Constrictor Response of Small Pulmonary Arteries to Acute Pulmonary Hypertension during Left Atrial Pressure Elevation

Mikiyasu SHIRAI, Ishio NINOMIYA, and Kouji SADA

*Department of Cardiac Physiology,
National Cardiovascular Center Research Institute,
Suita, 565 Japan*

Abstract Acute elevations in left atrial pressure (LAP) were induced by altering the volume of air within a balloon inserted into the left atrium; the changes in internal diameter (ID) of small muscular pulmonary arteries (100–600 μm ID) in response to the associated rises of pulmonary arterial pressure (PAP) were measured using an X-ray TV system on the *in vivo* cat lung. When LAP was elevated to 14 ± 1 , 24 ± 1 , and 30 ± 1 mmHg, PAP was increased to 21 ± 1 , 30 ± 1 , and 37 ± 1 mmHg, respectively. With PAP ranging from 16 (control value) to 21 mmHg the ID did not dilate significantly. With PAP of 30–37 mmHg significant ID dilation occurred. The magnitude of the ID dilation (16%) with PAP of 37 mmHg, however, was significantly smaller than that (20%) with PAP of 30 mmHg despite the greater pressure rise. When the elevated PAP of 30–37 mmHg was quickly returned to the control level by rapid balloon deflation, the ID constricted significantly below the control level. The magnitude of the ID constriction was proportional to the degree of the preceding PAP rise and was maximal in the arteries of 200–400 μm ID. A papaverine hydrochloride injection combined with the balloon deflation completely abolished the ID constriction. A phentolamine injection, on the other hand, significantly attenuated the constriction with approximately half of the constriction persisting. The results indicate that an increase in vascular smooth muscle tone occurred in the small muscular pulmonary arteries, particularly those of 200–400 μm ID, in response to the acute rise of PAP above 30 mmHg during the LAP elevation. In addition, the data suggest the partial participation of catecholamines in the active contraction of vascular smooth muscle. The arterial contraction may serve to protect the pulmonary capillaries from an excessive hydrostatic pressure and pulmonary edema.

Key words: left atrial pressure elevation, acute pulmonary hypertension, small pulmonary arteries, internal diameter, cat.

Received for publication October 19, 1990

An acute elevation in left atrial pressure (LAP) directly causes an increase in pressure throughout the pulmonary circulation. How the pulmonary vessels respond during such a hypertensive state has been an important problem, because it exerts a great influence on pulmonary function (LAWSON *et al.*, 1964; MURPHY and FISHMAN, 1988). Indirect information on the response of the pulmonary vascular bed has been provided from the measurements of pressure-flow (BORST *et al.*, 1956; CARLILL and DUKE, 1956; RABIN and MEYER, 1960; KURAMOTO and RODBARD, 1962; SHOUKAS, 1975; HOPKINS *et al.*, 1980) and pressure-volume (LAWSON *et al.*, 1964; KARP *et al.*, 1968; MASERI *et al.*, 1972; SHOUKAS, 1975; DAWSON *et al.*, 1986) relations, and the distribution of blood flow (WEST *et al.*, 1964). Most of those studies have been carried out in isolated lungs which were artificially perfused by a pump.

To supply direct information on the pulmonary vascular response during the acute pulmonary hypertensive state accompanying LAP elevation, it is necessary to measure the changes in internal diameter (ID) of the vessels. Moreover, because of the proximity and interdependence of the lung and heart (MURPHY and FISHMAN, 1988), it is important to study those cardiogenic pulmonary vascular responses in the intact cardiopulmonary system. However, no direct measurement has been carried out concerning the pulmonary vascular ID response in intact animals during acute pulmonary hypertension associated with LAP elevation.

In this study, we used an X-ray TV system (SADA *et al.*, 1985) to directly measure the ID of small muscular pulmonary arteries (100–600 μm ID) which are located in the pre-capillary area (FISHMAN, 1961; SOBIN *et al.*, 1966) and are important sites to regulate blood flow to the pulmonary capillaries and veins (SADA *et al.*, 1985, 1987; SHIRAI *et al.*, 1986, 1987, 1988). We experimentally induced acute LAP elevations by inflating the balloon in the left atrium of the intact cat, and quantitatively analyzed the relation between the increase in LAP or pulmonary arterial pressure (PAP) and the ID changes in the small muscular pulmonary arteries. Our results suggested that an active contraction of vascular smooth muscle occurred with LAP and PAP in excess of 24 and 30 mmHg, respectively. Therefore, we investigated the effects of a smooth muscle relaxant and an α -blocking agent on the ID responses due to the active contraction of vascular smooth muscle.

