes in CPP were,

1. fentanyl - 14 ± 3%
2. sufentanyl - 25 ± 5%
3. alfentanyl - 37 ± 3%

• the increases in l-CSFP observed were readily overcome by hyperventilation
• due to the possible confounding effect of hypotension (2° vasodilatation), they repeated the study maintaining MAP with phenylephrine
• they observed substantial increases in CSFP with both sufentanyl and alfentanyl, but no significant change following fentanyl
• subsequent work with animals has supported a ***direct vasodilatory effect*** with sufentanyl and possibly alfentanyl

NB: there have, however, been a number of blinded clinical studies of these three agents with no discernible clinical differences being found

• they should not therefore be contraindicated but used in conjunction with hypocapnia

- ***Lignocaine***

• produces a dose related decrease in $CMRO_2$ and CBF
• doses **~ 1.5 mg/kg** are as effective as boluses of thiopentone 3 mg/kg in blunting the ICP rises associated with painful stimuli during neurosurgery
• lignocaine is associated with a smaller fall in MAP and, therefore, is recommended as an adjuvant prior to known stimuli
• although lignocaine can produce seizure activity, this has not been documented during anaesthesia within the recommended dose range (1.5-2 mg/kg)

▪ *Volatile Anaesthetics*

• the order of vasodilatory effect of the commonly used volatiles is,

halothane >> enflurane > isoflurane

• there is less available data for desflurane and sevoflurane, however they appear to be similar in potency to isoflurane
• all of these agents cause a dose related decrease in $CMRO_2$ but in contrast to the IV agents an increase in CBF, ie. they "***uncouple***" $CBF/CMRO_2$
• however, there is evidence that metabolic coupling persists with the volatile agents
• the best evidence occurs during hypocapnia induced seizure activity with enflurane in dogs
• also, nociceptive stimuli during stable halothane anaesthesia increases both $CMRO_2$ & CBF

NB: it is therefore more accurate to say that the $CBF/CMRO_2$ ratio is ***reset***

• at 1.0 MAC the reduction in $CMRO_2$ in cats is ~ 25% with halothane and ~ 50% with enflurane and isoflurane
• however, with ***isoflurane*** maximal suppression of $CMRO_2$ is achieved simultaneously with the onset of isoelectricity, and this occurs at clinically relevant concentrations in humans (≤ 2.0 MAC)
• higher concentrations (≤ 6 MAC in dogs) produce no further reduction in $CMRO_2$
• halothane contrasts this, requiring ≥ 4 MAC to produce isoelectricity, and further doses result in additional decreases in $CMRO_2$
• this later effect is presumed to relate to reversible interference with oxidative phosphorylation

• the effects on CBF represent the sum of metabolic induced vasoconstriction and a direct vasodilatory effect by their action on smooth muscle
• as isoflurane suppresses $CMRO_2$ earlier, further doses may produce predominantly vasodilatation and there is some animal evidence to support this

• the ***regional CBF*** effects of these agents differs considerably
• halothane produces almost uniform changes in CBF throughout the brain
• with isoflurane, CBF increases more in the subcortical structures and hindbrain than in the neocortex
• these differences account for the variable findings of numerous studies in the literature, dependent upon the method of CBF measurement used (see later)
• the sum of these studies suggests that while isoflurane produces little vasodilatation in the cortex, it is however a global cerebral vasodilator and this needs to be considered when intracranial compliance (elastance) is low

NB: at equi-MAC levels isoflurane does produce a ***lesser increase*** in CBF, and is therefore probably the agent of choice

• the effects of the volatile agents are ***time dependent***, after the initial increase CBF falls markedly
• recovery to ***preanaesthetic*** levels of CBF occurs at 2.5-5 hours post introduction of volatile
• the mechanism is uncertain and the time lag is proportional to the initial magnitude of CBF rise

