HYDRODINAMICS OF THE LUNG INTERSTITIAL SPACE

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SUMMARY

Some important facts related to normal and abnormal lung hydrodynamics and particularly to its pathophysiological consequences are discussed, in order to define real basis for a clinical aproach, as well as for future investigations.

Peculiar properties of the pulmonary circulation, gravity influence on vascular and pleural pressures, pulmonary blood volume, bronchial circulation, the alveolo-capillary membrane, the lymphatic vessels and the lung functions, all are reviewed, as important aspects of a morphophysiological overview.

Interstitial lung fluid accumulation is discussed as a result from an imbalance between what enters into it and what is removed through th drainage system expressed by lymphatic vessels. The former is analysed as the net result from one or more of the following mechanisms, predominantly working in the pulmonary microcirculation, but potencially also in the bronchial microcircualtion, both including capillaries and terminal arterioles and venules : a) increases permeability, either independent or parcially dependent on microvascular pressure level; b) increased microvascular hydrostatic pressure; c) decreased colloidosmotic microvascular pressure; d) increased negative interstitial pressure; e) increased interstitial colloidosmotic pressure, related to local inflamatory processes. Sudden alveolar filling mechanism is also discussed.

Diferent pathophysiological consequences are defined for the interstitial and the alveolar lung oedema. The former determines vital capacity reduction, hypoxemia through an increases venous-arterial shunt effect, and pulmonary hypertension, formerly accepted as alveolo--capilar membrane block; in the second, surfactant lesion and foam formation appears as rellevant factors.

Interstitial and alveolar oedema are fundamental constant components in most of the processes affecting the distal portion of the lung, independently of being inicially cardiac or lung disease which create conditions for its formation. They are the substract for the severity of many of critical care medecine conditions.

Lung hydrodynamics stands nowadays as a subject of great importance and its regulation is accepted as a major function of the lung (Hoffmen, 1976).

Many of its disorders, reflecting liquid filling of a vast interstitial space, are determinants of serious pathophysiological consequences and of live-threatening situations.

Although many outstanding scientists in the past contributed to the knowledge of lung structure and function (Table 1), we may say that significant steps on its development occured only in the last half centuary

Remarkably, the new era started with two very peculiar different reports dated from 1929, one of Forsman's first cathetherization on himself (Cournand, 1947), the other of an only Neergard's experiment to postulate alveolar sufactant existence (Clements, 1969).

It would be difficult to recall all the important researchers who during the last fifty years created the actual knowledge on the field. Instead of doing so, looks fairish to symbolize all of them under the name of Cournand. Always with Richards, he did many of the fundamental work; in their C_6 Lab of Bellevue Hospital at Columbia University, they trained and stimulate many of the investigators who now lead the research in lung pathophysiology.

Our connections with Pulmonary Circulation studies started 25 years ago with experiments trying to define the effect of drugs on its haemodynamics (Sales-Luis 1955, 1956); and continued with studies on pulmonary oedema (Sales-Luis et al, 1961) pulmonary blood volume (Giuntini et al 1963; Sales-Luis, 1966, 1968) and pulmonary hypertension (Sales-Luis, 1956; Coelho et al 1958).

The present paper deals with some important facts related to normal and abnormal lung hydrodynamics and particularly to its pathophysiological consequences, in order to define real basis for a clinical approach, as well as for future investigations.

Table 1

Outstanding scientists who contributed to the knowledge of lung structure and function

Séc. III	GALENO
Séc. XIII	IBN-AN-NAFIS
Séc. XVI	SERVET
	COLUMBO
	HARVEY
Séc. XVII	MALPIGUI
Séc. XVIII	PRIESTLEY
	LAVOISIER
Séc. XIX	CHAVEAU, MAREY,
	CLAUDE BERNARD
	FICK

1. MORPHOPHYSIOLOGY. AN OVERVIEW

1.1. Lungs are large organs, predominantly filled with blood and water, in spite of a solid tissue which corresponds to a quarter of its weight. Almost half of the cells of this solid tissue (including 4% of macrophages) are in the interstitial space and not in the parenchima.

Most notorious is the existence of two (pulmonary and bronchial) types of circulation, giving the basis for a great part of its originality.

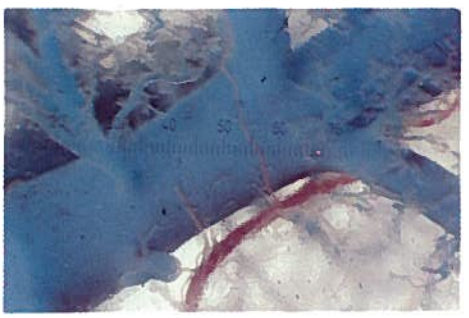
1.2. Pulmonary circulation is a net system serially linked between the left and the right hearts. Pulmonary arteries (Fig. 1, 2) early dicotomise themselves, becoming small-sized, quickly almost microscopic.

It is a low- pressure, permanently pulsatile, vascular system, having only a small pressure-gradient between its initial and terminal portions (15 to 5 mmHg). During the late dyastole all system has the same pressure from pulmonary artery till left ventricle, and no blood circulates.

On account of this low pressure system, vascular pressures are largely dependent on gravity. From the hilum, at left atrium level, arterial pressures in the standing patient decrease towards the lung apex and increase towards the diaphragmatic zones, being pressure difference between the top and bottom roughly 30 cm H_2O (Fig. 3). Gradient is less important in the supine patient, nevertheless it exists between the most anterior and posterior parts of the lungs.

Three main regions are then defined in the upright patient: the apical or zone one, in which alveolar pressures are greater than both arteriolar and venular pressures, thus resulting no blood circulating through the correspondent capillaries, or, so to say, apical alveolii are ventilated but not perfused; a second or zone two, in which alveolar pressure is greater than the venular but smaller than the arteriolar pressures allowing

capillary blood circulation during part of the cicle phasis; finally, a lower or zone three, in which alveolar pressure is lower than the vascular pressures, allowing the blood to circulate all along.



