ACTA MED PORT, Suppl 1: 79, 1980

ALTERATIONS OF THE PULMONARY MICROCIRCULATION AFTER OPEN HEART SURGERY

CORRELATION BETWEEN THE PULMONARY VASCULAR DYNAMICS AND ULTRASTRUCTURAL CHANGES AFTER THE OPERATION

M. Rodrigues Gomes, M. Miranda Magalhães, F. Queiroz Machado, António Rodrigues de Sousa, José Cabral, Maria de Lourdes Azevedo, E. Esteves Pinto

Serviço de Cirurgia Torácica. Instituto de Histologia e Embriologia da Faculdade de Medicina do Porto.

SUMMARY

The study of pulmonary hemodynamics after mitral valve replacement in 30 patients, during the first 18 post-operative hours, did show elevated pulmonary vascular resistance from the pre-operative levels in the majority of them. This rise varied directly with the bypass time and was associated with increased right ventricular work, intrapulmonary shunt and more severe ultrastructural lesions of the alveolar-capillary membrane. The pulmonary vascular resistance had tendency to lower to the pre-operative values at the end of 18 hours.

The microscopic changes, very similar with the observed on shock lung, fat emboli and in all non-hemodynamic pulmonary edemas, may well be due to excessive and prolonged stimulation of catecholamines, microemboli and hypoxia.

The control of perfusion pressure, better synthetic surfaces and oxygenators, and the use of assisted ventilation with positive end-expiratory pressure must be investigate to precise their exact role on the alterations of the pulmonary microcirculation after open heart surgery.

Pulmonary complications are a frequent cause of morbility and mortality after open-heart surgery, in spite of all the progress noted on the prevention and post-operative care (1, 2). This is due to the lack of knowledge about the pulmonary microcirculation in abnormal situations, such as extracorporeal circulation, so often already disturbed by the cardiac pathology which has justified the operation (3, 4).

Much research has been done about the effect of the extracorporeal circulation on the different organs. The disturbances on the lung have been much less studied, althoug we know that intrapulmonary shunt and O_2 alveolo-capillary gradient are increased and pulmonary compliance is lowered (5, 6).

The present study was done to precise the changes of the pulmonary vascular resistance early after open heart surgery and to correlate them with the ultrastructural changes of the alveolo-capillary membrane in a homogeneous group of patients.

CLINICAL MATERIAL AND METHODS

The study was done in 30 patients after mitral valve replacement for rheumatic mitral valve disease. Eight were male and 22 female, with age between 17 and 58 years (mean 42 years). Twenty five had mitral valve disease and 5 mitral mitras stenosis. Seven had significant tricuspid insufficiency. Fourteen patients were on the class IV of the New York Heart Association and 16 on the class III. Twenty patients were on atrial fibrillation and 10 on N.S.R. Right ventricular hipertrophy was present on the E.C.G. of all the patients. The auscultatory and radiologic findings were typical of the disease.

All the patients were cathaterized pre-operatively. The systolic pulmonary artery pressure varied between 34 and 95 mm Hg (mean 52 mm Hg) the pulmonary capillary pressure between 20 and 44 mm Hg (mean 24 mm Hg) and the pulmonary vascular resistance between 2.7 and 5.5 units (mean 4.2 U).

Pulmonary function tests were done preoperatively in all the patients. They were normal in 10, 9 had light obstructive insufficiency, 6 light restrictive insufficiency and 5 moderate obstructive insufficiency.

The techniques of anesthesia, extracorporeal circulation and valve replacement have been discribed previously (7). Microporous filters were used on the intracardiac suction and venous return line.

During the post-operative period the following parameters were monitored directly: ECG, right atrial, left atrial, pulmonary artery and systemic arterial pressures. Cardiac output was determined at 3, 6, 9, 12 and 18 post-operative hours using thermodilution. The position of the Swan Ganz cathater was always checked by chest XR.

Biopsy speciments were obtained from the right upper lobe of the lung of each patient 30 minutes before and 30 minutes after the end of extracorporeal circulation. The fragments were fixed in 4% glutaraldehyde in 0,1 M. cacodilate with pH=7,4 a 4° C, during 2 hours. The fragments were cleansed and fixed in osmium tetraoxide during 2 hours. After alcohol deshydratation inclusion in Epon 812 were made. Ultrathin cuts of 600 to 800 A° were stained with uranil acetate during 20 minutes and lead citrate for 5 minutes and observed on a electronic microscop Icol 100 B.

A semiquantitative classification of the following changes of the alveolo-capillary membrane (+ to ++++) was done: intersticial edema of the pneumocytes type II, intracapillary sequestration, degree of pynocitosis of the endothelial cells and dilatation of endothelial-junctions. All the post-operative biopsies were compared with the pre-operative ones biopsies made in lungs of 10 patients without known pulmonary pathology.

All the patients were kept in the same ventilatory and post-operative care, which is described elsewhere (7).

The cardiac index was calculated from the cardiac output and surface area. The intrapulmonary shunt was calculated using the formula (8).

$$\frac{QS}{QT} \times 100 = \frac{C_c\ O_2 - C_a\ O_2}{C_c\ O_2 - C_v\ O_2}$$

QT=cardiac output; QS=unoxigenated pulmonary flow; $C_c\ O_2$=O_2 content in the pulmonary capillary blood; $C_v\ O_2$=O_2 content in the pulmonary artery blood; $C_a\ O_2$=O_2 content in the arterial blood. As the pO_2 was higher than 150 mm Hg the O_2 contents were calculated using the following formulas:

$$C_c\ O_2 = (Hgb \times 1{,}34) + (P_a\ O_2 \times 0{,}0031)$$

$$C_a\ O_2 = (Hgb \times 1{,}34) + (P_a\ O_2 \times 0{,}0031)$$

Pulmonary vascular resistance was calculated using the formula (8):

$$R_p = \frac{\text{P. Art. } P_m - \text{L A } P_m}{\text{cardiac output}} \times 80$$

P. Art. P_m: mean pressure of the pulmonary artery.
L A P_m: left atrial mean pressure.

Right ventricular work was calculated from the formula (8):

$$RVW = \frac{\text{cardiac index} \times (\text{P Art. } P_m - \text{R A } P_m) \times 13{,}6}{1000} \text{ g/m/m}^2$$

The statistic analysis of the results was done by the linear correlation method.

