The "Big Five" in Physiology and Physics:
Laws-Equations-Principles

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Several physics equations are used to explain concepts of medical physics and human physiology, and are regularly applied in anaesthesia. Many of these concepts are being used on a daily basis in clinical practice without even thinking about the theory behind them. Philosophy gave birth to education and science! Most of the greatest scientists were also famous philosophers and started off with philosophical ideas. Several famous Philosopher-Physicists-Physiologists have their names connected to one or more "Law-Equation-Principle" in the medical field.

Laws-Equations-Principles used every day & that should be understood in preparation for the Primary and Final FCA Exam, and for the rest of the anaesthetist/clinician's working life, include:

1. *Starling and compliance* (cardiac function/mechanics, lung physiology, renal function)
2. *La Place, Ohm* (wall tension, preload, resistance, afterload, oxygen consumption)
3. *Bernoulli* (flow hydraulics, ultrasound-Doppler, pressure drop/flow across narrowing)
4. *Fick, Shunt and Dead Space* (cardiac, respiratory - diffusion, filters, oxygen supply and demand, monitoring)
5. *Hagen-Poiseuille* (flow through airways, tubes and tubing/vessels)

Also important, but not covered in this lecture:

6. *Boyle* (Body plethysmography, "syringe, antibiotics, air and vial")
7. *Bohr* (Haldane and Bohr Effects - O_2-Hb Dissociation Curve, Dead Space Ventilation)
8. *Henderson-Hasselbach* (Blood gas interpretation)
9. *Coanda* (air/fluid flow pattern)
10. *Venturi* (gas entrailment, flow pattern)
11. *Stewart-Hamilton* (Cardiac Output by thermodilution)
12. *Alveolar Gas Equation* (Altitude)

etc……

1. Starling (Law - Curve - Mechanism - Equation - Resistor – Forces - Principle)

Frank–Starling curve

The function of the heart as a pump is based on cardiac muscle. The contractile properties of heart muscle not only provide the engine to drive the cardiac pump but also give the heart an intrinsic ability to adapt its performance to a continually varying venous return. The mechanism underlying this adaptive ability is the Frank–Starling relationship.

Frank curve

Frank demonstrated in isolated muscle fiber preparations that the tension developed on contraction was dependent on the initial length of the fiber. As initial length increased from resting value, the tension developed during contraction increased, and reached a maximum. Above this, the tension declined as the sarcomeres became overextended.

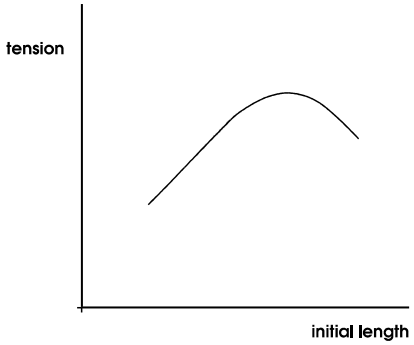

Figure: Frank curve for isolated muscle

Starling curve

The above property of isolated cardiac muscle fibers can be applied to the muscle fibers in the walls of an intact ventricle, where the length of muscle fiber is related to the volume in the ventricle. In this case tension per unit cross section (ventricular wall stress T), developed in the wall during contraction, is dependent on end-diastolic volume. Laplace's law relates the wall stress to internal pressure in an elastic sphere; thus, the Frank relationship for an isolated muscle fiber translates into a relationship between intraventricular pressure and EDV during isovolumetric contraction. Effectively, the greater the ventricular filling volume, the stronger the contraction of the ventricle – a mechanism that gives the intact heart its built-in ability to adjust to varying levels of venous return. Starling confirmed in ejecting mammalian hearts that with a constant aortic pressure, an increase in EDV produces a more forceful contraction and an increase in SV.

Frank–Starling Law/Frank-Starling Mechanism

In the intact heart, a ventricular function curve (Frank–Starling curve) can be plotted to demonstrate the ability of the ventricle to vary its mechanical output according to its filling volumes. An index of mechanical output (such as SV) can be plotted against a measure of filling pressure (such as CVP).