• CBF influences ICP due to the positive correlation between CBF and CBV
• CBV has been shown to increase in humans with the administration of both isoflurane and N_2O
• studies looking at lumbar CSFP during administration of the volatile agents, and fentanyl, show acute rises in l-CSFP which parallel changes in CBV

> ***NB:*** however, although CBV changes last up to 3 hours with all of these agents, l-CSFP normalises after **~ 20 *minutes*** with isoflurane

• this led to the concept of differential effects on ***CSF dynamics***, in addition to the effects 2° to CBV
• the magnitude of these effects has not been classified, but is thought to be minor in comparison to the CBV effects, due to,

1. the time course of change
2. the fact that the CSF space is usually open by the time any significant change is likely to have occurred

• **CO_2-*responsiveness*** is well preserved with all of the volatile agents
• in contrast ***autoregulation*** is impaired in a dose and anaesthetic related manner

• enflurane is unique amongst these agents due to its ***epileptogenic*** activity
• of particular note is the augmentation of this effect by ***hyperventilation***
• enflurane induced seizure activity is associated with substantial increases in $CMRO_2$ and CBF
• amitriptyline and ketamine have been reported to reduce the seizure threshold for enflurane
• this property has been used in cortical EEG mapping of seizure foci during surgery for resection
• isoflurane has been shown to produce EEG spike activity and myoclonus, but has not been associated with frank seizure activity

• ***sevoflurane*** is a relatively insoluble halogenated ether (B:G ~ 0.6)
• moderate F^- ion is released *in vivo* and it is unstable in the presence of soda lime
• the toxicity of the subsequent metabolites is still being established
• it is indistinguishable from isoflurane in its cerebral effects

• ***desflurane*** is also an insoluble halogenated ether (B:G ~ 0.42)
• it is a gas at room temperature (T_{crit} ~ 17°C) and therefore requires pressurised delivery systems
• there is limited available data, but it also appears to be similar to isoflurane
• a single study has shown an increase in ICP, ***not responsive*** to hyperventilation, and use of desflurane for neurosurgery should be limited until this is confirmed

- ***Nitrous Oxide***

• the available data show that N_2O can unequivocally ***increase*** CBF & ICP
• the most dramatic effects are seen in studies which use little or no background anaesthesia, and probably reflect 2nd stage arousal phenomena
• when administered with other agents these effects are considerably lessened
• pretreatment, or the concomitant administration of ***thiopentone*** or the benzodiazepines reproducibly ***prevents*** the increases in ICP seen with administration of 70% N_2O
• the opioids also appear to blunt this effect

• the interaction with the volatile agents is different
• data suggests that addition of N_2O to established volatile anaesthesia will result in increases in CBF/ICP
• there is vastly divergent data on the effects of N_2O on $CMRO_2$
• the "cleanest" work has been done in awake goats, showing a marked ***increase*** in,

1. $CMRO_2$ ~ 70%
2. CBF ~ 43%

• the following statement is from Miller,

NB: "it appears that N_2O induced cerebral vasodilatation can be considerably blunted by the simultaneous administration of fixed anaesthetics....N_2O has been widely used in neurosurgery and banishing it is inconsistent with the accumulated experience. Nonetheless, in circumstances in which ICP is persistently elevated or the surgical field is persistently tight, N_2O should be viewed as a potentiating factor."

Muscle Relaxants

• the only effect of nondepolarising muscle relaxants on CBF occurs via the release of ***histamine***
• vasodilatation results in a reduction in CPP by a simultaneous,

1. decrease in MAP and
2. increase in ICP

• whether the decrease in CVR (BBB intact) is a direct effect of histamine, or an autoregulatory response to the reduction in MAP is uncertain
• **dTC** is the most potent agent, with smaller amounts being released by metocurine, atracurium and mivacurium
• the clinical effects for the later two are not significant
• pancuronium, via changes in MAP, may increase ICP when changes are abrupt or autoregulation is impaired by disease processes
• all agents of this class effectively reduce ICP by the prevention of coughing, straining and the reduction in mean intra-abdominal/intrathoracic pressure
• ***laudanosine***, a metabolite of atracurium is potentially epileptogenic, though, this is not significant clinically