RESULTS

All the patients survived the post-operative period and had hospital discharge. They were divided in three groups, according to the mean pulmonary vascular resistance during the first 18 post-operative hours: group 1 (9 patients) with a mean pulmonary vascular resistance below 5 units; group 2 (11 patients) with a mean pulmonary vascular resistance between 5 and 7 units, and group 3 (10 patients) with a mean pulmonary vascular resistance above 7 units. The changes of the pulmonary vascular resistance during the period time of studied are shown on fig 1.

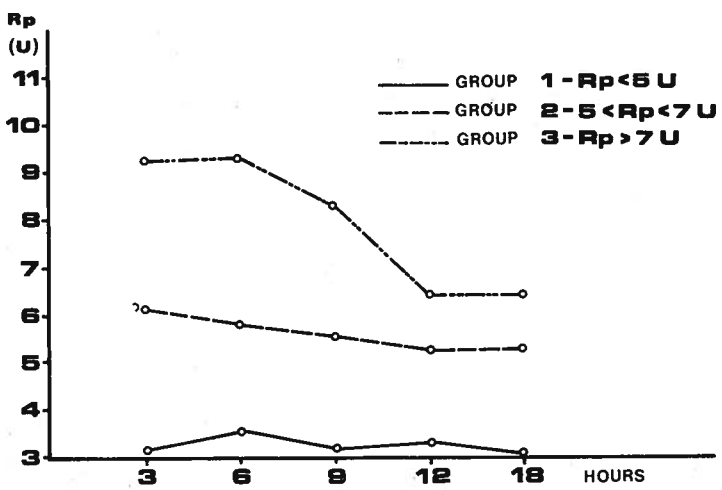

Fig. 1 — *Evolution of the pulmonary vascular resistance during the first 18 post-operative hours.*

In the analysis of the clinical history, physical examination, pulmonary function tests and pre-operative hemodynamics there was no difference between the three groups (Table 1). There was no correlation between the pre-operative and the post-operative pulmonary vascular resistance, during the first 18 post-operative hours (Fig. 2). There was a statistical significant correlation ($P<0,001$) between the pulmonary vascular resistance and the bypass time (Fig. 3, Table 2) not with the plasma free hemoglobin (Table 2).

Table 1
Pre-operative hemodynamics in the 30 patients

	P_P (mmHg)	P cap. pulm. (mmHg)	R_P (U)
Group 1 $R_P<5$ U	51 (38-85)	31 (20-40)	3,9 (3,2-5,5)
Group 2 $5<R_P<7$ U	48 (34-74)	29 (22-44)	4,5 (3,7-5,5)
Group 3 $R_P>7$ U	57 (46-95)	31 (20-38)	4,3 (2,7-5,5)

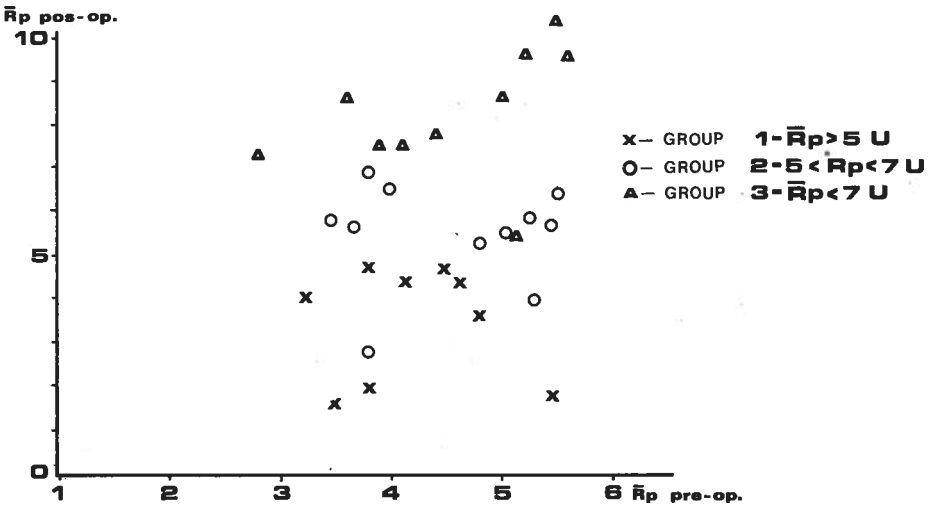

Fig. 2 — *Distribution of pre and post-operative pulmonary vascular resistances.*

Table 2
Bypass time and plasma free Hgb of the patient groups

	Bypass time	Plasma free Hgb
	minutes	mqm%
Group 1 $R_P<5$ U	57 (48-63)	58 (46-74)
Group 2 $5<R_P<7$ U	68 (38-81)	54 (36-78)
Group 3 $R_P>7$ U	90 (77-104)	47 (28-66)

