صدقة جارية عن المغفور له بإذن الله **عمر عطية** من دفعة 2023 – كلية الطب، الجامعة الأردنية.

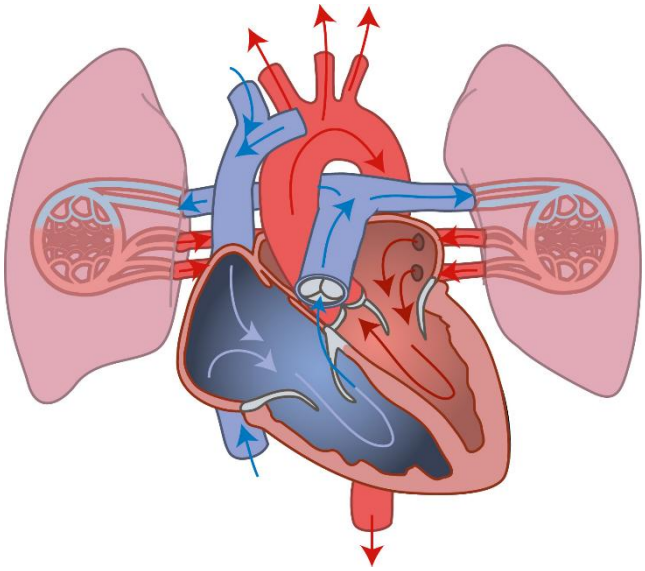
اللهم ارحمه واغفر له وأكرم نزله ووسع مدخله، لا تنسوه من دعائكم، إنا لله وإنا إليه راجعون.

#فريق_دوبامين_العلمي

Respiratory System Physiology

Comprehensive File 6 – V2

Dr. Yanal Shafagoj



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Pulmonary Circulation

The cardiac output from both sides (left and right) is about 5 L/min at rest. The pulmonary circulation has a systole and a diastole, which are in terms of time equal to that of the systemic circulation (0.8 sec = 0.5 sec + 0.3 sec) but in terms of pressure lower (pulmonary pressure 25/8 not 120/80). The mean pulmonary arterial pressure is about 14 mmHg. Mean pulmonary arterial pressure above 20 mmHg indicates pulmonary hypertension in contrast to the numbers taken in CVS for the systemic HT.

How can we relate systemic and pulmonary resistances?

$$\boldsymbol{Flow} = \frac{\boldsymbol{DF}}{\boldsymbol{R}} \; [\boldsymbol{Ohm's\ Law}]$$

The DF for the systemic circulation is the mean (systemic) arterial pressure ($P_a = 100\ mmHg = \frac{2}{3} dias.p + \frac{1}{3} syst.p$). For pulmonary circulation, the DF is the mean pulmonary arterial pressure ($P_p = 14\ mmHg \approx \frac{2}{3} * 8\ mmHg + \frac{1}{3} * 25\ mmHg$).

Substituting into the equation, the flow in both circulations is equal, so the ratio DF/R is also equal. This means that pulmonary resistance is equal to $\frac{14}{100} * TPR \approx \frac{1}{7} * TPR$.

This means that **systemic resistance is 7 times more** than pulmonary resistance.

Pulmonary Hypertension and Cor Pulmonale

The pulmonary arteries conduct blood to smaller vessels, such as arterioles and capillaries. The resistance in these small vessels is calculated in parallel, meaning that the total resistance is less than the least individual one, as discussed in the CVS. If one pathway is blocked, the total cross-sectional area (A) decreases; because the resistance is inversely proportional to A^2, the total resistance increases. The required pressure to maintain the flow will accordingly increase. If enough blockade occurs, the pressure needed to maintain the flow against increased resistance becomes higher than 20 mmHg, and this is termed pulmonary HT, which precipitates right-sided heart failure (cor pulmonale) due to increased afterload and dilatation of the right ventricle.

Recall that hypoxia causes vasoconstriction, not vasodilation, in the pulmonary circulation, which is opposite to other circulations. This effect can magnify the pulmonary HT, further worsening the condition.

