ELECTRON MICROSCOPIC STUDIES ON THE ALVEOLAR-CAPILLARY BARRIER IN THE PATIENTS OF CHRONIC PULMONARY EDEMA

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Electron microscopic studies on the alveolar-capillary barrier were carried out in 13 patients of chronic pulmonary edema and/or congestion resulting from heart disease of various etiologies. The characteristic findings are tremendous proliferation of type II granular pneumocyte and irregular thickening of alveolar epithelial and capillary basement membrane. These ultrastructural changes correlated to the duration of heart failure and mean pulmonary arterial wedge pressure despite of disease groups and the age of the patients. In particular, lamination of capillary basement membrane with fragmentation was more specific finding which was observed only in patients with mean pulmonary arterial wedge pressure above 35 mmHg and duration of heart failure over 6 years. There was no apparent relationship existed between the ultrastructural changes and pulmonary arterial pressure. In addition to these characteristic changes the remaining ultrastructural changes of the alveolar-capillary barrier were difficult to make a correlation to clinical course and cardio-pulmonary hemodynamics.

THE ultrastructural studies on the alveolar-capillary membrane of the patients with congenital and acquired heart diseases, associating with chronic pulmonary edema and/or congestion are still limited. Majority of the previous reports on acquired heart disease were confined to patients with mitral stenosis.¹⁻⁴ Giesecking² demonstrated separation of capillary endothelium and alveolar epithelium as well as irregular thickening of alveolar-capillary basement membrane in cases of chronic pulmonary edema as a consequence of mitral stenosis. Coalson et al⁴ reported alveolar-capillary basement membrane changes with varying fibrocellular manifestations in acquired heart disease, while congenital heart disease showed markedly increased fibrocellular changes in the alveolar-capillary wall.

The present communication dealt primarily

with the ultrastructural changes observed in the alveolar-capillary barrier in patients with chronic pulmonary edema resulting from heart disease of various etiologies. Attempts to correlate some specific morphologic changes at an ultrastructural level to cardio-pulmonary hemodynamics and also to duration of heart failure were made.

MATERIALS AND METHODS

This study was carried out on human lung specimens which were obtained at the time of open heart surgery. A total of 13 patients, that is, chronic rheumatic valvular heart disease 11 and congenital heart disease 2 were investigated. Informed consent was obtained in all patients. They were 5 men and 8 women, ranging in age from 19 to 45 years. All patients received daily maintenance dose of 0.25–0.5 mg digoxin. A

(Received in May 17, 1979; Accepted on July 5, 1979)

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TABLE I SUMMARY OF CLINICAL COURSE AND HEMODYNAMIC DATA IN 13 PATIENTS

Case No.	Sex	Age (yrs)	Diagnosis	Rhythm	Duration of symptom onset (yrs)	Duration of CHF	Systemic arterial O ₂ Saturation (%)	MPA pressure (mmHg)	Mean PAW pressure (mmHg)
1	F	36	MS	AF	16	9 yrs.	95	70/48 (59)	38
2	F	45	MS	SR	6	6 mon.	96	50/20 (37)	24
3	M	21	MS	SR	5	2 mon.	98	39/18 (27)	22
4	F	47	MS + AI	AF	6	2 yrs.	93	104/44 (68)	32
5	M	21	MS + AI	AF	9	5 mon.	98	55/30 (45)	24
6	M	17	MI	AF	5	2 yrs.	96	75/40 (52)	26
7	F	19	MI	SR	5	—	96	40/20 (31)	21
8	F	21	MI + TI	AF	8	6 yrs.	95	60/45 (50)	35
9	F	14	MI + TI	AF	2	4 mon.	90	60/20 (37)	30
10	F	25	MI + AI	SR	2	—	98	28/10 (17)	13
11	M	36	AS + AI	SR	2	4 mon.	98	40/20 (32)	21
12	M	37	ASD	SR	5	2 mon.	96	70/20 (40)	9
13	F	38	VSD	SR	6	3 mon.	94	110/58 (78)	8

Abbreviation: yrs: years; Mon: months; F: female; M: male; CHF: congestive heart failure; AF: atrial fibrillation; SR: sinus rhythm; MPA: main pulmonary artery; PAW: pulmonary artery wedge; MS: mitral stenosis; MI: mitral insufficiency; TI: tricuspid insufficiency; AS: aortic stenosis; ASD: atrial septal defect; VSD: ventricular septal defect. The numbers in the parentheses indicate mean pressure.

