TIME COURSE OF PULMONARY VASCULAR RESPONSE TO AN ACUTELY REPETITIVE PULMONARY MICROEMBOLISM IN DOGS

— An Analysis Using Pulmonary Vascular Impedance —

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To understand the mechanism leading to progressive pulmonary hypertension, we investigated the time course of vascular response to an acutely repetitive pulmonary microembolism in dogs by using pulmonary vascular impedance. In a normal state, the mean pulmonary arterial pressure (mPAP) was transiently increased by emboli, and the impedance moduli of 0 Hz (=R_{in}), 1.5 Hz and 3 Hz were slightly increased. A four-element electrical vascular model showed the transient increase in peripheral pulmonary vascular resistance (R₂) and inertia, and reduction in compliance (C). In contrast, in a state of a slight pulmonary hypertension, mPAP was continuously increased by the same amount of emboli, and the impedance moduli of both 0 Hz and 3 Hz were significantly increased. By a four-element model, a severe increase in R₂ and reduction in C were observed, and these changes continued. Therefore, although the vascular response to pulmonary microembolism basically depends on the degree of mechanical obstruction, this response is thought to be modulated by the responsiveness of pulmonary vessels at that time, which is involved in the alteration in the local characteristics of pulmonary vessels, and/or the recruitment of a new blood flow.

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REPETITIVE pulmonary microembolism causes irreversible pulmonary hypertension, underlying an increase in right ventricular afterload, which eventually leads to pulmonary heart disease. Emboli to lobar or segmental arteries may be associated with reflex or humoral vasoconstriction and bronchoconstriction! It has been pointed out that increased pulmonary arterial pressure accompanying pulmonary arterial obstruction differs in the large and small regions of

the pulmonary artery. A unilateral obstruction of the main pulmonary artery by a balloon increases the pulmonary arterial pressure in the opposite side. This is thought to be a phenomenon of blood flow shift by mechanical obstruction. In contrast, microembolism in a small pulmonary artery transiently increases the pulmonary arterial pressure which is subsequently decreased^{2,3}. Functional neuro-endocrine factors and/or mechanical obstruction is possibly the mechanism involved. The role of neuro-endocrine factor is, however, likely to be small because this phenomenon occurs even in the isolated perfused lung without nervous control³ or blood perfusate⁴. The vascular

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Fig. 1. A lumped electric model of the pulmonary vascular system. R_1 equals a characteristic impedance in the proximal pulmonary artery, which is combined to a fluid inertia L and a peripheral resistance R_2 in series, and to a lumped compliance C in parallel.

response to pulmonary microembolism may depend on the degree of mechanical obstruction as well as on a change in the local characteristics of vascular smooth muscle, e. g., the dilatation of the perfused vessels or recruitment of a new blood flow in underperfused lung regions.

The estimation of pulmonary vascular impedance provides a more complete description of the right ventricular afterload than does the estimation of total pulmonary resistance. In addition, it is well known that a change of this resistance does not necessarily indicate vasomotion. Therefore, to characterize the vascular responses to an acute pulmonary microembolism and their alteration with time, we measured the change in pulmonary vascular impedance, which was simulated as the changes in the parameters composed of a four-element electrical vascular model.

METHODS

Seven mongrel dogs weighing 8.8–11.1 kg (average 9.9 kg) were anesthetized by sodium pentobarbital (25 mg/kg) and ventilated by Harvard 613 respirator under a positive pressure. After thoracotomy at the left 5th intercostal, the pericardium was incised to the minimum and the main trunk of the pulmonary artery was separated. A probe (10–13 mm) was attached to measure pulmonary blood flow rate by a square-wave electromagnetic flow meter (Nihon Koden, MVF-1200). A microtip pressure transducer