Hypertension Cutpoint Recap

It was mentioned in the lecture that

- Systemic hypertension is systolic > 140 mmHg and/or diastolic > 90 mmHg
- For diabetic patients, due to potentiation of vascular damage, it is >130 and/or >80.
- Pulmonary hypertension: mean pulmonary arterial pressure **> 20 mmHg <u>at rest</u>.**

Effect of Exercise on Pulmonary Pressure, Resistance, and Flow

At rest, the driving force is ≈14 mmHg, and the resistance is 14 units. This pressure gradient and this resistance together yield a blood flow of 5 L/min.

During exercise, assume that blood flow increases to 20 L/min (4x the value at rest). For this change to happen, the driving force and the resistance must change accordingly such that the ratio DF/R is increased 4 times.

It was found that the pressure gradient can reach 30 mmHg during exercise, which is approximately double the "at rest" value. This means that the **resistance must be halved** in order to satisfy the condition mentioned in the previous paragraph.

How is the pulmonary resistance reduced during exercise?

Pulmonary vascular resistance decreases during exercise because pulmonary blood vessels are **highly compliant** and can accommodate increased blood flow with only a small rise in pressure. As pulmonary arterial pressure increases, resistance falls through two main mechanisms:

1. **Recruitment**: previously unperfused pulmonary capillaries are **opened by the rise in intravascular pressure**. At rest, **approximately one-third of pulmonary capillaries are perfused**, while during exercise many previously closed capillaries become functional, increasing the total cross-sectional area.
2. **Distension**: although pulmonary capillaries **lack smooth muscle**, they can be **passively distended by increased transmural pressure**, increasing their diameter and further reducing resistance.

The **systemic circulation** also exhibits recruitment and distension during exercise, but these mechanisms are **far more pronounced in the pulmonary circulation**, allowing it to handle large increases in blood flow efficiently.

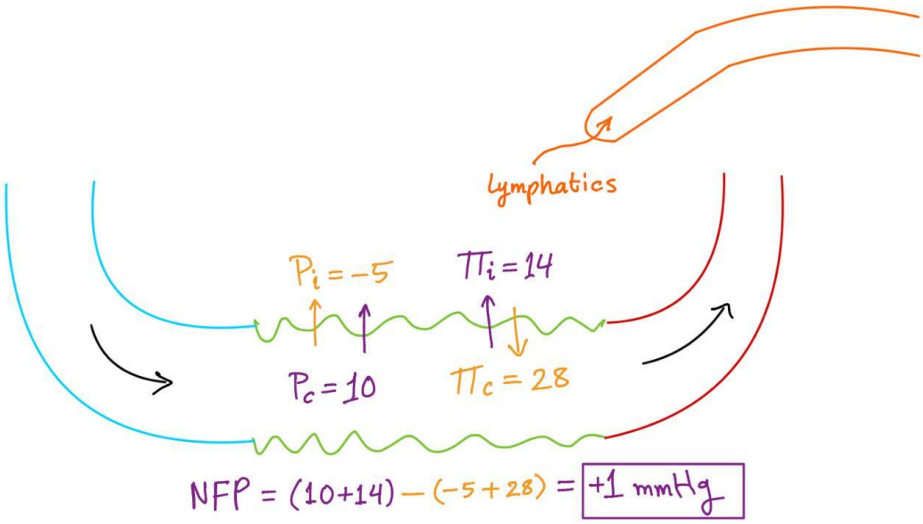
Starling Forces in the Lungs

Recall the 4 starling forces from first-year physiology (P_c, Π_c, P_i, Π_i).

The two sentences below are for positive pressure values:
P_c and Π_i favor filtration (outward movement from the **c**apillaries to the **i**nterstitium).
P_i and Π_c favor reabsorption (inward movement from the **i**nterstitium to the **c**apillaries).