METHODS

Experimental procedure and angiography. The experiments were carried out on 18 cats (2.7–3.4 kg body wt.). They were anesthetized with pentobarbital sodium (35 mg/kg, i.p.) and the level of anesthesia was maintained with supplemental doses of pentobarbital sodium (2–3 mg/kg, i.v.) at 0.5- to 1-h intervals. Each cat was intubated with an endotracheal tube and artificially ventilated with room air enriched with O_2 .

A catheter was introduced fluoroscopically from the right jugular vein into the left main pulmonary artery. A ballon-tip catheter was inserted directly into the left

atrium. Two additional catheters were inserted into the right femoral artery and vein. After all the catheters were positioned, partial excision of the left-side rib cage (ribs 6–8) was conducted to enable the left lower lobe (LLL) to be directly exposed to X-ray. The end-expiratory pressure was adjusted to 4.0 cmH₂O to prevent lung collapse. Heparin (500 IU/kg) was administered to prevent coagulation of blood.

The system and the experimental setup used for angiography have previously been described in detail (SADA *et al.*, 1985). Briefly, the cat was put into the X-ray apparatus box and fixed in such a manner that the exposed LLL automatically contacted the plate just above the beryllium faceplate of an X-ray-sensitive 1-in. vidicon camera (Hamamatsu Photonics). During a temporary cessation of ventilation at end expiration, the contrast medium (3.5 ml of 60% Urografin) was injected into the left main pulmonary artery at a constant speed (1.7 ml/s). Under the direct exposure of X-rays on the LLL, the passage of the contrast medium through the pulmonary vascular bed was serially recorded on a video tape recorder (model CR-850; Victor). During the experiment, the temperature in the box was maintained at 25–28°C, and the surface of the exposed lung was kept wet by warm saline at a temperature of 37°C.

Influence of contrast medium on ID of small pulmonary arteries. The influence of the contrast medium on the ID of the small pulmonary arteries was preliminarily examined following the two protocols. Initially, the effect of the repeated injection of the contrast medium on the ID of the small pulmonary arteries was measured; the contrast medium was injected three times with an interval of 7 s into the left main pulmonary arteries and each passage through the small arteries was recorded. Among the three arteriograms obtained, the ID of the small arteries was compared. Second, to check the effects of the congestion of the contrast medium in the pulmonary arteries on the ID of those vessels, the balloon-tipped catheter was wedged to the pulmonary artery and the contrast medium was injected into the peripheral side to make a wedge arteriography. The wedge arteriogram was recorded for about 10 s and the change in ID during that period was investigated. In these preliminary studies, there was no significant influence of the contrast medium on the ID of the small pulmonary arteries.

Experimental protocol. The control angiogram was first recorded, then an acute elevation of LAP was induced by altering the volume of the air within a balloon inserted into the left atrium. Following the LAP elevation, PAP was increased. In 10 of the 18 cats, PAP was increased to 21, 30, and 37 mmHg in this order. In the remaining cats, the order of PAP increase was reversed. To eliminate the influence of the preceding PAP rise on the ID of pulmonary arteries, there was an interval of about 30 min between each rise. The arteriograms during the PAP rises were recorded at the time when each rise of PAP was maintained for 3–4 min. To examine whether an active contraction of vascular smooth muscle occurred during the PAP rise, we rapidly deflated the balloon at the end of each period of the PAP rise and quickly changed the PAP from the increased level to the control level. The ID after the quick release of PAP rise was compared with the ID before

the PAP rise (control) at the same PAP level. The arteriogram after the quick release was recorded 4–7 s after each rapid balloon deflation.

Forty minutes after the above series of experiments, we studied the effects of a smooth muscle relaxant, papaverine hydrochloride, and an α -blocking agent, phentolamine, on the ID after the quick release of PAP rise. In this study the 18 animals were separated into groups 1 ($n=6$), 2 ($n=6$), and 3 ($n=6$). In every group, PAP was increased to 21 mmHg in 2 cats, to 31 mmHg in the next 2 cats, and to 37 mmHg in the remaining cats. At the end of the 3 min rise of PAP, the increased PAP was quickly released by the same technique mentioned above. Papaverine (1–2 mg/kg), phentolamine (2 mg/kg), and saline were injected directly into the pulmonary arteries 10–15 s before the quick release in groups 1, 2, and 3, respectively. The arteriogram was recorded 7–10 s after the quick release.