(Millar Inc., PC 350) was inserted to the same position from the periphery of the pulmonary artery to measure pulmonary arterial pressure. The aorta was catheterized for pressure measurement, and a catheter for emboli injection was fixed in the right atrium. When aortic pressure, pulmonary arterial pressure and pulmonary arterial blood flow were stabilized, a bolus of 0.7 ml lycopodium spores (50 mg/ml, 16,000–20,000 particles per ml) was injected via the right atrium. Then, the respective parameters were recorded at time 0, 30 sec, 1, 3 and 5 min by polygraphy (Nihon Kohden, RM-85) at a paper speed of 100 mm per sec (control groups). Following this, a small volume of lycopodium spore solution was repeatedly injected and when the mean pulmonary arterial pressure reached about 20 mmHg, a further bolus of 0.7 ml lycopodium spore solution was injected and the respective parameters were recorded in a similar way (pulmonary hypertension groups).

Then, a pair of pulmonary arterial pressure wave and flow wave on end-expiratory phase was divided equally into 10–20 msec interval, and then the amplitudes were read. Fourier analysis was performed by using our original program. Impedance modulus was obtained by dividing the amplitude of the corresponded component and the phase was obtained by subtracting the corresponded phase angle. The fundamental frequency of the impedance was heart rate divided by 60, and the characteristic impedance (Z_c) was defined as the average impedance modulus between 7–11 Hz. The final impedance modulus and phase were standardized at 1.5 Hz interval because the heart rate was different for each dog.

A circuit composed of four elements, R_1 - R_2 - C - L , was considered as a lumped electric model of the pulmonary vascular system in order to obtain a lumped pulmonary arterial compliance or inertia (Fig. 1). Input impedance (Z_o) of this circuit was represented as follows;

$$\begin{aligned} Z_o &= R_1 + j\omega L + R_2 / (1 + j\omega R_2 C) \\ &= R_1 + j\omega L + R_2 (1 - j\omega R_2 C) / (1 + \omega^2 R_2^2 C^2) \end{aligned}$$

Then, if $A = 1 + \omega^2 R_2^2 C^2$

$$\begin{aligned} Z_o &= R_1 + j\omega L + R_2 (1 - j\omega R_2 C) / A \\ &= (R_1 + R_2 / A) + j\omega (L - R_2^2 C / A) \end{aligned}$$

TABLE I HEMODYNAMICS IN THE CONTROL AND HYPERTENSION GROUPS

	after emboli injection				
	control	30 sec	1 min	3 min	5 min
Control Groups					
HR (beats/min)	137.2±14.6	137.9±14.1	139.4±15.0	138.5±18.1	141.1±16.4
mPAP (mmHg)	12.4±4.1	16.2±3.9**	16.3±4.1**	14.7±3.6**	14.0±4.0*
mAOP (mmHg)	112.9±27.2	109.9±30.4	106.6±28.4	104.5±28.2*	105.8±27.3*
PAF (ml/sec)	15.71±7.38	15.22±7.18	16.09±7.14	15.83±6.57	16.19±6.89
Pulmonary Hypertension Groups					
HR (beats/min)	131.3±14.3	125.8±17.6	126.3±20.5	125.8±21.4	122.1±25.5
mPAP (mmHg)	22.2±3.1	32.2±5.1**	31.4±4.7**	29.8±4.3**	27.9±4.7**
mAOP (mmHg)	105.3±37.0	97.7±37.0	93.3±37.2	92.9±36.2	94.4±36.5
PAF (ml/sec)	12.88±3.72	11.36±4.81	11.08±4.84	11.96±5.01	11.18±4.98

(N=7, mean±S.D.)

Abbreviation: HR, heart rate; mPAP, mean pulmonary arterial pressure; mAOP, mean aortic pressure; PAF, pulmonary arterial flow.

Fig.2. A: Time course of a representative pattern of pulmonary vascular impedance after emboli injection in the control groups.

B: After 30 sec of emboli injection in the control groups, the impedance moduli in 0 Hz (=Rin), 1.5 Hz and 3.0 Hz were significantly increased, but Zc was unchanged as compared with that of control condition.