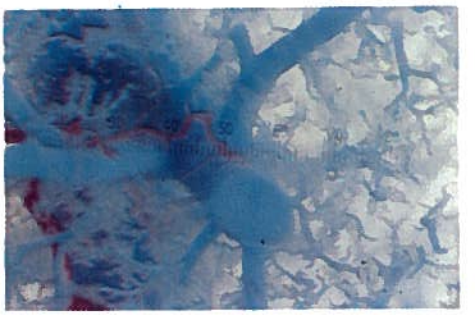


Fig. 1 and 2 — *Early dicotomization of pulmonary ateries. Original technique of Esperança Pina; pulmonary arteries colored as blue and bronchial arteries as red. Courtesy from the Department of Anatomy, Faculty of Medical Sciences, Lisbon.*

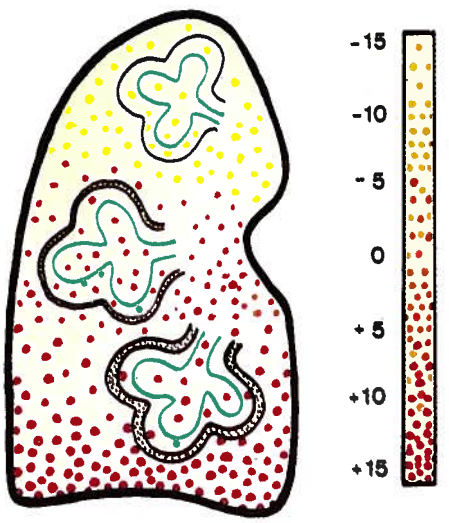


Fig. 3 — *Schematic representation of lung pressure zones. Showing by color density and vessel dilatation the differences between the 3 zones.*

1.3. Gravity also has important repercussion on pleural pressures (Fig. 4), which is more negative in the apical than in the basal regions, thus bringing consequences upon alveolar ventilation. As a matter of fact alveolii are better ventilated in the apex than in the basis, where many of them does not ventilate at all; even when a deep breath is taken, increasing the number of well ventilated alveolii, still some remain occlude in the basis. This zone, giving perfusion without ventilation, gradually increases with age, and it is highly influenced by the functional residual volume.

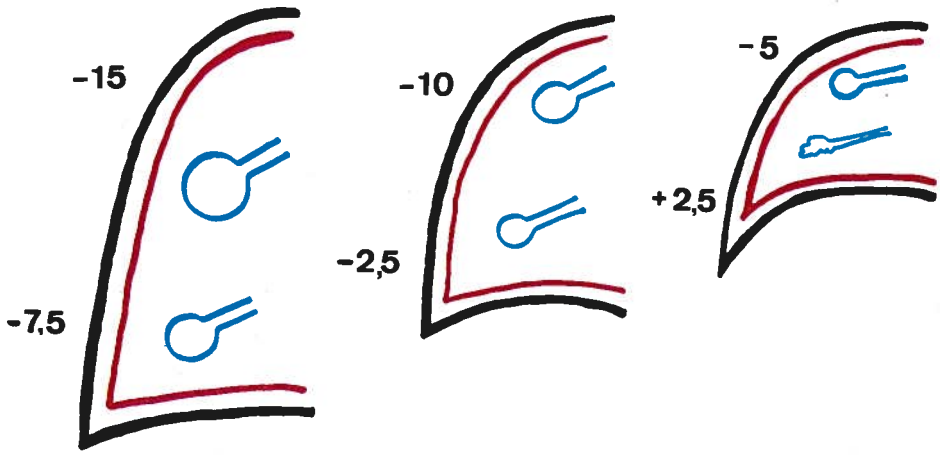


Fig. 4 — *Representation of gravity influence on pleural pressures, when breathing normally, pleural pressure range from —10 mmHg on the apex to —2.5 mmHg on the bottom; when breathing deeply, values change to —15 to —7.5 mmHg; in deep expiration. +2.5 is seen on the bottom, and the correspondent alveolii are occluded.*

1.4. Cardiac output through the pulmonary circulation is identical or more precisely slightly greater than that of the remaining body. Total blood volume cross the lungs one to five times in a minute and cardiac output may increase fivefolds without significantly changing vascular pressures.

Pulmonary blood volume (the volume instantly existing in the pulmonary circulation) is nowadays measured by a wide number of correct techniques being one of the most used that of Giuntini et al (1963) (Fig. 5). According to its normal values it varies from 240-300 ml/m^2 (Table 2) and corresponds to 10% of the total blood volume in almost every physiological or pathological condition. Mitral stenosis is one of the rare exceptions (Sales-Luis, 1966).

Pulmonary blood volume assures a regular blood flow to the left-sided heart when sudden blood flow changes are determined in the right-sided heart, as occurs with Valsalva maneouver, damping big aflux variations to the left ventricle.

Table 2
Normal values of PBV

Autors	MTPP	Q/m^2	PVB/m^2
	seg	ml/m^2	ml/m^2
Dock and col	4,8	2.700	219
	3,6	4000	239
	4,8	3200	257
	7,8	2100	269
McGaff and al	5,3 +0,49	2600	230 ±13,6
Vernauskas and al	3,68	4750	290
	5,04	4750	400
Lewis and al	4,7 ±0,68	4050	313 +58
Giuntini and al	4,5 ±0,54	3890±470	293 ±50
Freitas and al	6	3530	310 ±21
Sales-Luis, 1965	3,6 ±0,7	3850±550	240,5±48,8

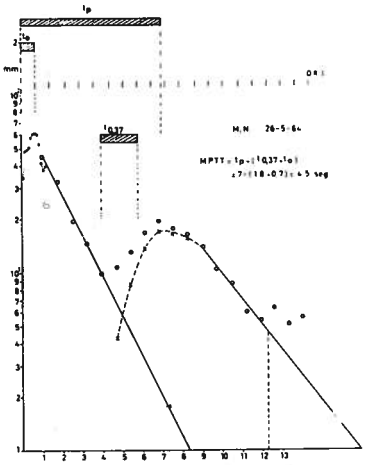


Fig. 5 — *When two chambers are directly connected, peak level on the second will appear on the turnover time of the first (T=0,37). If a circuit (pulmonary circulation) is connected between them, peak level on the second will be appear only after the mean pulmonary circulation time plus the turnover time. A semi-log plot of a radiocardiogram.*

1.5. As already mentioned the second type of circulation in the lung is the bronchial circulation. There are plenty of comunications between both the pulmonary and bronchial circulations (Fig. 6).

Bronchial circulation is a rather different system, close to the various parts of systemic circulation with similar funtion. So, it is through the bronchial supply that lung nutrition is warranted. In normal conditions lung consumes by itself 1-2% of the total 0_2 consumption of the body, more than which corresponds to the liver. In some pulmonary diseases figures may triplicate, not only for oxygen consumption but also for energetic material.

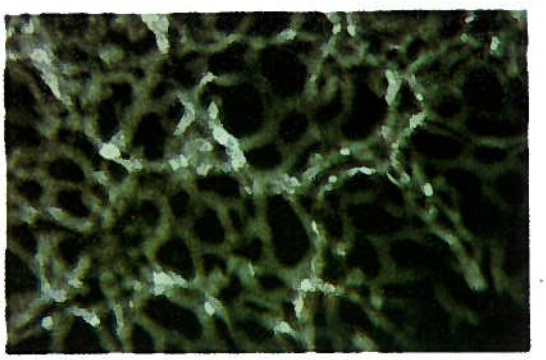


Fig. 6 — *Arterio-arterial anastomosis between the pulmonary (blue) and bronchial (red) circulations. Courtesy from the Department of Anatomy, Faculty of Medical Sciences. Lisbon.*

1.6. As can be seen on Fig. 7 pulmonary capillaries are very diferent from the systemic ones. They are almost as long as wide, and some fifty for each alveolous. More than isolated vessels, they look like vascular spaces between two paralel walls connected on each side with an alveolar wall, and kept apart by columns of connective tissue. Each

capillary vessel has one wall contributing to the paralel wall in contact with the alveolus and the other making part of the column of connective tissue which continues with the interestitial tissue of one interalveolar space.