• ***succinylcholine*** results in an elevation of ICP in lightly anaesthetised patients
• Minton studied patients with tumours and noted mean ICP changes from 15-20 mmHg, lasting 2-3 minutes and returning to baseline after 8-10 minutes
• the effects appear to be the result of ***cerebral activation***, via activation of the muscle spindle apparatus
• however, there is poor correlation between fasciculations & EEG activation
• consistent with the hypothesis of arousal is the observation that deep anaesthesia prevents this increase in ICP, as does prior paralysis with nondepolarising agents, or the use of "defasciculating" doses (metocurine)

NB: therefore, it is ***not contraindicated*** in the presence of raised ICP but due attention should be given the depth of anaesthesia and the prior use of "defasciculation"

Measurement of CBF

▪ *Washin-Washout Methods*

• according to the ***Fick principal***, the blood flow to any organ is equal to the amount of a substance added to, or removed from the circulation, divided by the arterio-venous concentration difference, per unit time

$$CBF = \frac{Q_X}{[A_X]-[V_X]}$$

• the Kety method uses subanaesthetic concentrations of N_2O
• as the blood:brain partition coefficient is ~ 1.0, and the equilibrium time is 9-11 minutes, viz.

$$CBF = \frac{100 \,.\, V_t \,.\, S}{\int_0^t [A-V].\delta t}$$

where, S = the blood:brain partition coefficient
V_t = the venous concentration at time t
t = time until equilibrium
A = the arterial concentration (see Ganong 32-6)

• this measures the ***average flow*** and gives no information about regional differences
• this method will not detect the decrease in flow produced by complete ***occlusion*** of a cerebral artery, as it measures ***flow/unit mass*** and the non-perfused area takes up no N_2O
• the original method described by Kety-Schmidt in 1945 has undergone numerous modifications
• measurements can be made of either the *time to equilibrium* or the *rate of washout*
• tracers used in ***washout*** techniques include,

i. H_2 - with a platinum electrode inserted in the brain substance
$\rightarrow 2H^+ + 2e^-$, clearance $\propto$ current
ii. N_2O
iii. heat
iv. ^{133}Xe
v. Xe - nonradioactive tracer

• the ^{133}Xe method is relatively noninvasive, is easily used in humans, the apparatus is reasonably portable and provides information on ***regional flow***
• however, it gives information only with respect to cortical flow

Embolic Techniques

• largely limited to ***radioactive microspheres***, usually **~ 15 µm** with gamma emitting isotopes
• these become trapped at a capillary level proportional to flow
• blood is continuously drawn into an artificial organ during the distribution phase
• tissue from the sample organs is then weighted and the radioactivity counted
• using different isotopes repeat measurements can be made allowing assessment of pharmacological interventions
• the technique is however,

a. a radiation hazard
b. expensive
c. not useful for recovery models, where CBF and outcome could be correlated

Autoradiographic Techniques

• these also employ the washin principle
• radioactive tracer is infused IV over a given time and an arterial concentration time curve constructed to establish tracer availability to the brain
• cerebral circulation is then interrupted, the brain is fast frozen and thinly sectioned
• the sections are then placed on radiographic media and images developed
• the method is moderately expensive, limited primarily to small animals and gives only one determination per animal
• evaluation of ***regional perfusion*** is however unparalleled

PET Scanning

• involves IV injection of short-lived isotopes (^{15}O, ^{11}C, ^{18}F) which decay emitting ***positrons***
• nuclear decay by positron emission emits 2 high energy annihilation ***gamma photons*** at 180°
• therefore, arrays of paired detectors, which register only coincident events, allow precise determination of the plane of origin of the decay
• this reduces radiation scatter, which decreases resolution with other radiographic techniques
• also, the high energy of the photons minimises tissue attenuation
• due to their short-lived nature, repeated measurements may be made
• 2D and 3D images can be constructed using triangulation, cf. CAT scanning
• this allows determination of information from deeper structures, including,

i. CBF
ii. $CMRO_2$
iii. CBV

• the principal disadvantages are,

1. extreme cost
2. need for a cyclotron to generate the short-lived positron emitting radionuclides