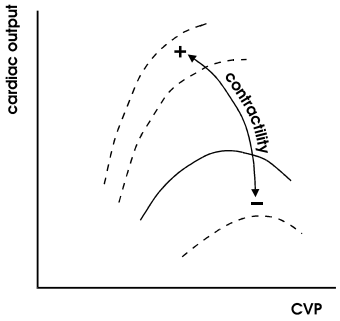

Figure: Ventricular function curve

Frank–Starling curve and cardiac failure

A normal ventricle never fills to an EDV that would place it on the descending limb of the Frank–Starling curve. This is because of decreased compliance of the ventricle that occurs at high filling pressures. Sarcomere length at optimum filling pressures (about 12 mmHg) is 2.2 μm; however, even if filling pressures are increased four-fold (>50 mmHg) sarcomere length will not increase beyond about 2.6 μm.

If the heart becomes pathologically dilated as in cardiac failure, ventricular function may shift to the descending portion of the Frank–Starling curve, and cardiac decompensation ensues. Cardiac function can also deteriorate when factors such as hypoxia, acidosis or β blockers shift the Frank–Starling curve down and to the right, depressing cardiac performance. Alternatively, other factors such as endogenous catecholamine or inotropes can shift the Frank–Starling curve upwards and to the left, enhancing cardiac performance.

Force–velocity curve for cardiac muscle

Starling not only investigated the sarcomere tension–length relationship, but also looked at the interaction between muscle force and velocity. The force–velocity curve demonstrates that the force generated and the velocity of muscle shortening is inversely related. Changes in preload and contractility will influence this relationship by shifting the force–velocity curve.

Starling was a wise man and thought about many other physiological principles, e.g.

He showed that there are opposing forces across any capillary wall, e.g. lung or kidney. Water is forced out through the pores in the wall by hydrostatic pressure, and driven in by the osmotic pressure of plasma proteins within the capillary. These opposing forces approximately balance and the concept is known as **Starling's Principle**.

Net fluid out = $K [(P_c – P_i) – \sigma (\pi_c – \pi_i)]$

Transmural pressure, P = hydrostatic pressure, π **=** osmotic pressure, K = filtration coefficient, σ = reflection coefficient

The hot topic of today is the "glycocalyx" of the vascular (alveolar/renal) membrane, which can conceptually be incorporated into K and **σ.** This still leaves the Starling Principle in situ!

The **Starling Resistor** was used in his isolated heart preparations that led to the description of "Frank-Starling Law of the Heart". It consisted of an elastic fluid-filled collapsible-tube mounted inside a chamber filled with air.

The static pressure inside the chamber was used to control the degree of collapse of the tube, so providing a variable resistor. This resistance was used to simulate TPR, or total peripheral (vascular) resistance. It is also used to describe pulmonary blood flow through the different "West Zones" and the influence of gravity and pressure.

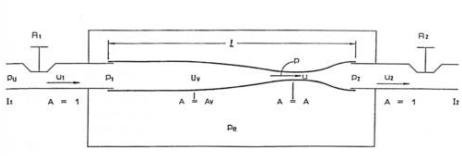

Figure: Starling Resistor

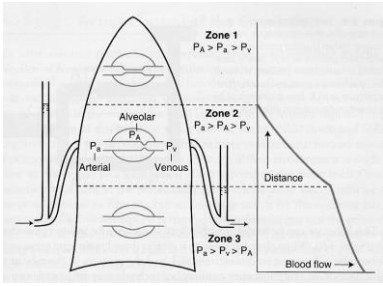

Figure: West Zones of the lung

From: Respiratory Physiology-the essentials, JB West, Ninth Edition

2. La Place Law

T=Pr/h

Where T = Wall Tension, P = Intracavity Pressure, r = Radius of Ventricular Cavity, h = Ventricular Wall Thickness

La Place's Law is often used in the setting of cardiovascular physiology as basic definitions like preload and afterload. It is also used to explain cardiac vulnerability in the setting of pathologies like ischemic heart disease, dilated cardiomyopathy, or valvular heart disease. The biggest physiological influence on oxygen consumption of the myocardium is the tension in its wall, which according to the equation is influenced directly by intraventricular pressure, cavity radius, and inversely by the wall thickness.