In front of a capillary network stands the alveolar wall with elongated end flat epitelial cells, type I pneumocites, and now and then other much bigger, very rich in organelles cuboid cells, type II pneumocites.

The latter are highly active as surfactant producers, and precursors of type I cells, substituting them on acute lesions of the wall.

There are leaks between both endotheliae and epitelial cells. Real pores between cells of the capillary walls are larger and uninterupted and their permeability is increased by many influences. Interepitelial pores are smaller and time to time interrupted by bridles.

They represent a sort of comunication between the two sides both of the endothelial and of the alveolar walls.

Finally, the lungs are provided with a very rich lymphatic network distributed all over the lung, except for the alveolii and the inter-alveolar septs, predominantly arround the vessels, the bronchioles and the bronchii.

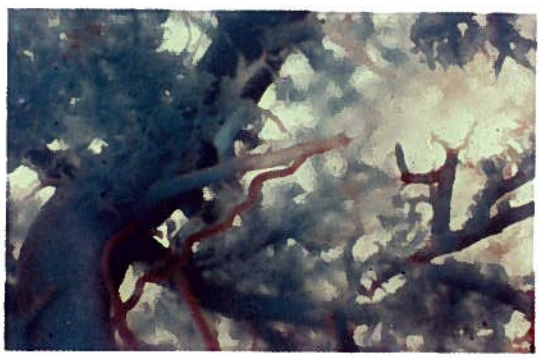


Fig. 7 — *Pulmonary capilarries in relation with one alveolus. Courtesy from the Department of Anatomy. Faculty of Medical Sciences. Lisbon.*

1.7. With such a structure, what are the lung functions?

We recalled already two of them, the regulation of the hydric circulation, and a buffer role of the blood supply changes in the left heart. Other fundamental functions may be expressed as biophysical and biochemical functions, according to Bakhle and Vane (1974) (Table 3). Biophysically, it removes CO_2, embolii, leucocytes and nuclear fragments from the blood stream, and adds oxygen and platelets to it.

Biochemically, we may say that it removes instantaneously circulating substances such as bradykinin or angiotensin I which will next be transformed into angiotensin II: removes, although less rapidly but with equal efficiency, serotonin, noradrenalin, some prostaglandines, very-low-density lipoproteins and peptides. Converselly, it «segregates» into the bloodstream activited angiotensin II, prostaglandins such as PGI_2 or protacyclin and histamine.

Having such a large variety of fundamental functions it is easy to imagine how important, even not yet well defined, will be the consequences of generalised lesions of the endothelium, the alveolar epitelium or even of the interstitial pulmonery space.

Table 3

Lung functions

	Biophysical F.	Biochemical F.
Removes from the blood	CO_2 Embolii Leucocytes Nuclear residuae	Serotonyn Bradykynin Nor-adrenalin Prostaglandins (PGE, PGF$_{2\alpha}$) Angiotensin I VLD lipoproteins Peptides
Adds to the blood	O_2 Trombocytes	Angiotensin II Histamin Prostaglandins (PGI$_2$)

2. LUNG HYDRODINAMICS

Keeping in mind basic ideas, we will go into lung hydrodynamics, recalling Starling's Law on exchanges through the capillary wall (Fig. 8) (Staub. 1974).

$$\dot{Q}_F = K_F\left[\left(P_{MV} - P_{P_{MV}}\right) + \sigma\left(\pi_{P_{MV}} - \pi_{MV}\right)\right]$$

Liquid movement depends upon various factors hydrostatic or microvascular pressure; perimicrovascular space pressure; plasma proteins coloidosmotic pressure, coloidosmotic pressure of the proteins existing in the perimicrovascular space; and upon the filtration rate (or *permeability*) of the vessel, as well as the protein reflexion rate.

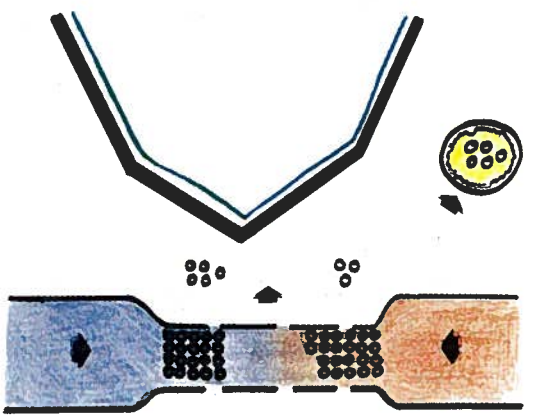


Fig. 8 — *Representation of an alveolus, a lymphatic vessel and a pulmonary capillary. In normal situations, there are liquid in the interstitial space, and drainage through the lymphatic.*

2.1. In normal conditions the microvascular pressure of pulmonary capilaries range around 5-6mmHg. The correspondent perimicrovascular pressure is highly dependent upon the pleural pressure: both are negative, and its values vary from point to point, although it is generaly accepted that 6mmHg as its median value.

Protein coloidosmotic pressure can be nowasdays directly measured in a sample of peripheral blood; or only assessed from the plasma protein content, indirect results being well correlated with direct readings.

It is not certain whether values obtained from peripheral samples correspond to the real coloidosmotic pressure in pulmonary capillaries, nor if that value increases significantly from the arteries to the venules. Accepting that these variations are insignificant, we may say colloidosmotic pressure is 28mmHg.

Perimicrovascular colloidosmotic pressure is dependent upon proteins in the interstitial space. As it is not yet possible to obtain enough sample of interstitial content to allow quantification, interstitial protein is usually assesed from drained samples of the local lymphatic vessels, and its colloidosmotic pressure accepted as 20mmHg.

Summing up, the final balance is positive and the filtration is determined by net pressures varying from 3 to 8mmHg. Using sheep experiments, Staub (1973) showed that the drainage of liquid per hour from interstitial space has a constant value ranging between 5 and 10ml, which means the filtration from the pulmonary capillaries is continuous. Extrapolating to the human size, values of 30-40ml per hour should be infered.

2.2. Changing the normal steady state conditions, for instance increasing hydrostatic pressure (Fig. 9) larger amounts of filtrated fluid will first increase lymphatic drainage, and afterwards it will accumulate in the pulmonary interstitial space, so to say, in the whole connective space, which include the juxta-capillary columns and the interseptal and perivascular connective spaces.