▪ ***Transcranial Doppler***

• relies on the principals of ultrasound and ***doppler shift*** caused by moving red blood cells
• the probe is placed over a "cranial window" which is usually the ***temporal bone*** immediately above the zygomatic arch
• the probe emits a 2 mHz signal which allows visualisation of various vessels, but the MCA is most readily used
• actually measures ***RBC velocity***, with the mean velocity being calculated from systolic and diastolic flows, mean velocity being a reflection of CBF
• the ***pulsatile index*** is calculated as,

$$PI = \frac{\text{(systolic velocity - diastolic velocity)}}{\text{mean velocity}}$$

• this may be a reflection of cerebrovascular ***resistance***
• the advantages include,

a. relatively cheap
b. non-invasive
c. portable

• disadvantages include,

a. difficulty in finding a strong signal ~ 10%
b. patient movement disrupts the signal
c. only ***trends*** can be determined, not absolute values

▪ ***Measurements of Regional Flow***

• usually determined by either ^{133}**Xe** uptake, or by the ***2-deoxyglucose*** method, combined with positron emission tomography (PET) scanning
• blood flow to the grey matter is **~ 5-6x** that of the white matter
• largest blood flow per gram tissue is the ***inferior colliculus***
• there are marked fluctuations in regional flow with activity in the respective regions of the brain
• flow remaining proportionate to metabolic activity

Measurement of CBF

• the type of CBF technique used depends upon,

a. human versus laboratory animal

b. cost constraints

c. global versus regional information

• further, the type of measurement will affect the results obtained
• numerous studies have shown that CBF is greater with halothane cf. isoflurane at equi-MAC concentrations
• other studies, using global CBF techniques, have shown no significant difference
• the studies showing higher CBF with halothane are those in which predominantly cortical CBF was determined
• in reality the two agents produce different flow distribution patterns within the brain,

a. ***global*** changes for the 2 agents are similar

b. cortical flows are greater with halothane

c. subcortical flows are greater with isoflurane

• with respect to raised ICP the global effects would seem most appropriate
• the best assay for predicting effects on ICP is actually ***cerebral blood volume***
• the assumption that CBV will parallel changes in CBF does not always occur
• if vasodilatation is predominantly venous there will be little increase in CBF, but CBV and ICP will both rise

Measurement of Cerebral Metabolism

a. **arteriovenous content difference**
   i. glucose
   ii. oxygen
      - usually venous sampling from the jugular bulb
      - lack of any regional information
      - combined with CBF measurements gives $CMRO_2$

b. **2-deoxyglucose**
   i. autoradiographic
   ii. PET scanning
      - 2-DG passes the 1st phosphorylation step only
      - thus it is metabolically & ***intracelularly trapped***
      - partial consumption of 2-DG is proportional to MRO_2
      - only 1-2 measurements / patient
      - invalid in many disease states, eg. ischaemia, as glucose is readily metabolised by anaerobic glycolysis
      - thus the marginal zones around an infarct light up, despite decreased perfusion & metabolism

- as for measurements of CBF, the effects of volatile agents on $CMRO_2$ depend upon the measurement used
- global measurement shows that the volatile agents uncouple $CMRO_2$ & CBF
- however, regional measurements show that the linear relationship is maintained, only the slope of the curve is altered
- the alteration of the ratio appears to be both dose & anaesthetic dependent