The net filtration pressure (NFP) is the directional sum of all 4 pressures:

$$\boldsymbol{NFP = (P_c + \Pi_i) - (P_i + \Pi_c)}$$



NFP of +1 mmHg indicates that net filtration occurs at the level of pulmonary capillaries. The extent of this filtration is, however, little compared to other tissues such as kidneys, where the primary function of the capillaries is filtration. Pulmonary capillaries primarily perform gas exchange, not filtration.

Pulmonary circulation pressures:

- Mean pulmonary arterial pressure = 14 mmHg (systolic 25; diastolic 8).
- Left atrial pressure (venous end) = 2 mmHg.
- Capillary pressure (P_c) is between 7 and 10 mmHg (10 was used in the example).

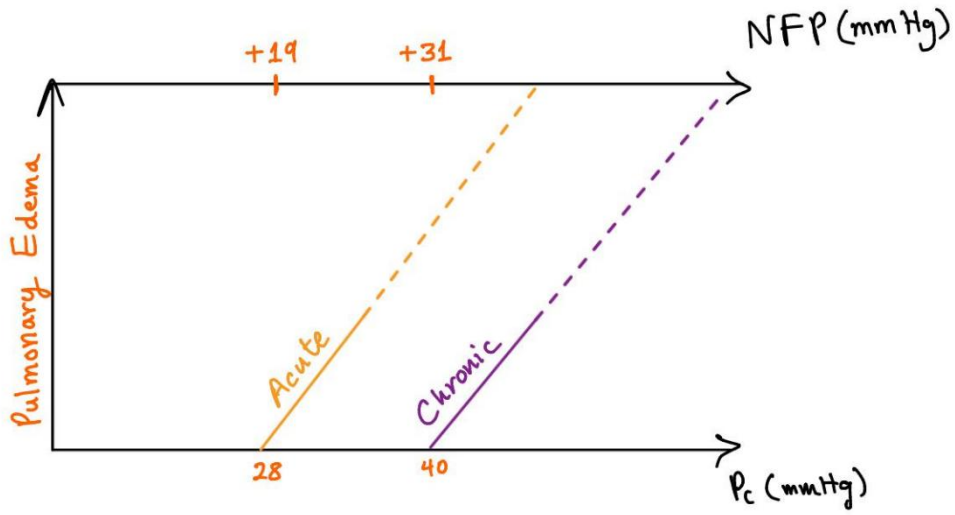
Typical values of the 4 starling forces in pulmonary capillaries:

- P_c = 10 mmHg, which is in between the arterial and venous pressures. Systemic P_c is 30 mmHg because arterial and venous pressures are higher.
- Π_c = 28 mmHg, which is equal to systemic values; albumin is the main cause.
- P_i = -5 mmHg, which is influenced by the negative intrapleural pressures (-4, -6). P_i of **-**5 mmHg favors filtration not reabsorption (reabsorption is with (+) #s).
- Π_i = 14 mmHg, which is relatively high and indicates that these capillaries are leaky to proteins. The value is calculated based on lung lymph protein content.

The net filtrated fluid is easily managed with the **abundant lymphatics in the lungs**.

Even if the NFP is increased, lymphatics can still manage it. This capacity is called the **pulmonary edema safety factor**, which occurs mainly due to the abundance of lymphatics; other reasons exist as well. This safety factor prevents accumulation of fluids, which can interfere with the primary function of the lungs – gas exchange.

The pulmonary edema safety factor is different in the case of acute changes from chronic changes. In acute changes, lungs can tolerate P_c of 28 mmHg, which causes the NFP to be +19 mmHg. However, in chronic cases, more tolerance is shown, and edema does not usually form until P_c exceeds 40 mmHg (NFP > 31 mmHg).



The lungs must stay dry (free of edema) to perform their function effectively. The diffusion of oxygen is significantly affected by edema since it increases the thickness of the respiratory membrane. Recall from lecture 1 that oxygen availability is not diffusion-limited. Oxygen can pass through any biological membrane as if it does not exist. However, in pathological conditions, such as pulmonary edema or fibrosis, the thickness (dx) of the membrane becomes too high, affecting oxygen diffusion.