Measurement of ID. The serial angiograms recorded on the video tape recorder were transferred to the digital image processor (TVIP-2000; Nippon Avionics). To obtain the arteriogram for measurement of ID, four serial frames, in which arterial tree was extensively filled with contrast medium, were added and averaged by the digital image processor. The processed image was electrically transferred to the imaging hard copy unit (model 4634; Sony Tektronix) and was clearly copied on a paper. The ID of the small pulmonary arteries on the copy was manually measured by use of a digitizer (model 9874A; Hewlett-Packard) coupled with a minicomputer. Details regarding the measurement method used for ID were described previously (SADA *et al.*, 1985).

Quantitative analysis of ID response. According to the method described in our previous study (SHIRAI *et al.*, 1986), the ID of the small arteries ranging from 100 to 600 μ m in size were measured at many different sites. The percentage changes in ID during the PAP rise and after the release of PAP rise against the control values were calculated at each vascular site measured. The measured sites were classified into five vascular groups with different ID sizes according to their control ID sizes.

Statistical methods. Differences in ID values and hemodynamic data before and during the PAP rise were assessed by a paired *t*-test. Comparisons among ID values after the quick release, after the quick release with papaverine, and after the quick release with phentolamine were made by analysis of variance (ANOVA) and a modified *t*-test (WALLENSTEIN *et al.*, 1980). Differences in ID responses to a given stimulus among the five vascular groups were also determined by ANOVA and a modified *t*-test. All results were expressed as means $\pm$ S.E., and $p < 0.05$ was considered significant.

RESULTS

Hemodynamic data

Mean pulmonary arterial pressure ($\overline{\text{PAP}}$) and mean systemic arterial pressure ($\overline{\text{SAP}}$) before and during the different degrees of increases in LAP (balloon inflation)

Table 1. Hemodynamic data.

Condition	<i>n</i>	$\overline{\text{LAP}}$ (mmHg)	$\overline{\text{PAP}}$ (mmHg)	$\overline{\text{SAP}}$ (mmHg)
Control	18	5 ± 1	16 ± 1	104 ± 4
Ballon inflation in left atrium	18	$14 \pm 1^*$	$21 \pm 1^*$	98 ± 5
	18	$24 \pm 1^*$	$30 \pm 1^*$	$70 \pm 5^*$
	18	$30 \pm 1^*$	$37 \pm 1^*$	$59 \pm 5^*$

Values are mean $\pm$ S.E.; *n*, No. of animals. $\overline{\text{LAP}}$, mean left atrial pressure; $\overline{\text{PAP}}$, mean pulmonary arterial pressure; $\overline{\text{SAP}}$, mean systemic arterial pressure. * Significantly different from control ($p < 0.01$).

Fig. 1. Typical arteriograms before and during rise of pulmonary arterial pressure (PAP) are shown. PAP was increased to 21 (B), 30 (C), and 37 (D) mmHg. See text for details.

are summarized in Table 1. All those parameters were measured just before injection of the contrast medium.

After the balloon deflation, $\overline{\text{LAP}}$ and $\overline{\text{PAP}}$ rapidly returned to the control level. However, $\overline{\text{SAP}}$ significantly increased to 127 ± 5 and 142 ± 5 mmHg with the release of PAP of 30 and 37 mmHg, respectively.

The papaverine injection combined with the balloon deflation significantly reduced $\overline{\text{SAP}}$ to 57 ± 6 , 60 ± 6 , and 63 ± 6 mmHg in the cases of the release of PAP of 21, 30, and 37 mmHg, respectively. $\overline{\text{PAP}}$ and $\overline{\text{LAP}}$ were reduced to 14 ± 1 and 4 ± 1 mmHg, respectively, in all the three cases. The phentolamine injection also caused significant $\overline{\text{SAP}}$ reductions to 65 ± 5 , 67 ± 6 , and 70 ± 6 mmHg in the cases of PAP of 21, 30, and 37 mmHg, respectively. $\overline{\text{PAP}}$ and $\overline{\text{LAP}}$ were reduced to 15 ± 1 and 4 ± 1 mmHg, respectively, in those cases.

Relationship between vessel size and magnitude of ID dilation in response to PAP rise

Figure 1 shows typical arteriograms before (A) and during the PAP rises (B, C, and D) in the same cat. During PAP of 21 mmHg the dilation of the ID was slight, but during PAP of 30 and 37 mmHg apparent ID dilation occurred in many arterial branches.