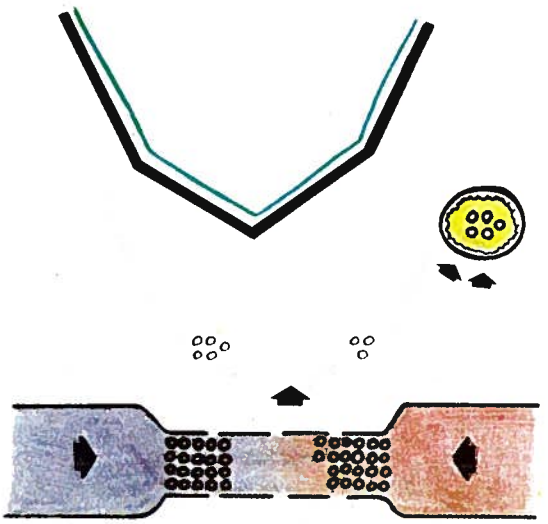


Fig. 9 — *When hydrostatic microvascular pressure increases. Transudation will increase, as the lymphatic drainage and interstitial liquid.*

It has been experimentally demonstrated that lymphatic flow increases as a function of hydrostatic capillary pressure increments. It has been shown that correlating directly assessed animal extra-vascular lung water with microvascular pressures, a

two-componnent curve is obtained, the first with clear rise of microvascular pressures without significant increase of extravascular water, and the second in which the two parameters proportionally change. It means that liquids will accumulate in the interstitial space only after lymphatic draining capacity saturation.

Transudated liquid is predominantly cristaloid; therefore protein concentration in the interstitium will progressivelly decrease at the same rate as oedema increases, becoming a limitant factor to it.

Interstitial fluid is distributed firstly in a thin coat all around the lungs, and afterwards will accummulate in pouches, which may increase and compress alveolii and form a sort of sleeves around small vessels and airways.

We must realize that this interstitial oedema is hardly defined or measured in clinical grounds, being its most direct and earlier espression obtained in chest radiograms (Fig. 10, 11).

Those are thr aureolar shadows around bronchiolli, bronchii, arterioles and veins; the septal lines (kerley lines); the hilar shadows; and the cisuritis lines.

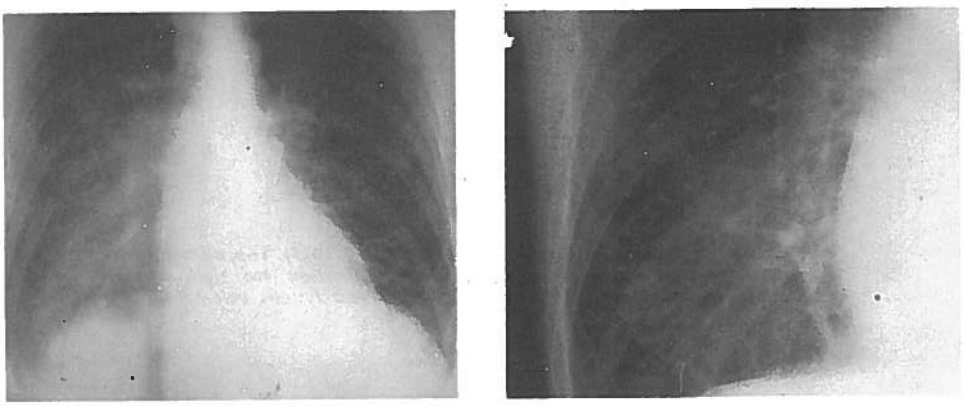


Fig. 10 and 11 — *X-Ray of a patient in the ICU, with myocardial infarction; Kerley B lines, areolar shadows. Hilar shadows and cisuritis lines seen.*

2.3. How rises microvascular hydrostatic pressure?

Using, as did Bradley (1977), atrial functions curves (Fig. 12) which correlates systolic volumes with pressures in the right and left atria, we see that increasing atrial volumes will increase pressures in both sides (after a short dumping effect of pulmonary blood volume variation). The pressure rise is nevertheless much more intense in the left atrium, and when such a value come to about 25 mmHg, hydrostatic pressure will be enough to determine large amonts of trans-endothelial liquid passage.

Similar target is easily attained when left function curve is flat, as it occurs in many of cardiac diseases (Table 4), Then, even small variations of systolic volumes will increase microvascular presures to that 25 mmHg critical level.

Table 4

Clinical situations with potential wedge pulmonary hipertension

Venous-occlusive pulmonary disease
Mitral or aortic valvulopathies
Cardiomyopathies
Hypertensive cardiopathy
Ischemic heart disease
Myocardial Infarction
Atherosclerotic cardiopathy

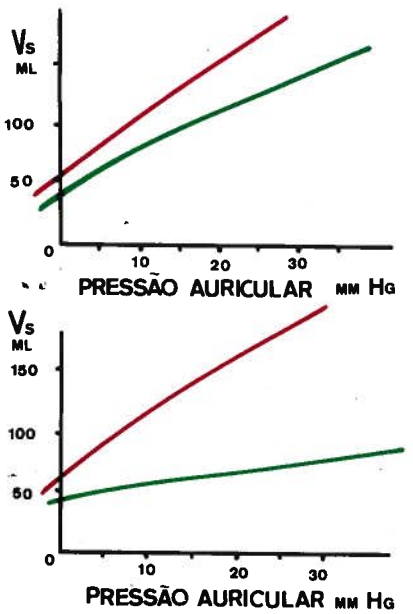


Fig. 12 — *Atria function curves (adapted from Bradley, 1977). Top, normal function for both atria; bottom diminished left atrium function (red, rigth atrium; green, left atrium). atrial pressure on the abcissa and systolic volumes in the ordinate.*

2.4. There are other conditions in which the fluid goes into the interstitial space. One is the decrease of the plasma colloidosmotic pressure, in result of hypoproteinemia (Fig. 13). Nephrotic syndrome and hepatic cirrhosis can be mentioned, yet not frequent determinants of significant interstitial pulmonary oedema. Much more frequent is the iatrogenic oedema determined by intemperate administration of cristaloid solutions, reducing plasma protein concentration.

Other mechanism to be recalled is an increase of permeability (Fig. 14) (Table 5).