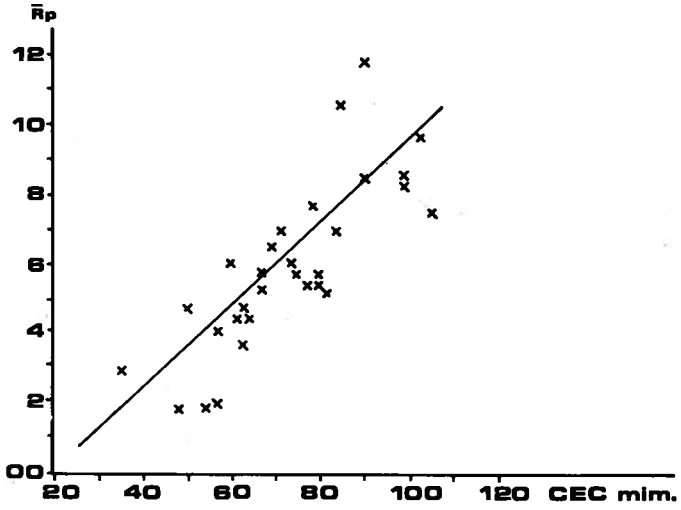

Fig. 3 — *Correlation between bypass time and pulmonary vascular resistance (p <0,005)*

There was an inverse and statistically significant correlation between the pulmonary vascular resistance and the cardiac output, (P<0,001) (Fig. 4) as well as with the pulmonary artery pO_2 (Fig. 5) and with right ventricular work (Fig. 6).

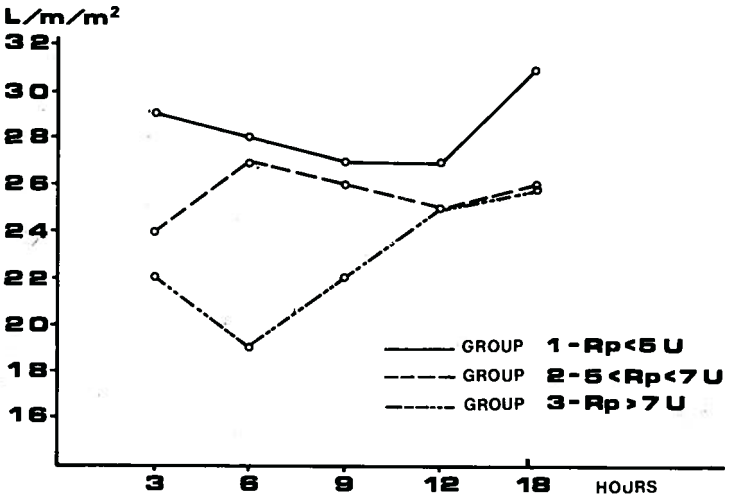

Fig. 4 — *Cardiac output of the 3 patient groups during the first 18 post-operative hours.*

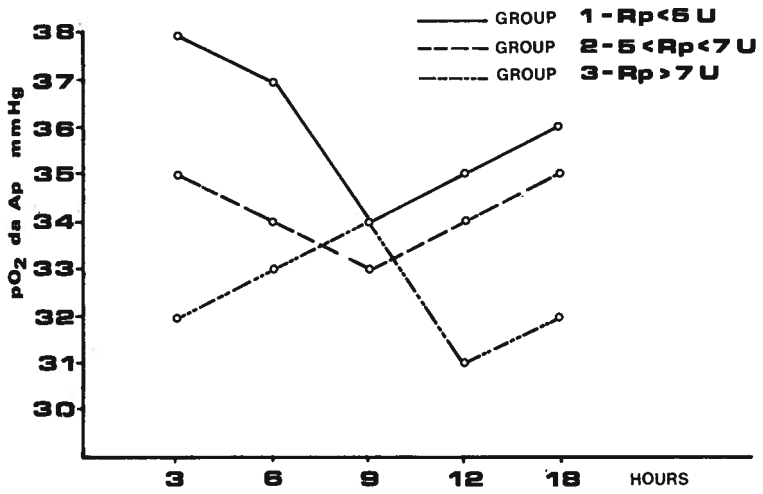

Fig. 5 — *Evolution of the pulmonary artery pO_2 during the first 18 post-operative hours.*

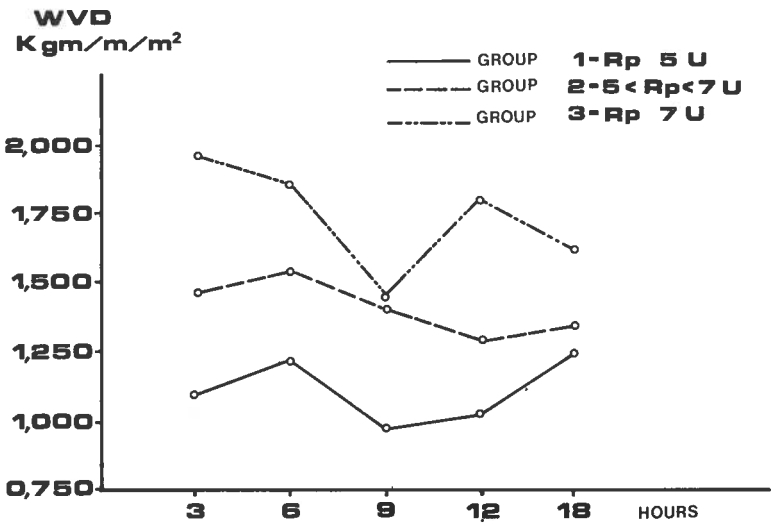

Fig. 6 — *Evolution of the right ventricular work during the first 18 post-operative hours.*

The analysis of the arterial gasimetry did show an inverse and statistically significant correlation between the pulmonary vascular resistance and the arterial pO_2 ($P<0,001$) (Figs. 7 and 8), but no correlation between pulmonary vascular resistance and the pCO_2 ($P>0,05$) (Figs. 9 and 10). The intrapulmonary shunt has shown a statistically significant correlation with the pulmonary vascular resistance ($P<0,001$) (Figs. 11 and 12).