Recall that permeability is governed by the following equation:

$$\boldsymbol{K = \left(\frac{A}{dx}\right) * \left(\frac{S}{\sqrt{MW}}\right) \rightarrow K \propto \frac{A}{dx}}$$

For membrane-specific parameters, the permeability is inversely proportional to dx.

Pulmonary edema can be caused by left-sided heart failure and acute myocardial infarction. The ineffective pumping by the left side of the heart transmits the increased hydrostatic pressure back to the lungs, and edema forms after the safety factor is surpassed. The threshold is different between acute and chronic cases as discussed.

Blood flow to different organs

Starting with a 5 L/min cardiac output from the aorta, the first liter goes to the skeletal muscles. Since muscle mass is approximately 40% of total body weight, this corresponds to about 28 kg in a 70 kg person. Dividing blood flow by tissue mass gives a perfusion of approximately 0.035 mL/g/min.

The kidneys receive 1 L/min, and with a combined mass of 250 g, their perfusion is approximately 4 mL/g/min. Another 1 L/min is delivered to the gastrointestinal tract, and another 1 L/min to the brain.

The remaining 1 L/min is distributed among other organs. Of particular interest, the heart receives approximately 250 mL/min, corresponding to a perfusion of 0.8 mL/g/min. The carotid bodies receive an exceptionally high blood flow of approximately 20 mL/g/min, reflecting their very small mass (in the milligram range). Numbers are approximations. Values are shown in the following table.

Tissue	Blood flow (ml/g/min)	A-V O_2] difference (Vol %)	Flow ml/min	O_2 consumption ml/min
Heart	0.8	11	250	27
Brain	0.5	6.2 (25-30% Extraction)	750-900	
Skeletal Muscle	0.03	6	1200	70
Liver	0.6	3.4 Reconditioner organ		
SKIN	0.1			
Kidney	4.2	1.4 Reconditioner organ	1250	18
Carotid bodies	20	0.5 Reconditioner organ	0.6	

O_2 vol % (oxygen volume percent) refers to the amount of oxygen contained in the blood, expressed as milliliters of O_2 per 100 mL of blood. It represents oxygen content, not oxygen partial pressure.

Essential organs such as skeletal muscles receive blood flow according to **metabolic** demand. At rest, total skeletal muscle blood flow is approximately 1 L/min (20% of the cardiac output). During exercise, it can increase to 66% (8 out of 12, for example).

When examining the arterial and venous ends of muscles' capillaries, skeletal muscle shows an arterial–venous O_2 difference of about 6 Vol %.

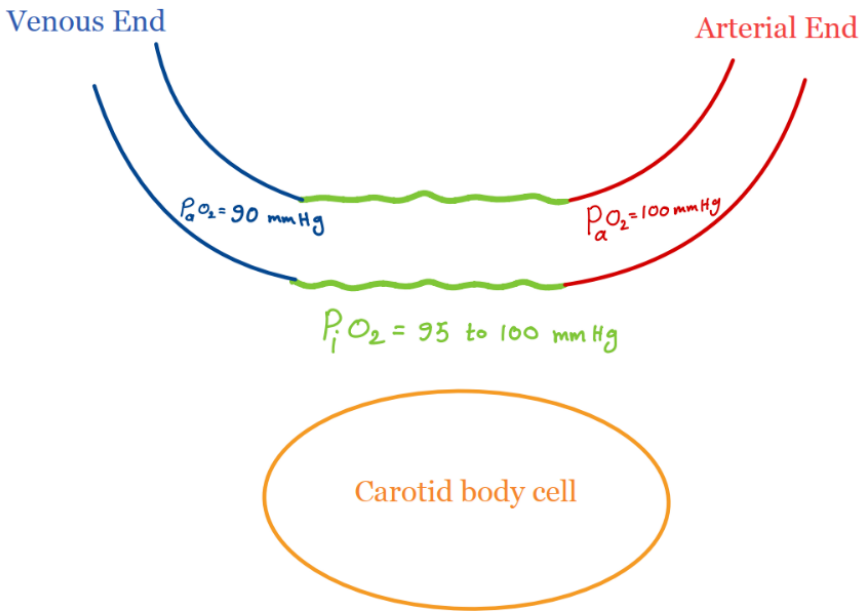
In contrast, reconditioning organs such as the kidneys have a small arterial–venous O_2 Vol % difference, because their O_2 delivery greatly exceeds metabolic demand.