Oxygen Consumption

• the cerebral rate of O_2 usage ($CMRO_2$) **~ 49 ml/min** for a 1400g brain
• this equates to ~ 20% of the total body O_2 consumption
• the brain is extremely sensitive to hypoxia, occlusion of the blood supply resulting in unconsciousness in **< 10 secs**
• the vegetative structures in the brainstem are more resistant to hypoxia than the cortex
• the ***basal ganglia*** also use O_2 at a rapid rate and hypoxia, therefore, frequently results in intellectual dysfunction and Parkinsonian symptoms

▪ *Energy Sources*

• ***glucose*** is the major ultimate energy source under normal conditions
• the normal ***respiratory quotient*** for cerebral tissue is ~ 0.95 to 0.99
• during prolonged starvation appreciable utilisation of other substances occurs
• even under normal conditions, as much as 30% of glucose taken up by the brain is converted to amino acids and lipids
• ***insulin*** is not required for the cerebral uptake of glucose
• uptake is increased in active neurones, as is that of 2-deoxyglucose
• however the later is not metabolised and uptake of radioactive labelled tracer is used to map cerebral activity
• there is an average decrease of 30% uptake of all areas during slow wave sleep

▪ *Hypoglycaemia*

• the symptoms of hypoglycaemia include,

1. mental changes, confusion
2. ataxia, convulsions
3. sweating
4. coma

• the available glucose and glycogen is exhausted within ***2 minutes*** of cessation of arterial flow
• thus the brain can withstand hypoglycaemia for longer periods than hypoxia
• as for oxygen, the cortical areas are more sensitive to sublethal exposures to hypoglycaemia
• diabetic patients exposed to chronic hyperglycaemia exhibit a reduced transport of glucose across the BBB and, therefore, may exhibit symptoms of hypoglycaemia at a "normal" BSL

▪ *Glutamate & Ammonia Removal*

• the brain uptake of ***glutamate*** is ~ equal to its output of ***glutamine***, thereby clearing the CNS of ammonia
• this is the reverse process to the clearance of ammonia by the kidney
• ammonia is very toxic to nerve cells and this process is necessary for normal CNS function, eg. the CNS effects of hepatic coma

CUTANEOUS CIRCULATION

NB: the oxygen and nutrient requirements of the skin are low,
therefore, in contrast to most other body tissues, the supply of these nutrients is not the chief governing factor regulating cutaneous blood flow →
the primary function of the cutaneous circulation is the maintenance of internal body ***temperature***

▪ ***Regulation of Skin Blood Flow***

• there are essentially two types or resistance vessels in the skin,

1. arterioles
2. arteriovenous anastomoses

• where the later shunt blood directly from arterioles to venules, bypassing the capillary circulation
• these are found primarily in the peripheries, and differ morphologically from arterioles →

a. 20 to 40 µm diameter
b. thick muscular walls
c. extensive SNS supply
d. either short & straight, or long & coiled

• nerve supply is almost exclusively ***SNS*** and these vessels maximally dilate when denervated
• maximal SNS stimulation → complete cessation of flow
• AV anastomoses,

1. do not exhibit basal tone
2. are highly sensitive to circulating vasoconstrictors
3. do not appear to be under metabolic control
4. fail to display autoregulation

• the principal control being the reflex nervous stimulation in response to activation of the temperature receptors of the ***hypothalamus***
• the bulk of skin resistance vessels do exhibit some ***basal tone***, and are under the dual control of the CNS and local factors, however the former predominate
• with chronic denervation, the preexisting basal tone is restored over several weeks
• NA & A elicit only ***vasoconstriction*** in cutaneous vessels, and the return of basal tone may represent denervation hypersensitivity

• PNS vasodilator fibres ***do not*** supply the cutaneous vessels
• however, ***SNS-ACh*** stimulation of the sweat glands does result in vasodilation, possibly by the local production of ***bradykinin***
• in contrast to AV anastomoses, arterioles do display autoregulation of blood flow and reactive hyperaemia
• due to the low metabolic demand of the skin, autoregulation is probably achieved by the myogenic mechanism