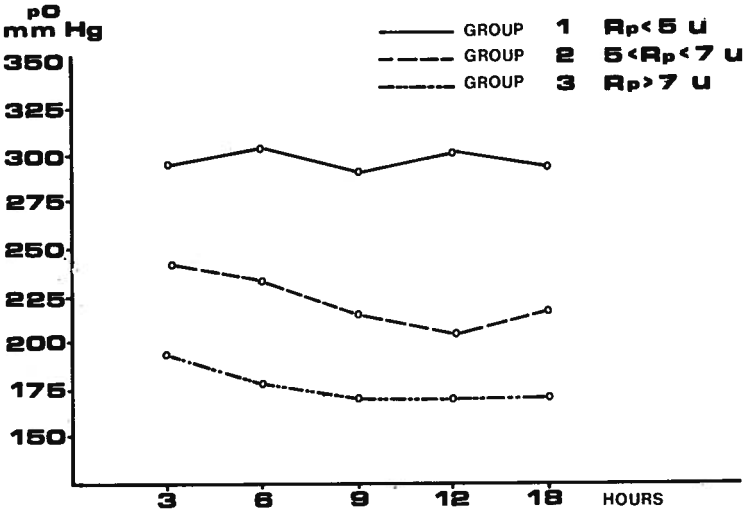

Fig. 7 — *Evolution of the arterial pO_2 during the early post-operative period.*

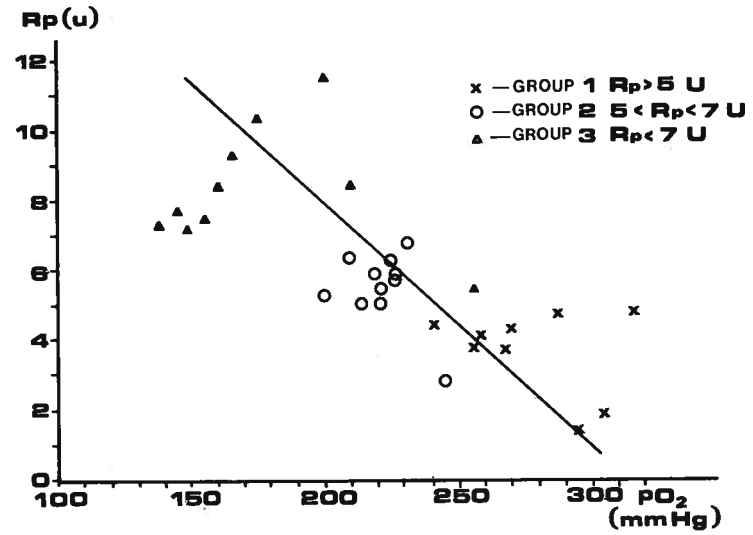

Fig. 8 — *Correlation between the arterial PO_2 and pulmonary vascular resistance ($p<0,001$)*

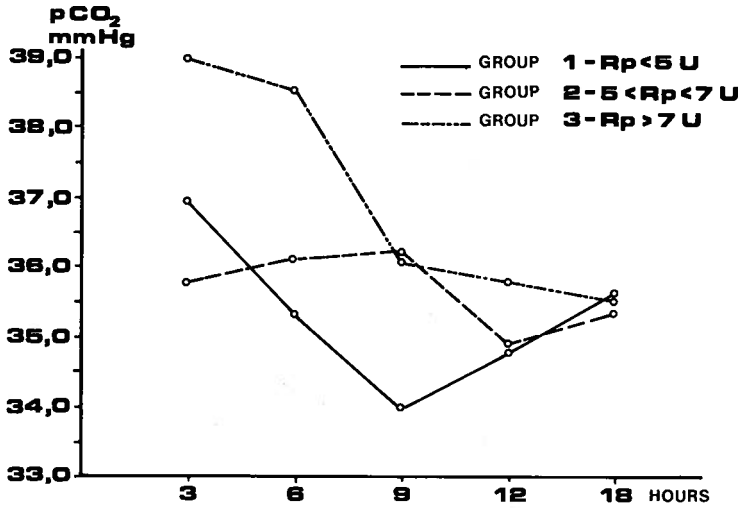

Fig. 9 — *There was no correlation between arterial pCO_2 and pulmonar.*

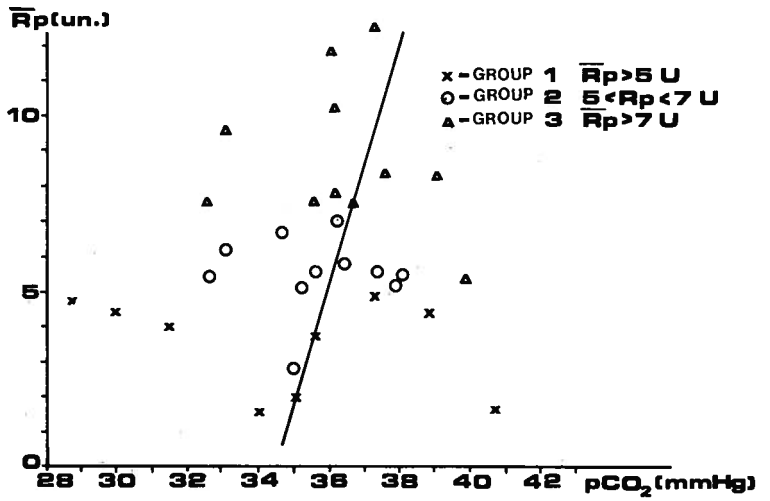

Fig. 10 — *Lack of Correlation between arterial pCO_2 and pulmonary vascular resistance.*