Preload

In clinical circumstances, 'preload' remains loosely defined and has become synonymous with a range of parameters including CVP, venous return and pulmonary capillary wedge pressure. A strict definition for preload can be obtained from the Frank relationship between muscle fiber length and developed tension. Here preload is the initial length of the muscle fiber before contraction. In the intact ventricle the preload would, therefore, be equivalent to the end-diastolic volume, since the pre-systolic length of the myocardial fibers will be directly related to EDV.

Different definitions of preload are therefore:

- LVEDV (impossible to measure directly in the clinical setting)
- LVEDP (PCWP, or extrapolated even further away from the truth when using CVP and blood pressure). Here the LV **Compliance = δV/ δP** (change in volume/change in pressure) is important to keep in mind
- Ventricular end-diastolic wall stress – **diastolic La Place – T=Pr/h**
- EDPV point on the pressure volume loop

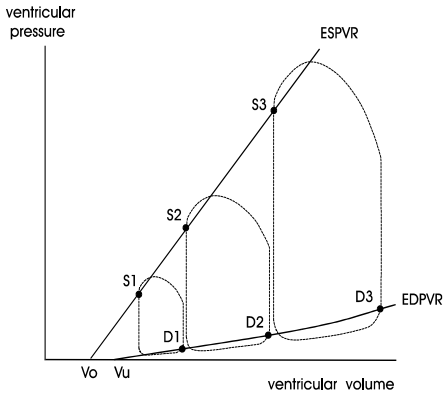

Figure: Preload and Afterload

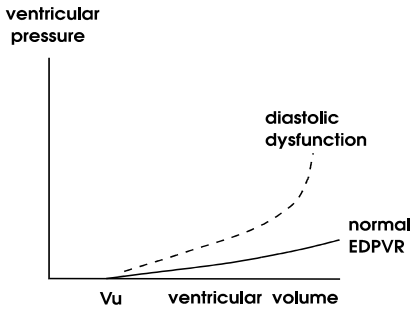

Figure: Compliance curve

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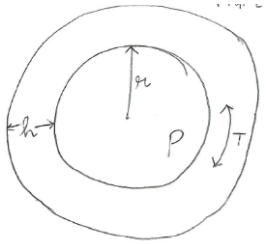

Figure: La Place

Afterload

In an isolated muscle fiber preparation, afterload is defined as the wall tension developed during contraction. Thus, afterload is related to the mechanical resistance to shortening of the muscle fiber. In the intact heart, afterload becomes the tension per unit cross section (T), developed in the ventricular wall during systole. This can be related to the intraventricular pressure during systole, by applying Laplace's law for pressure in an elastic sphere. Afterload is thus a measure of how forcefully the ventricle contracts during systole to eject blood.

The normal ventricle has an intrinsic ability to increase its performance in response to moderate increases in afterload, to maintain SV. If the afterload increases suddenly, it causes an initial fall in SV. The ventricle then increases its EDV in response to the change, which in turn restores the SV. This is called the Anrep effect.

Different definitions of afterload are therefore:

- Force resisting muscle fibre shortening
- Arterial impedance opposing LV ejection (Windkessel) - Systemic vascular impedance is the mechanical property of the vascular system opposing ejection and the flow of blood into it. This is composed of two components. One is the resistive or steady-flow component, which is the SVR. This component is mainly due to the frictional opposition to flow in the vessels. The other component is the reactive or frequency-dependent component, which is due to the compliance of the vessel walls and inertia of the ejected blood. This component is dependent on the pulsatile nature of the flow and rapidity of ejection. A major part of this reactive component is formed by the arterial elastance (Ea).
- Effective arterial elastance (Ea) - ventriculo-arterial coupling. Arterial elastance is the inverse of arterial compliance and is a measure of the elastic forces in the arterial system that tends to oppose the ejection of blood into it. Determination of Ea involves plotting a PV curve for the arterial system using different SV and recording end-systolic pressures. The slope of the curve then gives the effective elastance (compliance^{-1}) of the arterial system.
- Ventricular end-systolic wall stress – **systolic La Place – T=Pr/h**
- **Ohm's Law, R=P/Q** (Resistance=Pressure/Flow, dynes.sec.cm^{-5}) – using the PA catheter to calculate systemic vascular resistance. Systemic vascular resistance (SVR) is the most commonly used index of afterload in clinical practice, and can be calculated from mean arterial pressure (MAP), central venous pressure and CO, as follows:

  SVR=MAP - RAP/CO X 80 dynes.s.cm^{-5}

  The normal value for SVR ranges from 900 to 1400 dynes.s cm^{-5}. SVR is not a good estimate of afterload, since it is only one component determining afterload, and does not provide any index of intraventricular pressures generated during systole (i.e. how hard the ventricle is contracting). Clearly, if the ventricle only generates low intraventricular pressures by contracting softly, the afterload is low irrespective of the calculated SVR.

  In a similar manner the pulmonary vascular resistance (PVR) may be calculated as an index of RV afterload, using mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure and CO:

  PVR = MPAP – PCWP/CO X 80 dynes.s.cm^{-5}

  The normal PVR ranges from 90 to 150 dynes.s cm^{-5}. CO, PAP and PCWP have to be obtained with a PAC to calculate SVR and PVR.

3. Bernoulli Equation (and Doppler)

When a transvalvular velocity is measured with Doppler ultrasound, the Bernoulli equation is used to convert velocity into a pressure gradient (or pressure drop). To measure an accurate flow velocity with ultrasound, the rule of Doppler (Johan Christian Doppler, 1803-1853) states that the ultrasound beam of interrogation must be parallel to the blood flow, to avoid underestimation.

The average pressure drop/gradient to open a normal valve, i.e. aortic valve in systole, or mitral valve in diastole is anything between 2-4 mmHg.

This principle is well demonstrated with the Wiggers diagram:

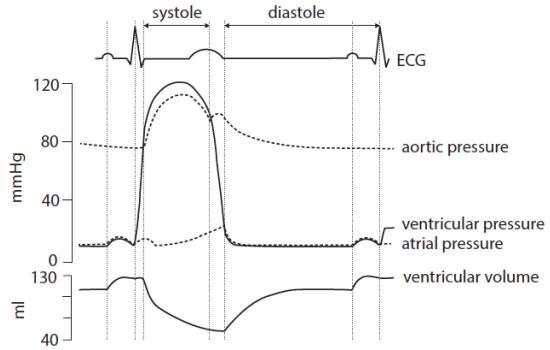

Figure: Wiggers diagram to explain pressure gradients across normal valves during systole and diastole

The Bernoulli equation in its full form has been described for flow dynamics (Daniel Bernoulli, 1738- "Hydrodynamica").

$$P_1 - P_2 = 0.5\rho\ (v_2^2 - v_1^2) + R(v) + r\int_1^2 dv/dt\ dS$$

Pressure Gradient	convective acceleration	viscous friction	flow acceleration

Equation: In its original form, the Bernoulli equation has three parts, which consider (i) convective acceleration where ρ (rho) refers to blood density, (ii) viscous friction and (iii) the rate of change of flow acceleration.

In the first part of the Bernoulli equation, blood density (ρ) multiplied by 0.5 is 3.98, but is rounded up to 4. The second and third parts of the original equation are then assumed to be more or less constant; hence the modified Bernoulli equation is created:

$$\textbf{Pressure Gradient} = 4 \times (V_2^2 - V_1^2)$$

Equation: The modified Bernoulli equation, where V_2 is the maximal velocity across the AV, and V_1 is the maximal velocity across the LVOT.

V_1 in the Bernoulli equation refers to the velocity upstream from the constriction (ie the velocity in the LVOT when being applied to AV velocities). If the LVOT velocity is less than 1 m/sec then the value for V_1 is assumed to be negligible and also ignored. This allows the simplified Bernoulli equation:

$$\textbf{Pressure Gradient} = P1\text{-}P2 = 4\ V^2$$

Equation: The simplified Bernoulli equation, where V is the maximal flow velocity across the AV.