Similarly, the carotid bodies have extremely high blood flow relative to tissue mass and a very low O_2 extraction (≈ 0.5 Vol %), which explains their relative resistance to hypoxia.

The heart demonstrates a high arterial–venous O_2 difference (≈11 Vol %), reflecting very high oxygen extraction, and therefore cardiac oxygen delivery depends primarily on coronary blood flow.

Carotid Body Cells Blood Flow

As we know, cells receive oxygen through capillaries, where oxygen diffuses across the capillary wall into the interstitium, and then into the cell down its partial pressure gradient. In the normal situation, interstitial PO_2 is about 40 mmHg.



However, this is not the case for carotid body cells, which are responsible for sensing arterial P_aO_2, reflecting lung function, and transmitting this information to the respiratory centers in the medulla oblongata. For these cells to function properly, their surrounding interstitial PO_2 must be close to arterial P_aO_2.

This can theoretically be achieved in two ways:

1. The cells consume very little oxygen, which would maintain a high surrounding PO_2. However, this is not the case for carotid body cells, as they have high metabolic activity.
2. The cells are supplied with extremely high blood flow, so that despite high oxygen consumption, interstitial PO_2 remains high, this is the case for the carotid body cells as their blood flow is approximately 20 mL/g/min.

Zones of Pulmonary Blood Flow

Remember that systemic arterial blood flow is pulsatile, with higher flow during systole and lower flow during diastole, with the important exception of the coronary arteries, where blood flow is greater during diastole.

At the level of the systemic capillaries, blood flow is steady and does not reflect systolic–diastolic variations. However, the presence of precapillary sphincters makes capillary perfusion intermittent; at rest, approximately one-third are open, while during exercise most are open.

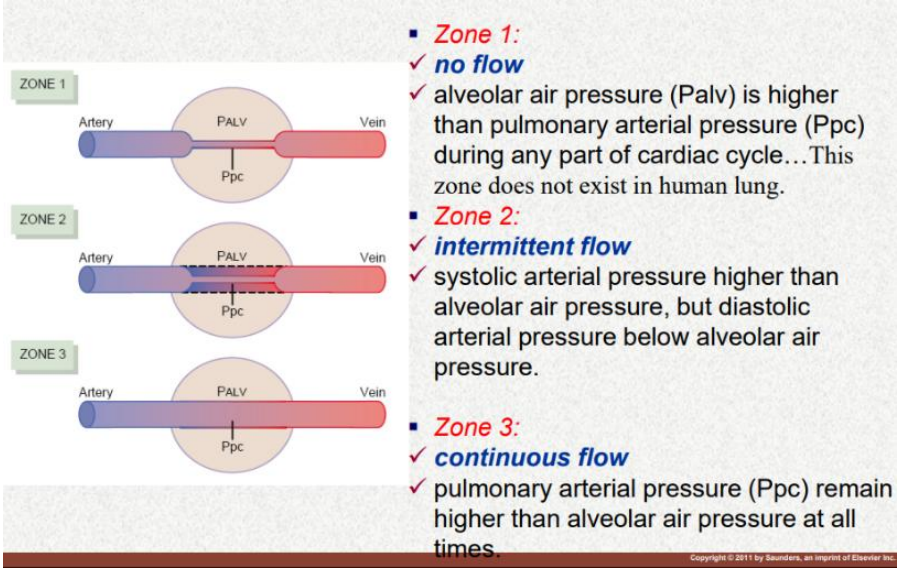
In the pulmonary capillaries, the situation is different. Pulmonary blood flow is strongly influenced by the relationship between alveolar pressure and pulsatile pulmonary arterial pressure. If alveolar pressure is higher than both systolic and diastolic pulmonary arterial pressures, no blood flow occurs at any point in the cardiac cycle, and this is known as **Zone 1 blood flow**.