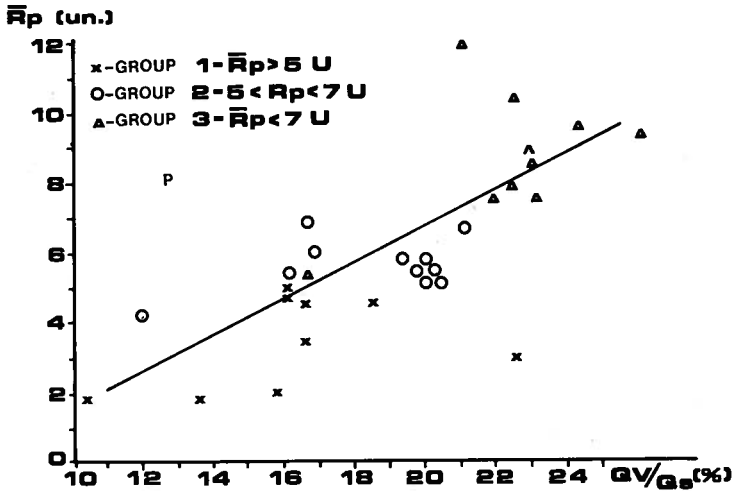

Fig. 11 — *Correlation between pulmonary vascular resistance and intrapulmonary shunt ($p<0,001$)*

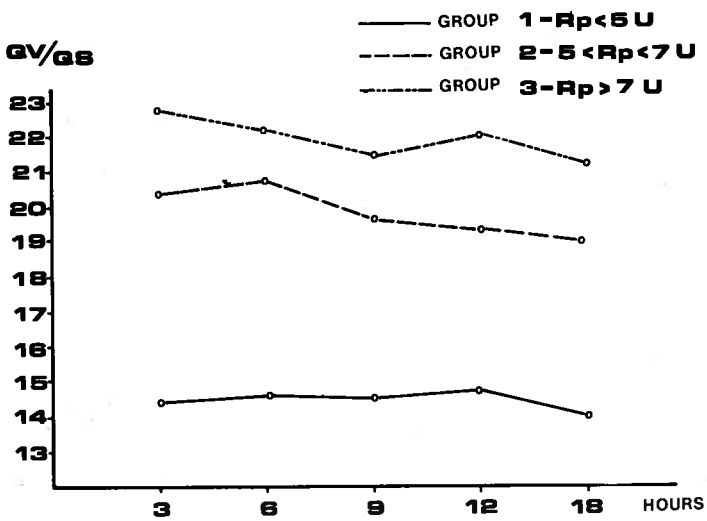

Fig. 12 — *Evolution intrapulmonary shunt and pulmonary vascular resistance during the early post-operative period.*

The ultrastructural study of lung biopsies before heart lung bypass has shown interstitial edema in all the cases and cytoplasmatic edema of the type I and type II pneumocytes very rarely (Table 3, Fig. 13). After heart lung bypass interstitial and cytoplasmatic edema was more evident and in larger number of patients, principally in those with higher pulmonary vascular resistance (Table 4). Nuclear edema, increase of the number of pneumocytes type II, intracapillary sequestration (Fig. 14) enlargement of endothelial lesions and increase of the number of pynocitocitosis were only seen after extracorporeal circulation mainly on patients with high pulmonary vascular resistance.

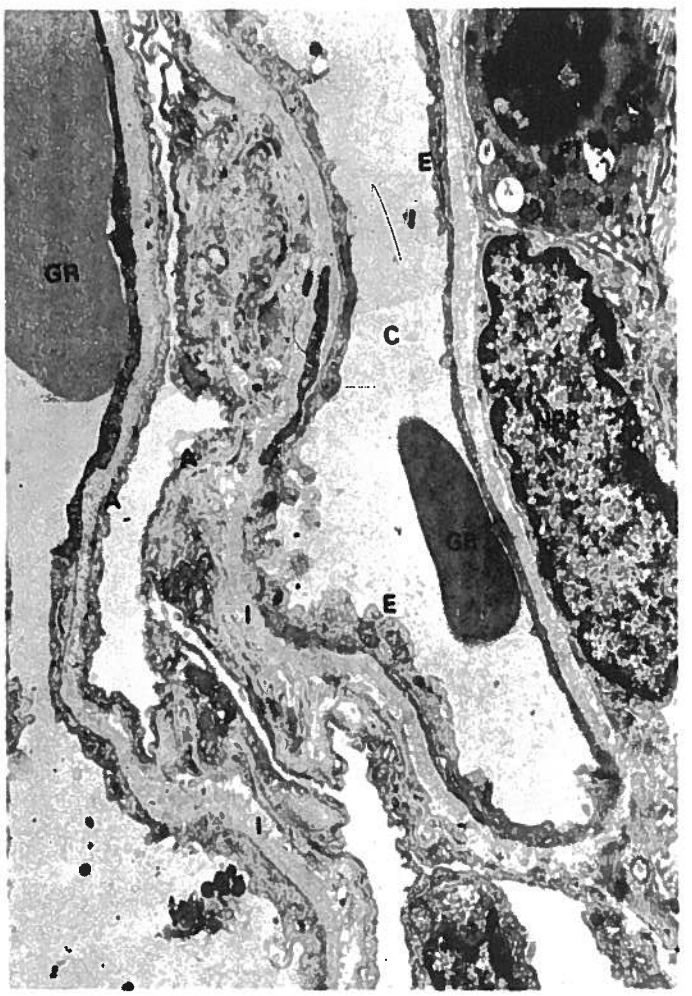

Fig. 13 — *Pulmonary biopsy after 38 minutes of bypass: Alveolar epithelium (A), capillar (C), capillary endothelium (E), interstitium (I) with moderate edema, type I pneumocyte (P_I), type II pneumocyte (NP_2) and erythrocyte (GR). The cellular structures are essencially normally normal.*