The relationship between vessel size and magnitude of ID dilation caused by PAP rise are shown in Fig. 2. During PAP of 21 mmHg (solid line), there was a

Fig. 2. Percentage change in internal diameter (ID) during PAP rises to 21 (solid line), 30 (chain line), and 37 mmHg (dashed line) are shown in each of 5 vascular groups with different diameter sizes. See text for details. *Significantly different from control ($p < 0.01$). Vertical bars, S.E.

tendency for the ID to dilate; however, the dilation was not statistically significant in all the five groups with different vessel sizes. During PAP of 30 (chain line) and 37 mmHg (dashed line), the ID dilated significantly in all the five groups. The magnitude of ID dilation was not statistically different among the five groups during PAP of 21 and 30 mmHg, but during PAP of 37 mmHg it was significantly smaller in the arteries of 200–400 μm ID than in those with other vessel sizes.

Relationship between PAP level and magnitude of ID dilation

By pooling all the data in the five groups shown in Fig. 2, the relationship

Fig. 3. Relationship between magnitude of PAP rise and dilation in internal diameter (ID) is shown. See text for details. * Significantly different from control ($p < 0.01$). Vertical bars, S.E.

Fig. 4. Typical arteriograms under control condition (left) and after quick release from PAP rise (right) are shown in the same cat. See text for details.

between the PAP level and the magnitude of ID dilation was obtained for the small arteries ranging from 100 to 600 μm ID (Fig. 3).

During PAP of 21 mmHg the ID dilated by $1 \pm 1\%$ from the control ID size, but not significantly. During PAP of 30 and 37 mmHg the ID dilated significantly by 20 ± 1 and $16 \pm 1\%$, respectively. It was noted that in spite of the increase in PAP from 30 to 37 mmHg, the magnitude of ID dilation did not increase but decreased significantly. This indicated that during PAP rise from 30 to 37 mmHg, the ID was not further dilated passively depending on an increase in intravascular pressure. An active contraction of vascular smooth muscle was probably induced with this range of PAP. To examine whether there was an active contraction during the PAP rise due to LAP elevation, we employed a quick release of the PAP rise (see METHODS).

Relationship between vessel size and magnitude of ID constriction caused after quick release

Figure 4 shows typical arteriograms under a control condition (left) and 5s after the rapid deflation of the balloon (right) in the same cat. Before the balloon deflation, PAP was raised to 37 mmHg for about 3 min. After the quick release from PAP rise, we found apparent ID constrictions in many arterial branches.

The relationship between vessel size and magnitude of ID constriction caused

Fig. 5. Percentage change in ID after quick release from PAP rises to 21 (solid line), 30 (chain line), and 37 mmHg (dashed line) are shown in each of 5 vascular groups. See text for details. * Significantly different from control ($p < 0.01$). Vertical bars, S.E.

4–7 s after the quick release are summarized in Fig. 5. When PAP of 21 mmHg was returned to the control level, there was a tendency for ID to constrict; however, the constriction was not statistically significant in all the five groups. When PAP of 30 and 37 mmHg was returned to the control level, the ID significantly constricted below the control ID size in all the five groups. The magnitude of the ID constriction was statistically larger in the arteries of 200–400 μm ID than in those with other ID sizes.

Relationship between PAP level before quick release and magnitude of ID constriction caused after quick release

By pooling all data in the five groups in Fig. 5, the relationship between the preceding PAP level and the magnitude of ID constriction caused after the quick release of PAP rise was obtained for the small arteries ranging from 100 to 600 μm ID (Fig. 6).

After returning the PAP of 21 mmHg to the control level the ID constricted by $1 \pm 1\%$ from the control ID size, but not significantly. After the release of PAP of 30 and 37 mmHg, however, the ID significantly constricted by 13 ± 1 and $21 \pm 1\%$, respectively. There were significant differences among those three values. This indicated that the ID constricted in proportion to the degree of the preceding PAP rise.

Effects of papaverine and phentolamine on ID constriction caused after quick release

The ID response after the quick release of the PAP rise is compared among the papaverine (solid line), phentolamine (chain line), and saline (dashed line) groups in Fig. 7. With papaverine, the ID constriction caused after the quick release disappeared. As indicated by the solid line in Fig. 7, the ID significantly dilated by

Fig. 6. Relationship between PAP level before quick release and ID constriction after quick release of elevated PAP. See text for details. * Significantly different from control ($p < 0.01$). Vertical bars, S.E.