Abbreviations: Rin, input impedance (mean arterial pressure/flow); Z, pulmonary vascular impedance; Zc, characteristic impedance.

TABLE II PULMONARY VASCULAR IMPEDANCE IN THE CONTROL GROUPS

Control Groups		after emboli injection				
frequency	control	30 sec	1 min	3 min	5 min	
<i>Z modulus (dyne. sec. cm⁻⁵)</i>						
0 Hz	1182±291	1644±437*	1547±394*	1408±346*	1073±348	
1.5	563±174	753±234*	731±196*	664±204*	536±138	
3.0	231±133	267±120*	254±139	254±139	247±138	
4.5	258±187	239±136	224±122	244±143	223±145	
6.0	310±321	259±181	229±149	251±145	247±174	
7.5	337±320	249±165	243±180	259±167	324±248	
9.0	336±224	354±217	252±172	291±138	287±175	
10.5	269±150	448±398	343±242	283±124	251±153	
12.0	276±188	289±143	274±193	251±176	275±158	
13.5	273±202	359±307	358±391	261±203	237±243	
15.0	194±117	319±223	311±317	252±200	235±268	
<i>phase (radian)</i>						
1.5 Hz	-0.60±0.94	-0.52±0.96	-0.24±0.88	-0.50±0.93	-0.14±0.76	
3.0	-0.98±0.88	-0.70±0.77*	-0.40±0.73	-0.96±0.91	-0.11±0.82*	
4.5	-0.64±1.02	-0.40±1.07*	-0.33±0.86*	-0.61±0.59	-0.27±0.49	
3.0	-0.43±0.93	0.08±0.93	-0.21±0.49	-0.20±0.97	-0.37±0.65	
7.5	-0.50±0.85	-0.16±1.05	-0.14±0.87	-0.23±0.68	-0.51±1.03	
9.0	-0.80±0.73	-0.89±1.04	-0.19±0.94	-0.33±0.89	-0.79±0.73	
10.5	-0.41±0.84	-0.90±1.16*	-0.34±1.01	-0.43±1.16	-0.60±0.81	
12.0	-0.01±0.66	-0.34±1.06	-0.26±0.86	-0.39±0.96	-0.01±0.72	
13.5	-0.61±0.86	-0.67±0.64	-0.69±0.9	-0.54±1.02	-0.39±1.06	
15.0	-1.47±1.13	-0.87±1.84	-0.54±1.30	-1.16±0.99	-0.36±0.56*	
<i>Frequency of first minimum (Hz)</i>						
	4.5±2.0	5.2±1.9	5.9±2.8	4.7±2.1		
<i>Characteristic impedance (dyne. sec. cm⁻⁵)</i>						
(7-11 Hz)	314±216	350±239	245±166*	277±134	293±181	

(N=7, mean±S.D.)

Significant difference in each value after emboli injection is indicated by * $P<0.05$ or ** $P<0.01$ as compared with that of control condition.

$$\text{Therefore, } Z_0 = \{(R_1 + R_2/A)^2 + \omega^2 (L - R_2^2 C/A)^2\}^{1/2}$$

$$\theta = \tan^{-1} \{ \omega (L - R_2^2 C/A) / (R_1 + R_2/A) \}$$

For the simulation of this four-element model, first, input resistance (R_{in}) of " $R_1 + R_2$ " was obtained from a value of mean pulmonary pressure divided by mean flow. Second, the approximate value of R_1 was estimated from the value of Z_c , so that the approximate value of R_2 was also obtained. And then, the approximate values of R_1 , R_2 , C and L were obtained through minimizing the sum-squared error criterion function by comparing above Z_0 with an each modulus of pulmonary vascular imped-

ance. Paired t test was used for statistical analysis, and $P<0.05$ was considered as significant.