Table 3

Classification of the ultrastructural lesions of the alveolo-capillary membrane. Patients with no lessions are marked — The lesions were classified from+to++++according to the severity and frequency of occurrence

	Pre-bypass intersticial edema					Post-bypass intersticial edema				
	—	+	++	+++	++++	—	+	++	+++	++++
Group I	—	5	2	1	—	2	1	4	2	—
Group II	—	6	4	1	—	—	4	4	3	—
Group III	1	5	3	1	—	—	1	2	2	5
	Pre-bypass citoplasmatic edema					Post-bypass citoplasmatic edema				
	—	+	++	+++	++++	—	+	++	+++	++++
Group I	7	2	—	—	—	4	1	4	—	—
Group II	9	1	1	—	—	6	—	1	4	—
Group III	6	3	—	—	—	3	—	5	2	—

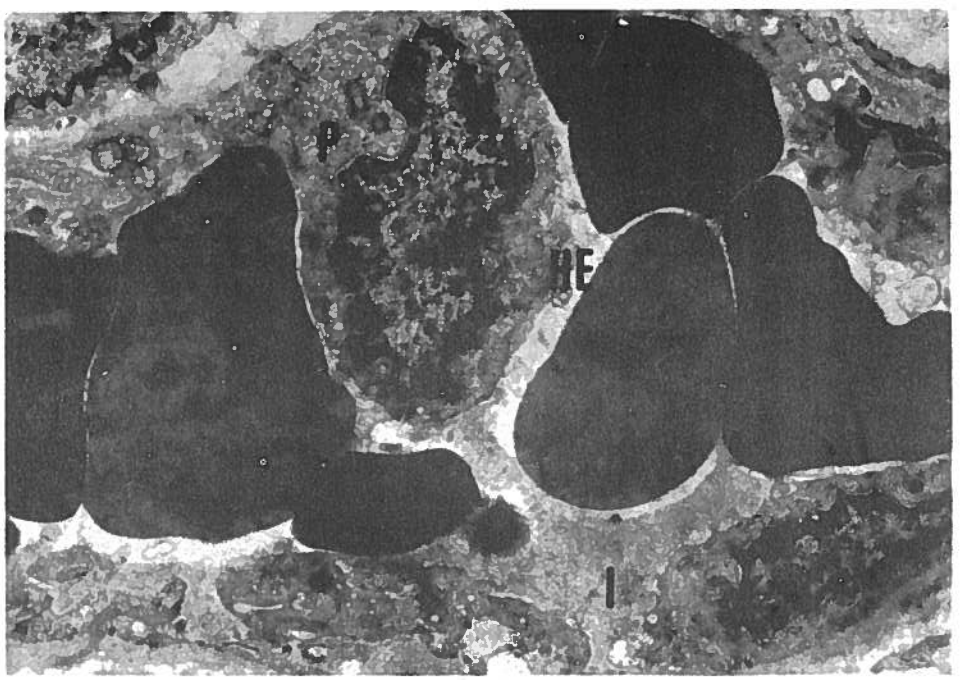

Fig. 14 — *Pulmonary biopsy of a patient after 79 minutes of extracorporeal circulation: type I pneumocytes (P) with moderate cytoplasmatic edema; generalized intersticial edema (I) and erythrocite sequestration (HE) 8400×.*

Table 4

Classification of the ultrastructural lesion of the alveolo-capillary membrane. Patients with no lesions are marked — The lesions were classified from +to++++according to the severity and frequency of occurrence

	Nuclear edema				Increase of pneumonytes tipe II				Incapillary sequestration				Dilatation of endothelial lesions				Increase of the number of pinocytosis vesicles in endothelial cells			
	—	+	++	+++	—	+	++	+++	++++	—	+	++	+++	++++	—	+	++	+++	++++	—	+	++	+++
Group 1	9	—	—	—	6	2	1	—	—	9	—	—	—	—	9	—	—	—	—	5	4	—	—
Group 2	11	—	—	—	6	4	1	—	—	9	2	—	—	—	10	1	—	—	—	4	3	4	—
Group 3	6	2	1	—	3	1	2	2	2	3	4	2	1	—	5	3	2	—	—	—	6	3	1

COMMENTS

Pulmonary vascular resistance has been very little studied afer open heart surgery: Rouleau and col. (8) and more recentely Bugge Asperheim and col. (10) did show a great elevation of the pulmonary vascular resistance from the pre-operative levels on a group of patients after intracardiac surgery, which has shown tendency to come back to the pre-operative levels afer a few days. Most patients of the present study did have the same transient rise of the pulmonary vascular resistance, associated with severe ultrastructural tensions of the alveolo-capillary membrane.

It is well documented today that the intersticial space is the initial targett of any acute pulmonary lesion, whether the agressive mechanism is by inhalation, by the pulmonary circulation on by direct trauma (11). Intersticial and cytoplasmatic edema, alteration of endothelial junctions, multiplication of the type II pneumocytes, mytochondrial swelling, pilling of the alveolar cells and incapillary sequestration of the red cells, leucocytes and platelets are the principal changes of the alveolo-celular membrane (12).