complete history taking, physical examination and chest roentgenograms were used to diagnose the first episode of overt heart failure. The duration of heart failure was estimated from the first attack of frank heart failure to the date of open heart surgery. Cardiac catheterization with angiocardiograms were performed to evaluate cardio-pulmonary hemodynamics in all patients. The etiologic diagnosis was further confirmed by surgical operation. Their clinical and hemodynamic profiles were summarized in Table I. They were divided into four groups. Group A consisted of 5 patients with mitral stenosis alone (3 cases) or associated with mild aortic insufficiency (2 cases). Group B included 5 patients who had mitral insufficiency alone (2 cases) or in association with functional tricuspid insufficiency (2 cases) or mild aortic insufficiency (one case). Group C had only one patient with pure aortic valvular disease (aortic steno-insufficiency). Group D had two patients with congenital heart disease (atrial and ventricular septal defect in one each). The duration of symptoms related to the heart disease ranged from 2 to 16 years. All but two patients in Group B had frank heart failure ranging in duration from 2 months to 9 years. The mean pulmonary arterial pressure and mean pulmonary arterial wedge pressure in these pa-

tients ranged from 27 to 78 mmHg and 8 to 38 mmHg, respectively.

Lung biopsies were obtained from the lower lobe of the right lung, almost at the same location in all patients. Biopsy was made soon after thoracotomy, and extracorporeal circulation was instituted thereafter. After being excised at surgery, all tissue specimens were dropped instantly into a 3% solution of iced glutaraldehyde in 0.1 M phosphate buffer (pH 7.2 to 7.4). Within one hour the tissue was minced into small sections (about one mm²) and left for two hours in glutaraldehyde solution. The tissue was then washed in phosphate buffer with several changes and postfixed with 2% osmium tetroxide in 0.1 M phosphate buffer (pH 7.2 to 7.4) for two hours. Subsequently the tissue was dehydrated in graded concentrations of alcohol and embedded in Epon-Araldite. The specimens were sectioned with the Sorvall MT-2 Porter-Blum ultramicrotome using glass knives and stained with uranyl acetate and lead citrate. The ultra thin sections were examined in the Hitachi HU-11 electron microscope operated at 75 KV.

RESULTS

Alveolar epithelium and capillary endothelium

A striking change observed in alveolar epithe-

Fig.1. A and B. Demonstration of striking proliferation of type II alveolar epithelial cells (EP II). Numerous microvilli (MV) intruding into alveolar space (AS) are noted with abundant osminophilic lamellated inclusions (OL) in the cytoplasm which are not infrequently observed free in the alveolar space (arrow).

A. $\times 5,500$. B. $\times 5,400$.

Fig.2. Illustration of capillary endothelial (EN) cell proliferation with narrow capillary (C) lumen. AS: alveolar space; COL: collagen fibrils. $\times 18,400$.

Fig.3. Disruption of capillary shown in the edematous (ED) lung (arrows).
AS: alveolar space; EN: capillary endothelium;
EP: alveolar epithelium; R: erythrocyte. $\times 10,800$.

Fig.4. A and B. The characteristic changes of alveolar-capillary basement membrane. Irregular thickening of epithelial (A) and endothelial (B) basement membrane is observed.

AS: alveolar space; BM: basement membrane; C: capillary; EN: capillary endothelium; EPI: type I alveolar epithelium; IS: interstitial space; R: erythrocyte. A. $\times 16,000$. B. $\times 18,400$.

(A)

(B)

Fig.5. A and B. Portion of two different capillaries (C) chosen to demonstrate the peculiar change of laminated basement membrane (BM) with fragmentation (asterisks). Note disruption of capillary endothelium (EN, arrow). IS: interstitial space. A. $\times 27,000$. B. $\times 18,400$.

Fig.6. The edematous (ED) fluid accumulated in the interstitium (IS). Note the fused portion (arrow) of epithelial and endothelial basement membrane is rarely observed to imbibe edematous fluid.

AS: alveolar space; C: capillary; EN: capillary endothelium; EPI: type I alveolar epithelium. $\times 8,400$.

lium was marked proliferation and enlargement of type II granular pneumocytes. Microvilli were numerous, and the cytoplasm contained abundant irregularly lamellar osminophilic inclusions which were not infrequently observed free in the alveolar cavity (Fig. 1. A and B). In spite of disease groups this characteristic finding was more frequently noted in patients with long-standing heart failure and high pulmonary arterial wedge pressure. Although detachment of the damaged epithelial cells from their basement membrane was often observed extensive disruption of the alveolar epithelium was never seen, even in patients with chronic congestive heart failure.