RESULTS

In the control groups, mean pulmonary arterial pressure (mPAP) was significantly increased from 30 sec to 5 min ($P<0.05$) after the injection of lycopodium spore solution. The mean aortic pressure (mAOP) was significantly decreased from 3 min to 5 min ($p<0.05$, Table I). The impedance moduli of 0 Hz (= R_{in}), 1.5 and 3.0 Hz were significantly increased at 30 sec after injection, but these returned to the control values in 5 min.

Fig. 3. A: Time course of a representative pattern of pulmonary vascular impedance after emboli injection in the pulmonary hypertension groups.

B: After 30 sec of emboli injection in the pulmonary hypertension groups, the impedance moduli in 0 Hz (=Rin) and 3.0 Hz were significantly increased, but Zc was unchanged as compared with that of control condition.

Abbreviations: the same shown as Fig. 2.

Zc (7–11 Hz) was significantly decreased only at 1 min (Fig. 2 and Table II).

In the pulmonary hypertension groups, as in the control mPAP was significantly increased from 30 sec to 5 min ($P < 0.01$). mAOP was slightly decreased (Table I). The impedance moduli of 0 Hz (=Rin) and 3 Hz were significantly increased at 30 sec after injection, and elevated Rin continued until 5 min (Fig. 3 and Table III). The first minimum of modulus (fmin) was slightly shifted to higher frequency in the control and pulmonary hypertension groups at 30 sec or 1 min (Table II and III).

The values of R_1 , R_2 , C, and L were estimated from a four-element electrical model. In the control groups, an increase in R_2 and L, and a decrease in C were observed at 30 sec after injection, but these values except R_2 returned to the previous values in 3 min. By contrast, in the pulmonary hypertension groups, a significant increase in R_2 and a decrease in C were observed at 30 sec after

injection, and these changes continued until 5 min without returning to the previous values (Fig. 4).

DISCUSSION

An increase in pulmonary arterial pressure after an acute pulmonary embolism is caused either by the passive mechanical effect of obstruction, active pulmonary vasoconstriction by neuro-endocrine factors, or both factors^{1,2,5}. To detect the elevation in pulmonary arterial pressure, more than 50% of the cross-sectional area of the pulmonary vascular bed must be obstructed⁶. However, it was reported that the degree of obstruction that resulted in pulmonary hypertension was often less in patients with a prior heart and/or lung disease than in those patients who were previously healthy^{1,7}. The decrease in cross-sectional area of the pulmonary vascular bed depends on the size of the emboli and their distribution. If the