Table 5

Toxic drugs which potentially increase permeability

Heroin
Methadone
Alloxan
Phosgen
Paraquat
Metalic oxydes
ANTU
Nitrogenated oxides
Immuno-alergenic substances
Ozone
Oxygen

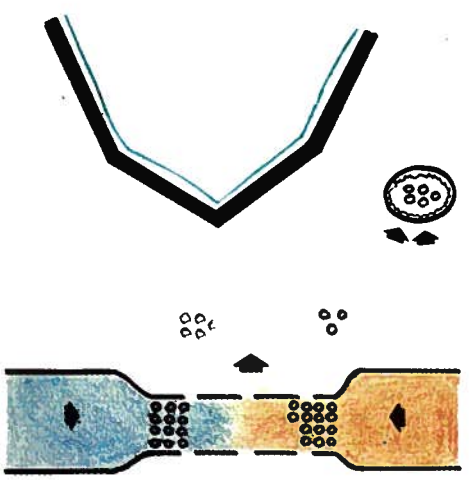


Fig. 13 — *Interstitial oedema may result from reduced plasmatic concentration of protein. Reducing protein colloidosmotic pressure.*

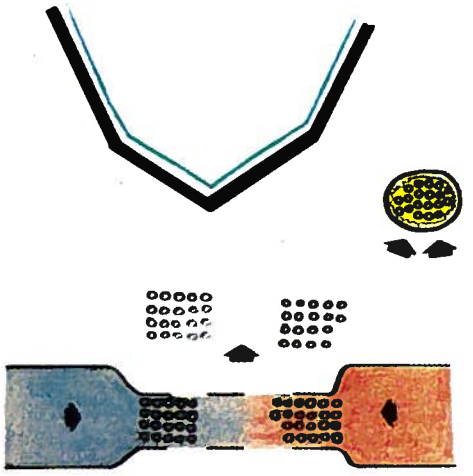


Fig. 14 — *Increased permeability with increase protein interstitial and lynophatic concentration.*

Then, only liquids but also plasmatic proteins cross the endothelial wall, thus increasing extravascular protein concentration, and the interstitial oedema tend to be perpectuated. In such circunstances, for instance, colloidal liquid administration into the circulation can play a role in iatrogenic oedema.

Oedema resulting from permeability changes has roughly the some protein concentration of the plasma. Therefore, drained lymph from lymphatic vessels will have aidentical protein composition (and the same will occur in the aspirated liquid from aisways, if pulmonary oedema results) This fact contrast to all other mechanisms of lung oedema formation, and allows clinical diagnosis.

2.5. Still continuing with Starlins'scheme, two other ways to obtained interstitial liquid have to be defined, although of dificult appraisal.

Interstitial protein concentration is one of them, as it may increase after inflamatory processes in the interstitial space.

The other will result from acute negative pleural rise as it happens after a quick and plentiful thoracocenthesis or paracenthesis. Moreover, it happens in the asthmatic patient, who may have pulmonary oedema when undergoing acute asthmetic crisis, only dependent upon the negative interstitial pressure resulting from deep breathing against partial airways obstruction (Stalcup et al, 1977).

2.6. Until now we discussed independent factors producing interstitial oedema, recalled from Starling'scheme. Leaving it now, it has to be mentioned, in other hand, the case of inappropriate drainage of normally formed liquids through the lymphatic system. So it happens in silicosis, some lymphomas, carcinomatous lymphangitis, etc.

On the other hand, filtration factors are not always independent, as it was shown experimentally. Fishmann and Pietra (1976) injected macromolecules which didn't appear in the interstitial space when working in the usual hydrostatic microvascular pressures, but did show off when that pressure was significantly rised. According to it, vessel permeability increases with microvascular hyperpressure.

2.7. During the last decade, it has been defined that liquids passage from vessels is not exclusively concerned to pulmonary capillaries, as endothelia from very small pulmonary arterioles and venules also permit transudation in a rather similar way. actually, they allows it not only for fluid, but also oxygen and carbon dioxide exchanges.

In what concerns arterioles, Lynne Reid (1977) showed progressively reduction of the muscular layer in the terminal arterioles, in such a way that previously to a portion of non-muscled arteriole next to the capillary there is another zone on which muscle exists in half of its circunstance, but not all around the lumen.

The shape of this partially muscled portion is particularly favourable for increased filtration. As a matter of fact, zonal hydrostatic hypertension resulting from an intense miocontraction of half vessel will tremendously stress the remaining half not--protected endothelium. Such a mechanism can possibly be recalled in different types of enigmatic pulmonary oedemas such as the «neurogenic», the «high altitude» or even that related with pulmonary embolization.

They are determined by mechanisms which have not yet been totally enlightened. a sudden stiffness of left heart is one of the proposed explanations, giving an extraordinary hypertension on the left ventricle and atrium, and in the wedge pulmonary pressure, though so far no convincing demonstration has been documented.

Recalling pulmonary oedema experimentally produced and studied, we registered pulmonary pressures in dogs in which silver nitrate was injected directly into the pulmonary artery or a lower limb vein or a carotid artery, or even directly into left myocardium (Sales-Luis et al, 1962). Results (Table 6) pointed to a direct effect on the pulmonary arteries dependent upon silver nitrate embolization in peripheral lung arterioles. That almost instantaneous lung oedema would be easily explained accepting the shape and morphology of those Lynne Reid' arterioles.

Table 6

Pulmonary edema induced by silver nitrate

Experience	Dog No.	Pulmonary artery pressure mmHg					Pressure rise within min.
		Before	Immediately after	1 min.	2 min.	5 min.	
Injection in the	39	18/10	30/21	60/42			Immediate
pulmonary artery	48	18/ 9	28/10	33/15	46/28	33/24	1 min
	49	20/11	30/20	71/40	70/38	50/40	Immediate
	50	16/ 9	36/24	65/36		42/36	Immediate
	51	24/10	39/22	56/34		50/40	Immediate
	52	20/ 9	30/14	62/36		60/38	Immediate
Injection in a	36	20/ 8	20/ 8		60/28	50/35	2 min
vein of the hinder	37	20/ 7	19/ 7	42/20	55/22	40/30	1 min
leg	38	17/12	17/12	38/30	42/38	45/40	1 min
	53	19/11	19/10	25/10	64/40	50/40	2 min
Injection in the	32	20/ 9	20/ 9	20/ 9	20/ 9	44/36	5 min
carotid artery	33	17/ 8	17/ 8	18/ 9	56/40	48/42	2 min
	34	15/ 9	15/ 9	15/ 9	15/ 9	68/44	3 min
	35	20/ 7	20/ 8	20/ 8	70/46	60/50	2 min
After ligature of both	40	18/ 9	33/10	46/22	33/24		1min
common carotid arteries.	41	18/10	50/27	48/27			Immediate
Injection in the	42	21/ 9	46/20			46/20	Immediate
pulmonary artery	43	20/ 6		55/22		50/38	1 min?
After ligature of both	44	20/ 8	50/25	50/25	80/50		Immediate
common carotid arteries,	54	17/ 9		38/27	38/27		1 min
injection in a vein of	55	19/10		60/34		66/40	1 min
the hinder leg	56	21/10	21/10	52/35	56/35	56/35	1 min

2.8. Besides the pulmonary circulation, we must also remember that bronchial microcirculation plays a potential role in the lung'interstitial liquid presence. It has been demonstrated that particles pass, under some circunstances, from inside to outside the vessels through both bronchial capillaries and venules (Fishman et al, 1976, 1978). Such a mechanism plays a role in clinical situations, as with the endotoxin shock (Pietra et al, 1974).