The capillary endothelium was less affected, and the plasma membrane junctions were intact. Proliferation and enlargement of endothelial cells were noted to vary considerably. There were some areas showing cell widening and luminal narrowing (Fig. 2). Destruction of capillary was often observed in the edematous lung (Fig. 3).

Alveolar-capillary basement membrane

The characteristic change of alveolar-capillary basement membrane was irregularly thickened and quite variable in width (Fig. 4. A and B). Regardless of the disease groups this finding was observed in all patients studied. A peculiar change of laminated thickened capillary basement membrane, along with fragmentation was noted in only two patients who had a long duration of heart failure, together with marked elevation of pulmonary arterial wedge pressure (Fig. 5. A and B).

Interstitium

The alveolar interstitial space was widened by septal edema, and by an increase in the interstitial cells and mononuclear cells. Although the edema fluid has accumulated in the ground substance space of the interstitium the portion of the alveolar-capillary barrier in which epithelial and endothelial basement membrane are fused was rarely observed to imbibe edema fluid (Fig. 6). The septal stroma was characterized by an

Fig.7. A and B. Demonstration of various stages of degenerative changes observed in the lung tissue.

CF: cytoplasmic fragments; COL: collagen fibrils; ED: edema;
R: erythrocyte. A. $\times 8,400$. B. $\times 10,200$.

increase of elastic and collagen fibers. Various stages of degenerative changes of lung tissue were often observed in the interstitium of the edematous lung (Fig. 7).

Correlation of the ultrastructural changes in alveolar-capillary barrier to hemodynamic data and duration of heart failure.

In correlating ultrastructural changes to hemodynamic parameters, there was a tendency that a striking proliferation of type II granular pneumocytes as shown in Fig. 1 seemed more often observed in patients with marked rise of mean pulmonary arterial wedge pressure (> 30 mmHg) and with longer duration of heart failure (> 2 years). Irregular thickening of capillary basement membrane, particularly with lamination and fragmentation as illustrated in Fig. 5, was noted in only two patients who had mean pulmonary arterial wedge pressure above 35 mmHg and the duration of heart failure beyond 6 years. The degree of thickened capillary basement membrane was very mild in two patients of congenital heart disease with normal pulmonary arterial wedge pressure and short duration of heart failure (2–3 months).

In conclusion, there was no apparent correlation of the ultrastructural changes to pulmonary arterial pressure. Likewise, no relationship was observed between the ultrastructural changes and the disease groups as well as the age of the patients. However, there seemed to be some relationship existing between the ultrastructural changes (striking proliferation of granular pneumocytes and irregular thickening of capillary basement membrane) and mean pulmonary arterial wedge pressure as well as duration of heart failure.

DISCUSSION

The alterations of the alveolar-capillary barrier in congenital and acquired heart diseases have been described by various investigators at the ultrastructural level.^{1–4} It has been widely agreed that thickening of the alveolar-capillary basement membrane with varying fibrocellular manifestations was observed in acquired heart disease, and marked increase of fibrocellular changes in the alveolar-capillary wall was predominantly demonstrated in congenital heart disease. However, the majority of their studies were limited to mitral stenosis in acquired heart disease. The reports concerning the ultrastructural changes in various kinds of acquired rheumatic valvular heart diseases were rarely seen,

particularly in those patients with chronic pulmonary edema.

With respect to the capillary basement membrane a peculiar change of laminated basement membrane with fragmentation was rarely reported in human pulmonary capillary in addition to the usual finding of thickened capillary basement membrane as described by various workers.^{1–7} Despite of disease groups the severity of irregularly widened capillary basement membrane was generally correlated to the duration of heart failure and the degree of pulmonary arterial wedge pressure. In particular, the lamination and fragmentation of capillary basement membrane were only observed in patients with mean pulmonary arterial wedge pressure above 35 mmHg and duration of heart failure over 6 years. In contrast to the study reported by Coalson et al.⁴ there was no relationship existed between thickened capillary basement membrane and pulmonary arterial pressure.

Striking proliferation and enlargement of type II granular pneumocytes as shown in Fig. 1 were another unusual finding which was also observed only in patients with high pulmonary arterial wedge pressure and long-standing heart failure. In addition to these two more specific findings (lamination of thickened capillary basement membrane and striking proliferation of granular pneumocytes) the remaining ultrastructural changes of alveolar-capillary barrier were difficult to make a good correlation to cardiopulmonary hemodynamics and clinical course.

It is concluded that lamination of thickened capillary basement membrane with fragmentation and tremendous proliferation of granular pneumocytes were more specific morphologic changes of alveolar-capillary barrier which correlated to the duration and severity of pulmonary edema and/or congestion in spite of the disease groups and the age of the patients.

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