TABLE III PULMONARY VASCULAR IMPEDANCE IN THE PULMONARY HYPERTENSION GROUPS

<i>Pulmonary Hypertension Groups</i>		<i>after emboli injection</i>				
<i>frequency</i>	<i>control</i>	<i>30 sec</i>	<i>1 min</i>	<i>3 min</i>	<i>5 min</i>	
<i>Z modulus (dyne. sec. cm⁻⁵)</i>						
0 Hz	2472±593	4283±1988*	4242±1832*	3734±1655*	3692±1552*	
1.5	900±320	1491±706	1369±532*	1253±156	1067±488	
3.0	360±115	450±113*	444±131	413±156	379±116	
4.5	309±110	318±112	330±144	314±166	301±132	
6.0	308±154	302±146	310±180	287±187	287±136	
7.5	286±133	349±219	362±226	304±203	266±108	
9.0	364±174	379±182	286±111	390±215	331±117	
10.5	391±164	326±139	286±150	346±168	446±220	
12.0	379±180	420±261	394±180	343±197	517±250	
13.5	361±144	449±197	529±266	401±227	440±155	
15.0	353±95	486±330	366±219	432±213	325±121	
<i>Phase (radian)</i>						
1.5 Hz	-0.83±1.19	-0.84±1.19	-0.57±1.28	-0.81±1.21	-1.23±1.06	
3.0	-0.91±0.74	-0.60±0.80	-0.14±0.83*	-0.47±1.13	-0.39±1.01	
4.5	-0.51±1.08	-0.80±1.19	0.16±0.58	-0.01±0.66	-0.50±0.91	
6.0	-0.10±0.57	-0.41±0.68	0.11±0.59	0.21±0.42	-0.53±0.74	
7.5	-0.14±0.79	-0.06±0.78	-0.14±0.95	-0.69±0.68	-0.09±0.77	
9.0	-0.40±0.69	-0.13±1.23	-0.19±0.60	-0.69±0.59	0.03±0.71	
10.5	-0.27±1.28	-0.34±1.25	-0.64±1.10	-0.50±0.65	0.07±1.02	
12.0	-0.17±1.41	-0.99±0.91	-0.29±1.27	-0.56±0.36	-0.81±0.54	
13.5	-0.34±1.17	-1.00±1.11	-0.39±1.09	-1.09±1.07	-0.29±1.24	
15.0	-0.74±0.88	-0.37±1.71	-0.14±1.44	-1.04±1.67	-0.51±0.94	
<i>Frequency of first minimum (Hz)</i>						
	6.0±2.0	8.0±2.3	7.7±2.4	7.1±2.2	6.3±1.6	
<i>Characteristic impedance (dyne. sec. cm⁻⁵)</i>						
(7-11 Hz)	347±130	351±134	311±110	346±143	348±88	

(N=7, mean±S.D.)

Significant difference in each value after emboli injection is indicated by * $P<0.05$ as compared with that of control condition.

diameter of the embolus particle is larger than 170 μm in diameter, enough particles to mechanically obstruct more than 50% of the cross-sectional area of pulmonary vascular bed are necessary to produce pulmonary hypertension. Because, they do not likely induce any reversible constriction of the small pulmonary vessels. On the other hand, if the particle is less than 170 μm in diameter, the same elevation in pulmonary arterial pressure can be produced by embolization of less than 50% of cross-sectional area of the pulmonary vascular bed⁸. In addition, although pulmonary arterial pres-

sure can rise to the same degree by mechanical obstruction of the main pulmonary artery or by microemboli of the size below 170 μm , in the latter pulmonary arterial pressure is subsequently decreased. The role of neuro-endocrine factor is likely to be small, because we observed this phenomenon in an excised perfused lung without nervous control³ or blood perfusate⁴. Thus, this phenomenon appears to be caused by mechanical obstruction as well as by local characteristics of the pulmonary vessels, e.g., the dilatation of the perfused vessels or the recruitment of a new blood flow in

Fig.4. Time course of changes in R_1 , R_2 , C and L after emboli injection determined from a four-element electric vascular model (Fig. 1). In the control groups, an increase in R_2 and L , and a decrease in C were transiently observed at 30 sec and 1 min after injection, these values except R_2 returned to the previous values in 3 min. In pulmonary hypertension groups, a significant increase in R_2 and a decrease in C were observed at 30 sec after injection, and these changes continued in 5 min without returning to the previous values. Significant difference in each value after emboli injection indicated by * $p < 0.05$ or ** $p < 0.01$ as compared with that of control condition.

underperfused lung regions.

It is often difficult to continuously evaluate the pulmonary arterial resistance, because the total pulmonary resistance used in most cases gives a misleading impression of the actual obstructive change of the pulmonary vessels. Thus, we investigated the time course of vascular response to an acutely repetitive microembolism on the basis of pul-

monary vascular impedance. Little is known about the pulmonary vascular impedance in an acute pulmonary embolism. Our results have partly agreed with Elkin et al⁹, who reported that the mean pulmonary arterial pressure rose from 16.3 mmHg to 46.3 mmHg, showing the increases of R_{in} , f_{min} and Z_c in an acute experimental pulmonary embolism. Their explanation is, that as the

pulmonary pressure rises, the main pulmonary arteries distend and become stiffer, which leads to the decrease in pulmonary vascular compliance and to the increase in wave velocity. They believe that the pulmonary vascular bed responds to acute embolism by local vasoconstriction that involves both small precapillary resistance vessels and larger pulmonary arteries.