• prolonged exposure of a periphery to extreme cold has a secondary vasodilator effect
• the initial vasoconstriction and pain are overcome by alternating periods of vasoconstriction and dilation, however the skin temperature rarely drops as far as with the initial immersion
• the reddened appearance of the skin on exposure to sever cold is largely due to the reduced O_2 uptake by the skin and the induced left-shift of the Hb-O_2 curve
• direct application of heat results not only in local vasodilation, but reflex dilation of vessels in other regions in the body
• the evidence for reflex activity from peripheral heat receptors is less than that for cold receptors
• most of the above being due to the return of heated blood to the hypothalamus

■ ***Triple Response***

• if the skin of many individuals is stroked with a blunt instrument, a white line appears within 20 secs and gradually disappears over 3-5 mins
• this white reaction is believed to be due to venular & venous contraction, as it occurs in the denervated limb
• if the skin is stroked more strongly with a sharp instrument then the triple response is elicited,

1. a red line - appearing within 3-15 secs
2. a red blush, or flare - extending 1-2 cm at ~ 15-30 secs
3. the wheal - following in 3-5 mins with fading of the red line

• the red line is the result of mechanical stimulation
• whereas the flare is the result of the ***axon reflex*** dilating neighboring arterioles
• the wheal is the result of increased capillary permeability as a result of,

1. direct trauma
2. release of ***histamine***, or a histamine-like, H-substance
3. partly due to the release of ***substance P*** from sensory nerves due to the ***axon reflex***
   • this leads to vasodilation and increased capillary permeability

CIRCULATION OF SKELETAL MUSCLE

• the rate of blood flow to skeletal muscle varies directly with the ***contractile activity*** and the ***fibre type*** of muscle,

a. fast-twitch → low oxidative, low capillary density muscle

b. slow-twitch → high oxidative, high capillary density muscle

• at rest, the precapillary arterioles exhibit asynchronous, intermittent contractions and relaxations such that at any one time a large portion of capillary bed is not perfused
• consequently the total blood flow to quiescent muscle is low,

→ normal MBF ~ 1.4 to 4.5 ml/min/100g

• with exercise the flow may increase by up to 15 to 20 times

Regulation of Skeletal Muscle Blood Flow

NB: control is achieved by two factors, 1. neural control
2. local control

• at rest neural and myogenic factors are dominant, whereas in exercising muscle metabolic control supervenes
• as for any tissue, the factors governing flow include the arteriovenous pressure gradient, tissue pressure and blood viscosity
• however, for exercising muscle, another factor is important

→ the pumping effect of the intermittently contracting muscle on vessels

• this, combined with the effect of venous valves, enhances muscle perfusion

■ *Neural Factors*

• the resistance vessels of muscle display a high degree of ***basal tone***
• however, there is additional tone attributable to continuous low frequency SNS activity (1-2 Hz)
• maximum vasoconstriction is observed at SNS frequencies ~ 8-10 Hz
• this is achieved by the action of neurally released NA at α-receptors
• intra-arterial NA produces only vasoconstriction, c.f. small doses of adrenaline which produce vasodilation by their action at β_2-receptors
• tonic activity of the SNS is greatly influenced by activity of the baroreceptors
• the vasodilation caused by their stimulation being the result of ***inhibition*** of SNS activity
• as muscle is the major body component by mass, and therefore has the largest vascular bed, its resistance plays a major role in the regulation of TPR & BP
• muscle is also supplied by vasodilator SNS-ACh fibres, which arise in the cerebral cortex and are thought to operate before exercise, stress, etc.