If systolic pulmonary arterial pressure exceeds alveolar pressure, but diastolic pulmonary arterial pressure is lower than alveolar pressure, blood flow occurs only during systole, resulting in intermittent flow, which is termed **Zone 2 blood flow**.

If pulmonary arterial pressure remains higher than alveolar pressure throughout both systole and diastole, blood flow is continuous, and this is known as **Zone 3 blood flow**.

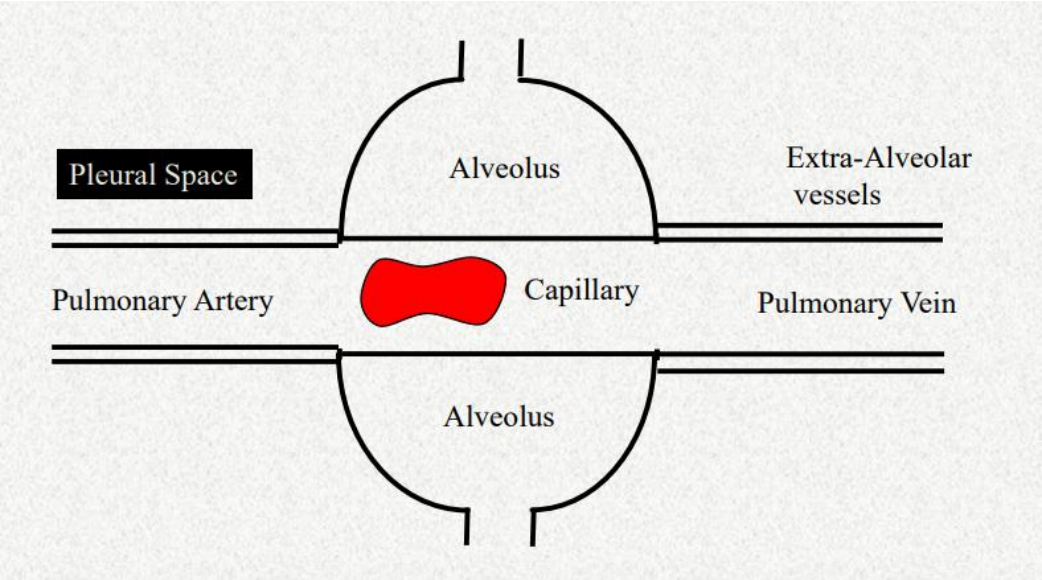
Under normal physiological conditions, most lung regions are perfused because pulmonary arterial pressure is usually sufficient to exceed alveolar pressure for most of the cardiac cycle. In conditions such as severe hemorrhage, pulmonary arterial pressure may fall, allowing alveolar pressure to exceed arterial pressure in apical regions, producing **Zone 1 blood flow**.

During exercise, pulmonary arterial pressure increases, converting intermittent or absent flow into continuous flow, so most of the lungs exhibit **Zone 3 blood flow**.