Summing up, we may now state that, as a whole, liquid acumulation in the interstitial lung space will result from an imbalance between what enters into it and what is removed through the drainage system. The latter comes up by compression or obliteration of the lymphatic vessels. The former is the net result from one or more of the following mechanisms, predominantely working in the pulmonary microcirculation but potentially also in the bronchial microcirculation, both including capillaries and terminal arterioles and venules: a) increased permeability, either independent or parcially dependent on microvascular pressure level: b) increased hydrostatic or microvascular pressure; c) decreased colloidosmotic microvascular pressure; d) increased negative interstitial pressure; e) increased interstitial colloidosmotic pressure, related to inflamatory local processes.

2.9. We do not yet know when or how alveolii are invaded by this fluid. Permeability of the alveolar wall is not the way because it is very low and on the other hand, fluid passage into the alveolii either does nor occur at all or instead it does occur with identical composition to that of the interstitial space. Also it is not the result from a pressure gradient mechanism.

What is though known for sure is that, under certain circunstances and in certain moments, some alveolii become invaded (Staub, 1974). It works as an alternative route of lymphatic drainage, to remove the interstitial fluid.

Alveolii are always invaded in the same way: firstly only by corners occupation and after by a most sudden filling up of the whole alveolli (Fig. 15, 16).

So, no partially-filled alveolii are found; side by side with the invaded alveolii there are others entirely fuid-free.

The substance which fills alveolii is serum, which potencially changes susfactant's proprieties.

Sudden alveolar filling can be related to this surfactant alteration.

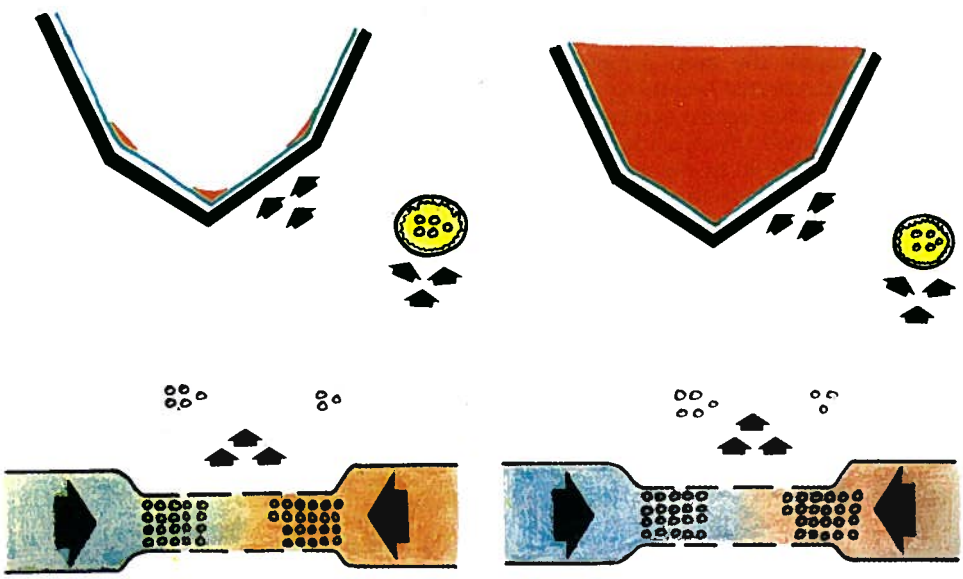


Fig. 15 and 16 — *Alveolii are invaded as an alternative of lymphatic drainage, always in the same sequence: firstly only corners occupation, after by a sudden filling up of the whole alveolus.*

Some authors accept a second way for the alveolar liquid invasion based on the compression of the terminal bronchii by interestitial fluid, thus allowing fluid filtration in an opposite direction to that until now mentioned. Such a mechanism has not yet been demonstrated and is not accepted by the majority of researchers.

2.10. So far, lung interstitial or alveolar liquid come up with no significant endothelial or pneumocyte changes, though increased endothelial permeability could represent the first step of a cellular alteration.

Further on, endothelial cells may become enlarged and undergo to necrosis; type I pneumocytes are easily destroyed, leaving alveolii without celular coat, afterwards gradually replaced by the cuboid, type II pneumocytes. Although this is the usual sequence, sometimes only the endothelium or the epitelium is compromised.

Interstitial oedema and subsequent pulmonary oedema are common occurences in all these types of lung disorders (Table 7), which include immunoallergic phenomena, infection diseases, gases or other toxic agents.

Table 7

Lung disorders determining interstitial oedema

Widespread granulomas
Collagens diseases
Tumours
Congenital dysplasias
Extrinsic allergic alveolitis
Hypersensibility responses to drugs
Cryptogenic alveolitis
Virus or fungii pneumonitis

Amongst the most dangerous toxic agents, is fundamental to consider highly oxygen concentrated breathing air, or the ozone which liberates oxygen. These gases, as most of the toxic agents earlier mentioned, usually act in the lung through the production of superoxid which is a highly toxic biologic intermediate. This superoxidys quickly destroyed (Table 8) by the action of a superoxid dismutase, which steals its free radical, and by a catalase which transforms it into water and oxygen. By excessive presence of oxygen, in overload concentrations, leaving to increased superoxid production, or by enzyme destruction or neutralization, in relation with many toxic agents, the biological intermediate gets time enough to determine tissular lesion and destruction.

Table 8

Ozone, Oxygen

Superoxide (O_2^-)

Highly toxic biologic intermediate

For its destruction superoxide dysmutase is needed:

$$O_2^- + O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$

And also catalase

$$H_2O_2 \rightarrow H_2O + O_2$$

The clinical expression of it is an alveolitis or interstitial pneumonitis; it may be the result of immunoallergic diseases, extrinsic alveolitis, the presence of granulomas such as sarcoidosis, some connective tissue diseases, vasculitis, etc. (Table 7).

Lung's reaction to so different agressors is relatively uniform. Interstitial oedema is always present. Alveolitis may progress to an sub-acute evolution, may develop into a rapid resolution or keeps itself in a slow progression sometimes with desquamative cells presence, others with an eosinophila or even fibroblastii predominance.

Interstitial fibrosis is the common terminal phase with interstitial oedema always present.

3. PATHOPHYSIOLOGICAL CONSEQUENCES

Liquids in the interstitial lung may persist chronically silent until it increases five to six fold (Fig. 17). Even then, only incharacteristic symptoms such polypnea and dyspnea may occur and no physical signs will define the interstitial oedema. But many pathophysiological consequences exist from the beginning, and it is important to evaluate them and their clinical significance.

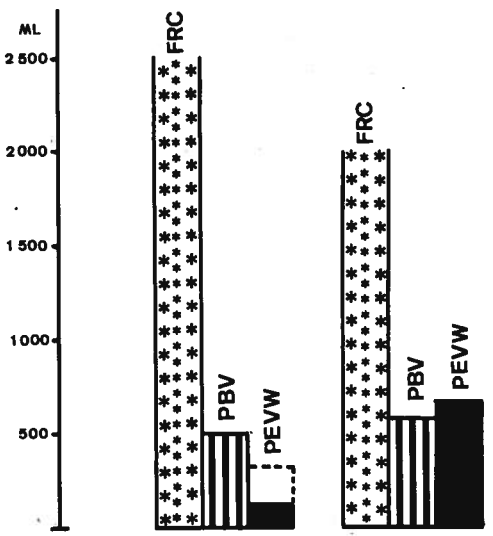


Fig. 17 — *Relationship vetween pulmonary extravascular water, pulmonary blood volume and functional residual capacity in normal situations (left) and with significant interstitial oedema (right).*

3.1. Interstitial oedema determines occluded alveolii and lung's small vessels compression. The first sign of both these changes is the increased venous-arterial shunt effect and hypoxemia.