The causal mechanisms of the pulmonary vascular resistance elevation occurs at the microcirculatory level during the operation, as this rise is directly correlated with the bypass time and with the ultrastructural lesions of the alveolo-capilar membrane. Several artificial conditions of the extracorporeal circulation have been incriminated as possible causes of the pulmonary changes after open heart surgery: non-pulsatil flow (13), low perfusion pressure (13), blood oxygenation by direct contact, non-endothelial surfaces (14), blood transfusions, some times in large quantities, trauma to the blood cells with the formation of microembi (15), alterations of the clotting mechanisms (16), wide and fast variations of the temperature (17), etc. The plasma level of catecholamines is increased during extracorporeal circulation, varying with the bypass time, and from patient to patient (18). There is experimental and clinical evidence that excessive and prolonged stimulation of catecholamines is deleterious for the lung, resulting in increased intrapulmonary shunt and, in the dog, histological lesions of the alveolo-capillary membrane very similar with the ones we found in the human (19, 20).

Intersticial edema and atlectasis which occur early after extracorporeal circulation can explain the intrapulmonary shunt (21). But the simultaneous occurrence of elevated pulmonary vascular resistance and increased intrapulmonary shunt is difficult to explain. The arterioles and small arteries constriction could cause elevation of the resistance but should decrease the shunt, because it would increase the ventilation flow ratio. The vasodilatation could increase the shunt but would decrease the resistance. Therefore, to explain the elevation of pulmonary vascular resistance and increase of intrapulmonary

shunt, it is necessary to have vasoconstriction in some areas of the lung and vasodilatation in others. In the former there are ventilated non-perfused areas and in the latter perfusion and hypoventilation (22). It was shown in the animal that adrenaline can cause vasoconstriction in certain areas of the lung, and vasodilatation of other (20). The small pulmonary arteries and arterioles have α and β receptors, and the type of response may depend not only of the intensity of the stimulus, but also of the gasous contents of the alveolus; if the α stimulation is stronger, the arteriovenous shunts open, as a scape to the increased pressure, which lowers the alveolar perfusion (23).

But besides the alterations of the pulmonary microcirculation vasomotricity, adrenaline in excessive and prolonged concentrations have direct effect on capillary permeability (19).

The importance of the pulse amplitude and contour during bypass is controversial (24, 25). The secretion of catecholamines is regulated, in a very significant part, by the stimulation of the baro-receptors of the carotid body. The decrease of a pulsatil flow below 80 cc/Kg causes a small elevation of catecholamine levels. The same occurs with a non-pulsatil flow of 110 cc/Kg. A non-pulsatil flow of less than 80 cc/Kg, however, causes great elevation of the catecholamine secretion, with increased vascular resistance and acidosis. The effect of hypothermia on the baroreceptors of the carotid body is still unknown (25).

The importance of the capillary permeability as a primary mechanism in all non-hemodynamic pulmonary edemas, as in extracorporeal circulation, seems to be recognized by all (17). The importance of the catecholaminestimulation needs, however to be investigated, as well as the direct effect of microemboli, hipoxia, prostaglandins, serotonin, etc.

Very little is known about lymphatic drainage of the pulmonary interstitium after extracorporeal circulation. It is well documented its importance in situations of increased capillary permeability, removing large amounts of fluid with high oncotic pressure (26).

There are, therefore, a multiplicity of factors associated with the alterations of the alveolo-capillary membrane and with the elevation of pulmonary vascular resistance after open heart surgery, and further investigation is necessary to prove the importance of the catecholamines as a primary mechanism of those changes. These multiple factors make the interpretation of the results difficult in a way that clinical conclusions of interest can be taken. Besides if these alterations may not be important after short bypass times, their occurrence after long bypasses is associated with morbididy and, probably, mortality.

The progresses of manufacturing blood oxygenators, filters and tubing used in the extracorporeal circulation and the use of small amounts of homologous blood are well documented steps given to prevent post-operative pulmonary dysfunction. The use of large doses of steroids and platelet anti-agregants are important also, for some researchers (17, 27).

Elevation of the perfusion pressure and pulsatil flow during extracorporeal circulation must be investigated further.

Since there is an alteration of the capillary permeability the use of colloids and diuretics doesn't seem to be advisable in the treatment of post-operative pulmonary dysfunction. Assisted ventilation with positive end expiratory pressure is, probably, the best way to treat this dysfunction, because of its compression from inside the alveolar wall stimulating the lymphatic drainage.

RESUMO

ALTERAÇÕES DA MICROCIRCULAÇÃO PULMONAR DEPOIS DE CIRURGIA DE «CORAÇÃO ABERTO»

Em 30 doentes submetidos a substituição da válvula mitral foi feito um estudo da hemodinâmica pulmonar nas primeiras 18 horas depois da operação. Na maioria deles registaram-se resistências vasculares pulmonares mais elevadas que as encontradas no pré-operatório, e verificou-se que a elevação era relacionada com o tempo de duração do by-pass, que se associava a um trabalho aumentado do ventrículo direito, a um aumento de shunt intrapulmonar e a mais intensas lesões ultraestruturais da membrana alvéolo-capilar. A resistência vascular pulmonar tinha tendência a baixar para os níveis pré-operatórios ao fim das 18 horas.

As alterações microscópicas são semelhantes às registadas no pulmão de choque, no embolismo gordo ou em todos os edemas pulmonares *não-hemodinâmicos*, e podem com probabilidade ser devidas a estimulação prolongada de catecolaminas, a microembolismo e à hipóxia

Para definir a relativa importância de cada factor na genese das modificações da microcirculação pulmonar depois da cirurgia de *coração aberto*, torna-se indispensável garantir controlo da pressão de perfusão, usar melhores membranas sintéticas e melhores oxigenadores, e utilizar ventilação assistida com pressão positiva no final da expiração.