If the velocity is higher than 1 m/sec in the LVOT (like e.g. in HOCM) then the value for V_1 cannot be ignored and the modified Bernoulli equation must be used.

The Bernoulli principle has many more assumptions than just those referred to in the equation above. For example, in aortic valve (AV) stenosis it is assumed that the diameter of the left ventricular outflow tract (LVOT) prior to the AV constriction is of the same diameter as that of the ascending aorta, and the surface area of the LVOT is the same as that of the ascending aorta. Other assumptions are that the inflow shape in aortic stenosis has a flat, orifice-like shape as opposed to a funnel shape, and that flow through the constriction is laminar, not turbulent.

Severe AS in a native valve is defined as a flow velocity more than 4.5 m/sec, a mean pressure gradient (mean pressure drop) of more than 50 mmHg and a peak pressure gradient (peak pressure drop) more than 80 mmHg. The mean pressure gradient is obtained by accurately tracing the outline of the velocity time integral signal, away from the transducer when Continuous Wave Doppler (CWD) is placed across the aortic valve. The mean gradient is more appropriate in reflecting the severity of pressure gradient as several factors can alter the peak velocity.

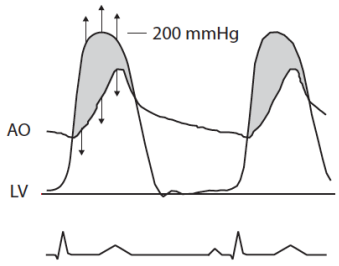

Figure: Pressure gradient during systole in Aortic Stenosis

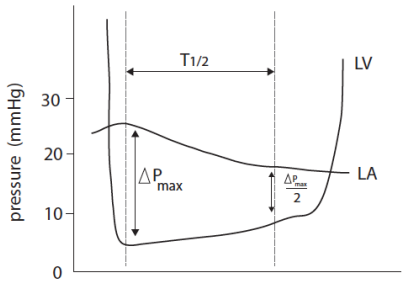

Figure: Pressure gradient during diastole in Mitral Stenosis

Compare the numbers of **severe AS** with that of across **normal valve** (PG = 4 x V^2) therefore more or less, flow velocity 1 m/sec, peak pressure gradient of 4 mmHg, mean pressure gradient of 2 mmHg.

4. Fick (Principle vs Law vs Equation), Shunt and Dead Space

The **Fick principle** states that the amount of a substance taken up by an organ (or the whole body) per unit time is equal to the arterial concentration of the substance minus the venous concentration (a–v difference), multiplied by the blood flow. This can be applied to the oxygen content of blood to determine Cardiac Output (CO).

First, the steady-state oxygen content of venous (CvO_2) and arterial blood (CaO_2) is measured. Then oxygen uptake in the lungs is measured over 1 minute (VO_2). Finally, the Fick principle is applied to calculate the blood flowing in 1 minute:

$CO = VO_2/(CaO_2 - CvO_2)$

Errors in sampling, and the inability to maintain steady-state conditions, limit this technique.

In clinical practice the intensivist applies the Fick principle when a pulmonary artery catheter (PAC) is used in the critically ill patient. It is important to distinguish between indices measured with the PA catheter (right atrial pressure, right ventricular pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, etc.) and those indices derived and calculated from the measured parameters (e.g. stroke volume, stroke work index, and the vascular resistances). It would border on negligence to have a PA catheter in situ and ignore

the oxygen demand and supply parameters (mixed venous oxygen content, oxygen delivery, oxygen consumption, etc).

Rearranging the equation:

$CvO_2 = CaO_2 - VO_2/CO$

The saturation of the mixed venous blood (SvO_2) can therefore be measured in the RV or proximal PA, and give a good indication of peripheral oxygen consumption on cellular level, as well as the oxygen delivery ($DO_2 = CaO_2 X$ CO).

Over the years there have been innovative changes in design of the PA catheter using Fick principle, including special purpose PA catheters for monitoring continuous cardiac output, continuous mixed venous oximetry (SvO_2), etc.