The easiest way of defining the shunt effect is through alveolar-arterial PO_2 gradient, which is either obtained calculating it or ploting PO_2/PCO_2 in a graphic including the respiratory rate line (Fig. 18).

Going further in the consequences of fluid presence in the lung' interstitial space, vital capacity, mainly through the residual volume, will reduce, and the same will happen to the pulmonary blood volume.

Vital capacity reduction beyond 80% of normal predicted values will increase pulmonary arterial pressure. An important pulmonary hypertension will be present when there is a 50% or more reduction (Enson, 1978).

For many years, a clinical picture which included hypoxemia without hipercapnea and pulmonary hypertension used to be called as alveolo-capillary block. Is was though that it was the result of a fibrosis thickning the thin «membrane» separating blood from air in the lungs. It was then accepted hypoxemia as the result of inadequate O_2 difusion capacity through the tickned membrane. This idea has been greatly defeated as it has hardly ever been saw any changes in the alveolo-capillary membrane itself. It can sometomes become thickened, although not until late phases; even then, it can give way to significant O_2 difusion impairment only on patients during the exercise tests.

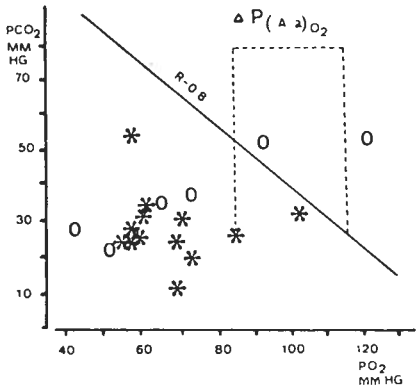


Fig. 18 — *Data obtained from patients with myocardial infarction alveolo-arterial PO_2 gradient is red from the horizontal distance between each point and the respiratory rate list.*

3.2. When the fluid penetrates into the alveolii, the physiopathological consequences are different and have nothing to do with what has been mentioned. In fact, proteins presence in the alveolar fluid will reduce surfactant function; it becomes thicker, forming piles and reducing significantly its negative tenso-active efficacy. The mixture of air and albumin-rich fluid leads also to foam formation with large bubbles, which occludes the airways in pronounced desproportion to the liquid volume itself.

Respiratory impairment, if not urgently treated, will lead to death.

Concomitantly, presence of unneficient surfactant will cause sequencially a greater breathing effort, breathlesness, a greater fluid retention in the interstitial space, and so a larger quantity of fluid into the alveolii.

3.3. Most of the patients with one or other disorder bringing to interstitial oedema are submited to positive breathing pressure, and lately to end-expiratory positive breathing pressure. This procedures will create some particular pathophysiological changes which have to be known. Looking particularly to pulmonary end-expiratory pressure, intra-pleural and alveolar pressures become positive, so, the difference betweem them, which is known as intrathoracic pressure, will remain numerically equal, nevertheless changing also from sub-athmospheric to positive. Interstitial pressure will also become positive, and interstitial and alveolar oedema will diminished. However, cardiac output tend to decrease as pleural pressure increases reducing the right heart filling. Venous-arterial shunt effect decreases (as the opening-up of alveolii have greater affect than th decrease of cardiac output), leaving to an oxygen saturation

and PO_2 improvement. Pulmonary resistence increases through the direct compression of small vessels, occluding some of them. As pulmonary venous pressure becomes always inferior to the alveolar pressure, the so called zone 3 doesn't exist, remaining only zones 1 and 2 of West, (that it is, there are no zones with complete perfusion all along a respiratory cicle).

Every intrathoracic structure is submitted to some pressure, which will now under the circunstances, be higher. But the relation between these pressures is identical, the difference being that they will meet at a higher level, depending naturally on the positive pressure transmitted to every structure. So, transmural pressure of vessels, which is assessed from inside to the outside of each thoracic vessel remains identical. Nevertheless, pulmonary hypertension exists, comparing it to extrathoracic circulation system.

3.4. All the clinical condition we have been mentioning, wether or not they are treated with positive pressure, frequently become progressivly worse and end in a syndrome characterized by an hypoxaemia lower than 50 mmHg when breathing greater than 80% oxygen-enriched athmosphere.

In such circunstances the patient, will, from this phase onward be in a dilema, which is the chance of peripheral cells not tolerating such hypoxaemia, thus entering in a process of quick deterioration, and the lung cells not tolerating an enriched athmosphere of this kind.

This is the condition known previously as *schock lung, wet lung* or *catastrophic lung* and recently as Adult Respiratory Distress Syndrome (ARDS). The etiology of these conditions is most versatile, often resulting from trauma, sometimes resulting from inflamatory or infectious diseases, or even, ecloding during a shock state. Always there is epithelial and endothelial injury, intra-alveolar hyaline membranes, haemorrhagic and atelectasic zones.

Everyone of these conditions lead invariably to death, the main difficulty being to know when will it happens. The uniform pathology permit to interpret it in one out of two different ways, either the lung has a monotonous reaction to external agression, (which probably is the case), or it reacts in this manner to a severe condition when yatrogenic factors, particularly O_2 high concentration air and positive pressure breathing, is introduced. Although this idea can not be demonstrated it justifies some precaution concerning the use of oxygen the least time possible., with the least possible concentration.

4. FINAL REMARKS

Approaching the end of this exposition it would dare to state that the knowledge on pulmonary interstitial hydrodynamics has been greatly developped in the last few years but it is still full of doubts, gaps, unfounded or even competitive hypothesis.

Interstitial oedema is a fundamental constant component in the processes affecting the distal portion of the lung and it is the substract for the severity of many of the clinical conditions of the so-called Critical Care Medicine.

I would dare say that knowledge may develop, only with the gathering of a multidisciplinar team, in which morphologists, biochemics, hemodynamists, physiopathologists, clinicians, physicians and mathemacicians will play an important role.

RESUMO

A HIDRODINÂMICA NO ESPAÇO INTERSTICIAL PULMONAR

Discutem-se alguns aspectos relacionados com a hidrodinâmica pulmonar normal e patológica, com destaque especial para as consequências fisiopatológicas determinadas, na tentativa de estabelecer bases para uma correcta abordagem clínica e para futuras investigações.