The pattern of pulmonary vascular impedance is affected by several components. In the present study, impedance moduli of 0 Hz ($=R_{in}$), 1.5 and 3.0 Hz were significantly increased at 30 sec after emboli injection in the control groups, but these returned to the control values in 5 min (Fig. 2 and Table II). Judging from these results, the increase in peripheral pulmonary arterial resistance produced the dilatation of a large pulmonary artery after an acute pulmonary embolism. This dilatation of a pulmonary artery not only increases the modulus of the low-frequency area, but also decreases pulmonary vascular compliance!¹⁰ However, the increase in Z_c was not observed in the present study (Table II). The increase in the cross-sectional area of blood vessels after embolism might cancel the influence of the increase in wave velocity on the basis of Womerley's equation!¹¹ All values except R_2 were returned to control values 3 min after injection (Fig. 4). This change may be due to the increase in vascular compliance or the recruitment of a new blood flow.

In contrast to this, the impedance moduli of 0 Hz ($=R_{in}$) and 3 Hz were significantly increased at 30 sec after emboli injection in the pulmonary hypertension groups, and then elevated R_{in} continued until 5 min (Fig. 3 and Table III). The pulmonary vessel was already slightly dilated before emboli injection, accompanied by a slight reduction of pulmonary vascular compliance. In this condition, administration of emboli distinctly increased the peripheral pulmonary vascular resistance with the reduction of pulmonary vascular compliance. However, there was no increase in vascular compliance or recruitment of a new blood flow as observed in the control groups. Thus, the respective parameters do not return to control values even after 5 min after injection (Fig. 4).

By using pulmonary vascular impedance, Calvin et al¹² studied the difference in right

ventricular afterload between pulmonary artery ligation and embolism produced by glass beads of 100–200 μ m size. As the pulmonary arterial pressure was increased equally in both cases, the ligation of the pulmonary artery increased both R_{in} and Z_c , and the glass beads increased only R_{in} . They believe that the glass beads produce the microvascular injury in distal pulmonary arteries alone without any accompanying vasoconstriction of the proximal vasculature. Similarly, Fitzpatrick and Grant¹³ studied the effects of three forms of pulmonary vascular obstruction on right ventricular afterload. An ensnarement of the left main pulmonary artery increased Z_c but decreased the pulmonary arterial compliance, whereas pulmonary embolism (autologous clots; at least 5 mm in internal diameter) decreased both Z_c and pulmonary arterial compliance. By the simulation of this experiment in a vascular model, they suspect that the increase in Z_c by the ensnarement is due to active neurohumoral effects, and the response to pulmonary embolism is due to passive mechanical effects.

In summary, different embolus sizes may have different effects on pulmonary vascular impedance. Indeed, in the present study the emboli of lycopodium spores (28–30 μ m) transiently increase a peripheral pulmonary vascular resistance in a normal state, but this increase concomitantly makes the vessels dilated to suppress an increase in Z_c . The dilatation of pulmonary vessels leads to an increase in vascular stiffening, to increase Z_c , concomitantly producing an increase in intra-vascular volume, to decrease Z_c . Further, the recruitment of the new blood flow may also reduce the peripheral pulmonary vascular resistance. In contrast, in pulmonary hypertension, the emboli further increased the peripheral pulmonary vascular resistance, indicating that pulmonary blood vessels already had a reduced reserve capacity. Thus, these results suggest that repetitive pulmonary microembolism gradually decreases the reserve capacity of pulmonary vessels, which impairs compensatory mechanisms for pulmonary vascular dilatation or recruitment of a new flow, eventually leading to irreversible pulmonary hypertension.

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