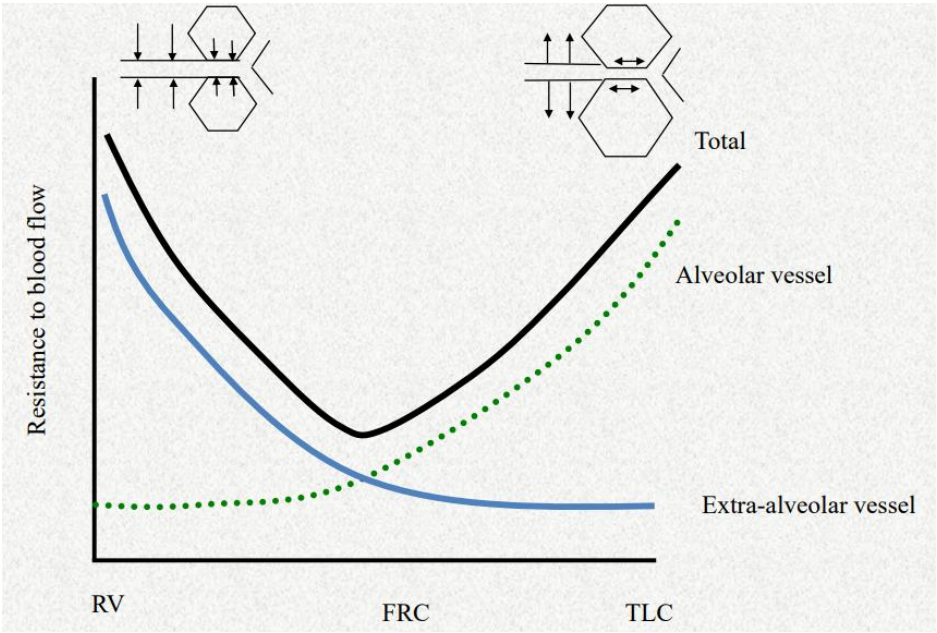


Intra-alveolar and Extra-alveolar Vessels

When pulmonary vessels lie between alveoli, they are functionally described as two segments: intra-alveolar and extra-alveolar vessels. During a deep inspiration reaching total lung capacity, the intra-alveolar vessels are compressed due to expansion of the surrounding alveoli. In contrast, the extra-alveolar vessels expand due to exposure to a more negative pleural pressure (≈ −6 mmHg).



When plotting vascular resistance of intra-alveolar and extra-alveolar vessels against lung volume, resistance in the extra-alveolar vessels decreases, while resistance in the intra-alveolar vessels increases as lung volume rises.



Because these vessels are arranged in series, the total pulmonary vascular resistance is obtained by adding the two resistances, producing a U-shaped curve. The lowest total resistance occurs at functional residual capacity (FRC).

At functional residual capacity (FRC), total pulmonary vascular resistance is minimal. In emphysema, air trapping causes FRC to shift to the right, resulting in an increase in total pulmonary vascular resistance. In restrictive lung disease, FRC is shifted to the left, and pulmonary vascular resistance also increases.

This displacement of FRC away from its normal position leads to an increase in pulmonary vascular resistance, which causes an elevation in pulmonary arterial pressure to overcome the increased resistance. As a result, right ventricular afterload increases, which may eventually lead to right ventricular failure (cor pulmonale).

Changes from VERSION 0 to VERSION 1:

- $\frac{100}{14} * TPR \rightarrow \frac{14}{100} * TPR$ (in page **2**)
- Added the italicized line (page **4**; **top**)
- Change in page **7** (**1st** paragraph):
  From "… kidneys have a small arterial–venous O_2 pressure difference"
  To "… kidneys have a small arterial–venous O_2 Vol % difference"
- Change in page **7** (**4th** paragraph):
  From "In the normal situation, intracellular PO_2 is about 40 mmHg."
  To "In the normal situation, interstitial PO_2 is about 40 mmHg."
- PO → PO_2 (in page **7**; **bottom**; **1st** point)
- **Blood flow depends on the relationship between alveolar pressure and systolic and diastolic pulmonary arterial pressures, rather than mean arterial and venous pressures. Changes were made accordingly in the text and figures explaining zones of pulmonary blood flow (Page 8).**

Changes from VERSION 1 to VERSION 2:

Page **5**; **second** paragraph **after** the blue table.

Essential organs such as skeletal muscles receive blood flow according to **metabolic** demand. At rest, total skeletal muscle blood flow is approximately 1 L/min, while during exercise, it can increase to 8-12 L/min (before).

Essential organs such as skeletal muscles receive blood flow according to **metabolic** demand. At rest, total skeletal muscle blood flow is approximately 1 L/min (20% of the cardiac output). During exercise, it can increase to 66% (8 out of 12, for example).