Revêem-se inicialmente aspectos relevantes morfofisiológicos, como as propriedades peculiares da circulação pulmonar, a influência da gravidade nas pressões pulmonares e pleurais, o volume sanguíneo pulmonar, a circulação brônquica, «a «membrana alveolo-capilar», a circulação linfática e as funções pulmonares.

Analisa-se a possibilidade de presença de líquido intersticial pulmonar, que resulta do balanço entre o que entra no interstício e o que é removido pelo sistema de drenagem representado pelos vasos linfáticos. A passagem de líquido para o interstício é analisada como efeito de um ou mais dos seguintes mecanismos, actuantes predominantemente na microcirculação pulmonar, mas potencialmente também na circulação brônquica, incluindo em ambos os casos os capilares, e as vénulas e arteríolas terminais: a) permeabilidade aumentada, quer independente quer parcialmente condicionada pelo nível de pressão microvascular; b) aumento da pressão hidrostática microvascular; c) diminuição da pressão coloidosmótica microvascular; d) aumento da pressão negativa intersticial pulmonar; e) aumento da pressão coloidosmótica intersticial, condicionada por processos inflamatórios locais. O mecanismo de brusco enchimento alveolar é também discutido.

Definem-se depois as várias consequências fisiopatológicas provocadas pelo edema intersticial e pelo edema alveolar. Através do primeiro regista-se redução da capacidade vital hipoxémia devida a aumento do efeito shunt veno-arterial, e hipertensão pulmonar — um quadro que inicialmente se rotulou de bloqueio alvéolo-capilar. No edema alveolar, os factores relevantes são a destruição do surfactante e a produção de espuma.

O edema intersticial e alveolar são componentes obrigatórias e fundamentais em muitos dos processos que afectam a porção distal do pulmão, independentemente de terem sido primariamente cardíacas ou pulmonares as doenças que os originaram. Eles são o substracto de gravidade de muitas das situações de Medicina de Cuidados Intensivos.

BIBLIOGRAFIA

HOFFMAN JIE: Water Exchange in the Lung. A major function. *Am Rev Resp Dis* 116: 147, 1977.

COURNAND A: Recent observations on the dynamics of the pulmonary circulation *Bull N. York Acc Med.* 23: 27, 1947.

COURNAND A: The historical development of the concepts os pulmonary circulation *in Prel Circ Adams and Veith* ed. Course Stratton, 1959, New York.

CLEMENTS JA: Pulmonary surfactant *Am Rev Resp Dis* 101: 984, 1970.

SALES-LUÍS A: Fisiopatologia da Circulação Pulmonar *Gaz Med Port* 8: 7, 1955.

SALES-LUÍS A: Aspectos da Patogenia da Hipertensão pulmonar *Gaz Med Port* 9: 19, 1956.

SALES-LUÍS A, DUARTE CS: Experimental study on the pathogenesis of acute pulmonary oedema *Mall Cardiovolari* 1: 39, 1960.

GIUNTINI C, LEWIS M, SALES-LUÍS A, HARVEY R: A Study of the pulmonary blood volume in man by quantitative radiocardiography *J Clin Invest* 42: 1589, 1963.

SALES-LUÍS A: Volume sanguíneo pulmonar *Thesis*. Faculdade de Medicina de Lisboa, 1965.

SALES-LUÍS A: O espaço vascular pulmonar nos doentes com estenose mitral *Bol Soc Port Card* 6: 49, 1968.

COELHO E, PÁDUA F, AMRAM S, BORDALO E SA, A, SERRAS PEREIRA J, MALTES J. DUARTE CA, SALES-LUÍS A, MARIA AB: L'hypertension pulmonaire dans la valvulopathie mitrale et ses relations avec la physiopathologie de la valvule tricuspide *Cardiol* 31: 426, 1958.

STAUB NC: Pathogenesis of pulmonary oedema *Am Rev Resp Dis* 109: 358, 1974.

BRADLEY RD: Studies in acute heart failure *Ed Arnold*, 1977, London.

REID L: The Lung. Its Growth and remodeling in Health and disease. *Am J Roentgen* 129: 777, 1977.

FISHMAN AP, PIETRA GG: Permeability of Pulmonary vasculary endothelium in Lung Liquids, Ciba Symposium 38, Elsevier. Excerpta Medica North Holland, Amsterdam, 1976.

PIETRA GG, SZIDON JP, CARPENTIER HA, FISMAN AP: Bronchial venular leakage during endotoxin shock *Am J Path* 77: 387, 1974.

ENSON Y: Pulmonary heart disease: relation of pulmonary hypertension to abnormal lung structure and function *Bull N York Acc Med* 53: 551, 1977.

WEST J: Pulmonary poathophysiology. Williams & Wilkins Co Ed, Baltimore, 1977.

SYKES MK, MCNICOL MW, CAMPBELL EJ: Respiratory failure Blackwell, Oxford, 1976.

PONTOPPIDAN H, WILSON RS, RIE MA, SCHNEIDER RC: Respiratory intensive care *Anesthesiology,* 47: 96, 1977.
FISHMAN AP, RENKIN EM: Pulmonary Edema *Am Physiological Society,* Bethesda Md, 1979.
TIERNEY DF: Intermediary metabolism of the lung *Fed Proc* 33: 2232, 1974.
OSWALT CE, GATES GA, HOLMSTROM FM: Pulmonary edema as a complication of acute airway obstruction *JAMA,* 238: 1833, 1977.
RACKOW EC, FEIN JA, LEPPO J: Colloid osmotic pressure as a prognostic indicator of pulmonary edema and mortality in the critically ill *Chest,* 72: 709, 1977.
WARNICA JW, WHITE AV, BURGESS JH: Cardiorespiratory function and extravascular lung water following acute myocardial infartion *Am HJ* 97, 469, 1979.
WILSON JW: Pulmonary microcirculation *Crit Care Med,* 2, 186, 1974.
FUNG YC: Fluid in the interstitial space of teh pulmonary alveolar sheet *Microv Res* 7: 89, 1974.
ERDMANN AJ, VAUGHAN TR, BRIGHAM KL WOOLVERTON WC, STAUB NC: Effect of increased vascualr pressure on lung fluid balance in unanesthetized sheep *Circ Res* 37: 271, 1975.
SMITH-JP, BRISCOE WA, KING TK: Catastrophic pulmonary failure: Clinical manifestations and concepts of therapy *Bull NY Acad Med* 53: 537, 1977.
LAMY M, FALLAT R, KOENIGER E, DIETRICH HP, RATLIFF J, EBERHART H, THCKER H, HILL D: Pathologic features and mechanisme of hypoxemia in adult respiratory distress syndrome *Am Rev Resp Dis,* 114: 267, 1976.
WEIBEL ER: Morphological basis of alveolar-capillary gas exchange *Phys Rev* 53: 419, 1973.
HEATH D: Pathology of the lung *Rec Advances in Resp Med* Churchill, Livingstone, Edinbourgh, 1976.
TURLBECK WM, ABELL M: (Ed) The lung Williams Wilkins Co Baltimore, 1978.

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