Fig. 7. Effects of papaverine and phentolamine on ID constriction induced after quick release of PAP rise. Solid, chain, and dashed lines indicate percentage ID changes to quick release with papaverine, those with phentolamine, and those with saline, respectively. See text for details. * Significantly different ($p < 0.01$) from ID size after quick release with saline (dashed line). Vertical bars, S.E.

24 ± 2, 23 ± 2, and 24 ± 2% from the control ID size in the cases of the release of PAP rise to 21, 30, and 37 mmHg, respectively. No significant differences were present among those three values. This indicated that the papaverine-caused ID dilation was independent of the degree of the preceding PAP rise. With phentolamine, as shown by the chain line, the ID constriction after the quick release was significantly attenuated. The magnitudes of the constriction were 0 ± 1, 5 ± 2, and 9 ± 2% with the release of PAP rise to 21, 30, and 37 mmHg, respectively. It is noted, however, that part of the constriction still persisted under the phentolamine-administered condition, and the constriction depended on the degree of the preceding PAP rise.

DISCUSSION

Using an X-ray TV system, we measured the internal diameter (ID) in the small muscular pulmonary arteries (100–600 μ m ID) of the *in vivo* cat lung. We analyzed the ID responses during the acute rise of LAP and PAP caused by the inflation of the balloon in the left atrium. In addition, we investigated the ID responses just after the quick release of such pressure rise and how those responses were affected by the administration of a smooth muscle relaxant and an α -receptor antagonist.

Responses of pulmonary vessels during acute pulmonary hypertensive state due to LAP elevation. The problem of how the pulmonary vessels respond during the acute PAP rise associated with LAP elevation has been studied indirectly by many investigators. Most of the studies (BORST *et al.*, 1956; CARLILL and DUKE, 1956;

KURAMOTO and RODBARD, 1962; LAWSON *et al.*, 1964; WEST *et al.*, 1964; KARP *et al.*, 1968; MASERI *et al.*, 1972; SHOUKAS, 1975; DAWSON *et al.*, 1986) were conducted in the isolated perfused lung. They suggested passive distension or recruitment of the pulmonary vessels in response to the pressure rise in pulmonary vessels. In the intact cardiopulmonary system, one study (HOPKINS *et al.*, 1980) suggested vascular recruitment as LAP was raised to 28.6 mmHg, whereas another (RABIN and MEYER, 1960) suggested the possibility of active pulmonary vasoconstriction with LAP above 15 mmHg.

In the present study, we considered that the ID change is better explained as an index of local vasomotor response in a given vessel than the change in calculated resistance estimated from the pressure-flow relation, in the vascular volume, or in the flow distribution. In addition, we employed the intact cardiopulmonary system rather than the isolated perfused lung with a consideration of the importance of the coordinated interactions between the heart and the lung (MURPHY and FISHMAN, 1988). The results indicated that the ID of the small muscular pulmonary arteries (100–600 μm ID) significantly dilated above the control level when PAP was increased to 30–37 mmHg in association with LAP rise to 24–30 mmHg. The magnitude of the ID dilation with PAP of 37 mmHg, however, was significantly smaller than that with PAP of 30 mmHg despite the greater pressure elevation (Fig. 3). This suggests that with PAP of 30–37 mmHg, an increase in vascular smooth muscle tone occurred in the small pulmonary arteries. In addition, we showed significant ID contractions below the control level 4–7 s after the quick release of PAP rise to 30–37 mmHg (Fig. 6). This also suggests that an active contraction occurred in the small arteries with this range of PAP.

Possible mechanisms of ID constrictor response of small pulmonary arteries during acute PAP rise above 30 mmHg. As shown in Fig. 7, the smooth muscle relaxant papaverine abolished the ID constriction due to the quick release of PAP rise and induced significant ID dilation. Thus, we assumed that the difference between the ID responses to quick release with (solid line in Fig. 7) and without (dashed line) papaverine reflects the degree of vascular smooth muscle contraction at each PAP of 21, 30, and 37 mmHg. The difference was 25, 35, and 44% at PAP before quick release of 21, 30, and 37 mmHg, respectively. There were significant differences among those three values. It is conceivable that the smooth muscle contractility of the small pulmonary arteries increased in proportion to the magnitude of PAP rise. Indeed, with PAP above 30 mmHg the ID constricted against the pressure rise (Fig. 3). It is possible that with PAP above 30 mmHg, the increase in active ID constriction due to the smooth muscle contraction exceeded the increase in passive ID dilatation due to the pressure rise.