▪ ***Local Control***

• neural control of muscle is superseded by metabolic regulation when changing from the resting to the active state, however, local control is still partially active at rest → ***autoregulation***
• the common factor for autoregulation of skeletal muscle blood flow is a low PvO_2, and presumably a low PmO_2
• direct measurements of resting muscle → PmO_2 ~ 0 to 10 mmHg (mean ~ 4)
• also, flow is low and O_2 extraction is high, venous O_2 saturation < 50%
• during exercise local metabolic factors assume control, irrespective of the level of SNS activity

SPLANCHNIC CIRCULATION

• consists of the blood supply to the gastrointestinal tract, liver, spleen, and pancreas

▪ ***Intestinal Circulation***

• the GIT is supplied by the,

1. coeliac artery
2. superior mesenteric artery
3. inferior mesenteric artery

• the SMA is the largest of all of the branches of the aorta and carries over 10% of the CO
• the SMA and IMA join and give off multiple small mesenteric arteries, which form an extensive vascular plexus in the submucosa
• their branches penetrate the longitudinal and circular muscle layers and give rise to third and fourth order arterioles
• some third order arterioles become the main ***central arterioles*** to the villi
• the direction of blood flow in the capillaries and venules is opposite to that in the arterioles, therefore forming an effective ***countercurrent exchanger***, facilitating the absorption of water, solute and nutrients
• this countercurrent exchanger also permits the diffusion of O_2 from arterioles to venules, reducing the P_{O2} at the tip of the villus
• this predisposes the mucosa to ***ischaemia***, especially under conditions of reduced flow
• the neural control of the GIT circulation is almost entirely SNS, constricting mesenteric arterioles, precapillary sphincters and capacitance vessels by action on a-***receptors***
• β-receptors are present, however the α-receptors are ***prepotent***
• ***autoregulation*** in the intestine is ***not*** well developed
• mechanisms acting possibly including metabolic ± myogenic
• the ***adenosine*** concentration in mesenteric venous blood rises 4x after brief arterial occlusion
• adenosine, being a potent vasodilator in the mesenteric circulation, is possibly the major active metabolite, however, K^+ and osmolality are also active
• the **O_2** ***consumption*** of the small intestine is more tightly controlled than is blood flow
• in one series the O_2 uptake was constant over the perfusion pressure range of 30 to 125 mmHg

- food products in the lumen →
    a. glucose & free fatty acids → principal vasodilators
    b. gastrin & cholecystokinin → which augment vasoditation

▪ ***Hepatic Circulation***

- the normal blood flow to the liver ~ 25% of the CO (R: 0.5-2.5 l/min)
  ~ 20-25 ml/kg/min
- flow is derived from two sources,
    1. ***portal vein*** → supplying ~ 3/4 of the hepatic ***blood flow***
    2. ***hepatic artery*** → supplying ~ 3/4 of the hepatic $\mathbf{O_2}$ ***uptake***

- these give rise to ***portal venules*** and ***hepatic arterioles***, which enter the ***acinus*** at the centre
- blood flows radially from these through the ***hepatic sinusoids*** to the peripheral terminal hepatic venules
- these venules drain into progressively larger veins → hepatic veins
- the mean pressure in the,
    a. portal vein ~ 10 mmHg
    b. hepatic artery ~ 90 mmHg

- the pressure within the sinusoids is only ~ 2-3 mmHg above the hepatic veins and IVC
- the ratio of precapillary/postcapillary resistance is greater in the liver than any other vascular bed
- drugs which affect presinusoidal resistance → little effect on P_{hs}
- conversely, changes in hepatic venous & CVP → ~ proportionate δP_{hs}

- blood flow from the portal vein & hepatic artery vary almost ***inversely***, however with decreases in flow from one system, compensation by the other is usually incomplete
- the portal system ***does not*** autoregulate, as P_{pv} rises, resistance either remains constant or decreases
- in contrast, the hepatic arterial system does autoregulate
- the liver tends to maintain a constant O_2 consumption by varying the O_2 extraction from perfusing blood
- this ability is facilitated by the seperation of arteriolar and hepatic venular vessels, preventing countercurrent exchange of O_2
- SNS activity constricts presinusoidal vessels via α-receptors in both systems, however the effects are greatest on capacitance vessels

- the liver contains **~ 15%** of the circulating blood volume and ~ 1/2 of this can be rapidly mobilised during hypovolaemia
- some species the spleen is more important, but not for humans