The perfusionist also uses the Fick principle when caring for a patient on the cardiopulmonary bypass (CPB) machine during a heart operation. He/she monitors the drained from the right atrium (inline SvO_2), and then uses the Fick principle to balance the patient's oxygen supply and demand by adjusting machine blood flow (perfusion) rates.

Fick's Law of Diffusion

Fick was a clever physiologist-physicist who described not only a principle-equation, but also a law!

The transfer of a gas across the blood-gas barrier of the alveolar membrane is called diffusion. Diffusion across the alveolar membrane is well described by Fick's law, which states that the rate of transfer of a gas through a sheet of tissue is proportional to the tissue area (A) and the difference in gas partial pressures between the two sides (P1-P2), and inversely proportional to the tissue thickness (T). The area of the blood-gas barrier in the lung is enormous and the alveolar membrane is very thin, therefore ideal for diffusion of oxygen. The rate of gas transfer is also proportional to a diffusion constant (D), which involves the solubility of the gas (sol) and the square root of its molecular weight (mw).

$Vgas = A/T \times D \times (P1-P2)$ **$D = sol/\sqrt{mw}$**

The alveolar partial pressure of oxygen (PAO_2) is the driving force (P1) behind the diffusion of O_2 across the alveolar membrane into the pulmonary capillaries. In the capillaries the O_2 combines with haemoglobin in the red blood cells. When the haemoglobin is saturated with O_2, the partial pressure of oxygen in the pulmonary capillary blood (PcO_2) will rise. Under normal resting conditions the PcO_2 will almost reach that of the alveolar gas (PAO_2) when the red cell is about one-third of the way along the capillary. Therefore the O_2 uptake can be regarded as occurring in two stages:

- diffusion of O_2 through the blood-gas barrier including the plasma and red cell interior.
- reaction of O_2 with haemoglobin

The resistance to this reaction can be described by the following reaction:

$1/DL=1/DM + 1/q.Vc$

where DL is the diffusing capacity of the lung, 1/DM is the resistance of the blood-gas barrier, q is the rate of O_2 reaction with haemoglobin and Vc is the volume of pulmonary capillary blood.

In a perfect lung the PO_2 of arterial blood (PaO_2) would be the same as that in alveolar gas (PAO_2). In real life this is not true. As blood travels through the pulmonary capillary, its PO_2 rises closer and closer to that of alveolar gas. Under normal conditions there is always a small difference between alveolar and end-capillary PO_2 (A -a gradient), because of incomplete diffusion.

5. Hagen-Poiseuille

What is the Hagen-Poiseuille Equation?

The Hagen-Poiseuille Equation describes laminar flow through a tube:

$Q = Pr^4\pi/8\eta L$

Q = flow
P = pressure gradient across tube/vessel
r = radius of tube/vessel
η = fluid viscosity
L = tube/vessel length

How does laminar flow differ from turbulent flow? What is the Reynolds number (Re)?

With laminar flow the layers of fluid are moving smoothly, with the central "lamina" flowing fastest, and the outer layer slowest. Turbulent flow, on the other hand, is chaotic, with fluid eddies. The Reynolds number predicts whether flow will be turbulent or laminar. A Re < 2000 means laminar flow, while > 2000 predicts turbulent flow.

$Re = V\rho d/\eta$

V = fluid velocity
ρ = fluid density
d = vessel or tube diameter
η = fluid viscosity

What affects the rate of turbulent flow?

Flow is directly related to the square root of the pressure gradient ($\sqrt{P}$)
Flow is directly related to the square of the radius (r^2)
Flow is inversely related to the vessel or tube length (1/L)
Flow is inversely related to fluid density (1/ ρ)

The influence of the Hagen-Poiseuille principle is appreciated in daily clinical practice when discussing the respiratory airways, or considering the thickness and length of an endotracheal tube, ventilation/breathing circuits, fluid-giving sets, intravenous/arterial cannulas, Cardiopulmonary Bypass or ECMO Circuits, etc.

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