REFERENCES

1. LLAMAS R, FORTHMAN HJ, BEACH M: Respiratory discress after cardiopulmonary bypass. *J Am Med Assoc* 225: 1183, 1973.
2. SILVA J, IRRIBAREN CO, EKESHOM S: The causes of death after open heart surgery *J Thor Cardiov Surg* 47: 72, 1964.
3. TURUBULL KW, MYAGUSHIMA RT, GEREIN AN: Pulmonary complications and cardiopulmonary bypass: a clinical study in adults. *Can Anesth J* 21: 181, 1974.
4. SWANK RL: Microemboli and cardiopulmonary bypass; treatment and perfusion, in Forscher BK, Lillehei RC and Stubbs. In: Shock in low and high flow states. Ed. *Except Med* Amsterdam 1972.
5. LESAGE AM, TSUSHIOKA H, JOUNC MH, SEALY WC: Pathogenesis of pulmonary damage during extracorporeal perfusion *Arch Surg* 93: 1002, 1966.
6. PENNOCK JL, PIERRE WS, WALDHANSEN JA: The management of lungs during cardiopulmonary bypass. *Surg Gyn Obst* 145: 917, 1977.
7. RODRIGUES GOMES M, NETO J, GUERREIRO M, BASTOS PT, MOUTINHO C, MACHADO FQ, GRAÇA AS, SOUSA AR: Cirurgia da válvula mitral com circulação extracorporal. *J do Médico* XCVII: 97-101, Abril 1978.
8. JANG SS, BENTIVOGLIO LG MARANHÃO V, GOLDBERG H: From cathaterization data to hemodynamic parameters. Ed. *F A Davis,* Philadelphia 1972.
9. ROULEAU CA, FRYE RL, ELLIS FH, Jr.: Hemodynamic state after prosthetic replacement of the mitral valve with a bal and disk valve in Prosthetic Heart Valtes. Ed. *Brewer L. A. Charles C. Thomas.* Springfield 1969.
10. BUGGE ASPERHEIM B, GULVSIK A, RENDAHL H, SEMB G: Hemodynamics and pulmonary punction following mitral valve replacement. A study of early and late post-operative changes. *Scand J Thorac Cardiov Surg* 12: 9, 1978.
11. WILSON JW: Microcirculatory considerations in extracorporeal oxygenation. *New York J Med* 73: 2337, 1973.
12. WILSON JW: The pulmonary cellular and subcellular alterations of extracorporeal circulation. *Surg Clin N Am* 54: 1203, 1974.
13. DUNN J, KIRSH MM, HARNESS J, CARROL M, STRAKER J, SILVAN H: hemodynamic, metabolic and hematologic effects of pulsatil cardiopulmonary bypass. *J Thor Cardiov Surg* 65: 523, 1973.
14. HILL DG, DELANEROLLE P, AGUILLAR MJ HILL D: The pulmonary filtrophylogy membrane and bublle oxygenators. *Am Soc Ar Int Organs* 4: 25.
15. BRUCE IH, WHITTAKER AN, NICOLL P, GRAEME ER: Microembolism syndrome: acute respiratory farlune and dissemined intravascular coagulation. *Aust N Z J Med* 3: 495, 1973.

16. LEE WH, KRUMHAAR D, FOUKALSUD EW, SCHEIDE OA, McLONEY JV: Denaturation of plasma proteins as a cause of morbility and death after intracardiac operations. *Surg* 50: 29, 1961.
17. ARRANTS JE, GADSEN RH, HUGGINS MB, LEE WH: Effects of extracorporeal circulation upon blood lipids. *Ann Thor Surg* 15: 229, 1973.
18. CLOWES GHA: The physiologic basis of cardiac surgery in Norman JC *Cardiac Surg* 2.ª Ed. Appleton--Centry Crofts, NY 1972.
19. BERK JL, HAGEN JF, KOO R, BAER W, DOSHAT GR, RUPRIGHT M, NOMOTO S: Pulmonary insufficiency caused by epinéphrine. *Ann Surg* 178: 423, 1973.
20. KADOWITZ PJ, JOINER PD, HYMAN AL: Effect of sympathetic nerve stimulation on pulmonary vascular resistance in the intact spontaneonsly breathing dog. *Proc Soc Exp Biol Med* 147: 68, 1974.
21. ARTUS JC, LLORY, BONNET H, LESBROS D: Le surfactant pulmonaire. *Ann Anesth Franç* 16: Suppl II e III, 33, 1975.
22. LLOYD TC: The influence of blood pH on hypoxic pulmonary vasoconstriction. *J Apph Phys* 21: 358, 1968.
23. HARRISON TS, CHAWLA RC, SETON JF: Carotid sinus origin of adrenergic response comprising the effectiveness of artificial circulatory support. *Surg* 68: 20, 1970.
24. HARRISON TS, SETON JF: An analysis of pulse frequency as an adrenergic exciting in pulsatil circulatory support. *Surg.* 73: 868, 1973.
25. LAURENYNS JM, BEART A, BOUSEAU VL: The pulmonary lymphaties: macroscopic and microscopical studies. *Am Rev Resp Dis* 101: 448, 1970.
26. WILSON JW, RATLIFF NB, MIKAT E: Leucocyte changes in the pulmonary circulatory circulation; a mechanism of acute pulmonary injury by various stimuli. *Chest* 59: Suppl. 5, 365, 1971.

Adress for reprints: *M. Rodrigues Gomes*
Serviço de Cirurgia Torácica
Faculdade de Medicina do Porto
Portugal.