With the alpha-receptor antagonist phentolamine, the ID constriction due to the quick release was significantly attenuated (Fig. 7). This results suggests that an activation of sympathetic nerve activity to the pulmonary vessels and/or an increase in plasma catecholamine concentration partly contributed to the active contraction of the small pulmonary arteries with PAP above 30 mmHg. Changes in baroreceptor

reflexes associated with systemic hypotension (Table 1) may mediate some part of the sympathetic activation and increased catecholamine release. It is possible that the reflex resulting from the excitation of pressoreceptive endings of the pulmonary veins (SANGER *et al.*, 1959; VAN BOGAERT and TOSETTI, 1963; LLOYD and SCHNEIDER, 1969) and of left atrial receptors (LINDEN, 1987) may increase pulmonary sympathetic nerve activity.

Under the phentolamine-treated condition, about half of the ID constriction still persisted (Fig. 7). This suggests the possibility that local mechanical factors within the lung and/or humoral factors other than catecholamines partly mediated the active contraction of the small pulmonary arteries with PAP above 30 mmHg.

Possible site of active contraction of pulmonary vessels during acute pulmonary hypertension due to LAP elevation. In the present study, we found that the ID dilation with PAP of 37 mmHg was nonuniform in the series-arranged arteries (100–600 μ m ID), and it was minimal in the arteries of 200–400 μ m ID. In addition, the ID constriction due to the quick release of the PAP rise was maximal also in the arteries of 200–400 μ m ID. Those results suggest that the magnitude of the active contraction due to the PAP rise was maximal in the arteries of this size.

The angiograms of the small veins (100–600 μ m ID) could not be recorded during PAP of 30–37 mmHg, but could be recorded just after the quick release of the PAP rise. In the obtained venograms, no significant ID changes were found as compared with the controls. The results strongly suggest that during the acute pulmonary hypertension, the active contraction of the vessels occurred chiefly in the small muscular pulmonary arteries.

Possible role of arterial ID constriction during acute pulmonary hypertension caused by LAP elevation. With PAP in excess of 30 mmHg, the ID constriction occurred mainly in the small pulmonary arteries, particularly in those of 200–400 μ m ID. This locally induced arterial vasoconstriction may serve to damp surges of output by the right ventricle and to protect, as precapillary barrier, the most vulnerable part of the pulmonary vascular bed from an excessive hydrostatic pressure.

As shown in Table 1, when PAP reached 30 mmHg, LAP was 24 mmHg (nearly the colloid osmotic pressure of the plasma). It was previously shown that with LAP above 24 mmHg significant transudation of fluid from the pulmonary capillaries occurs, but not with LAP below this value in the dog (GUYTON and LINDSEY, 1959). Considering those results together, such arterial ID constriction with PAP above 30 mmHg seems to reduce the risk of pulmonary edema.

This study was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Culture and by research grants for Cardiovascular Diseases from the Ministry of Health and Welfare, Japan.

REFERENCES

- BORST, H. G., MCGREGOR, M., WHITTENBERGER, J. L., and BERGLUND, E. (1956) Influence of pulmonary arterial and left atrial pressures on pulmonary vascular resistance. *Circ. Res.*, **4**: 393–399.
- CARLILL, S. D. and DUKE, H. N. (1956) Pulmonary vascular changes in response to variations in left auricular pressure. *J. Physiol. (Lond.)*, **133**: 275–286.
- DAWSON, C. A., RICKABY, D. A., and LINEHAN, J. H. (1986). Location and mechanisms of pulmonary vascular volume changes. *J. Appl. Physiol.*, **60**: 402–409.
- FISHMAN, A. P. (1961) Respiratory gases in the regulation of the pulmonary circulation. *Physiol. Rev.*, **41**: 214–280.
- GUYTON, A. C. and LINDSEY, A. W. (1959) Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. *Circ. Res.*, **7**: 649–657.
- HOPKINS, R. A., HAMMON, J. W., Jr., MCHALE, P. A., SMITH, P. K., and ANDERSON, R. W. (1980) An analysis of the pulsatile hemodynamic responses of the pulmonary circulation to acute and chronic pulmonary venous hypertension in the awake dog. *Circ. Res.*, **47**: 902–910.
- KARP, R. B., GRAF, P. D., and NADEL, J. A. (1968) Regulation of pulmonary capillary blood volume by pulmonary arterial and left atrial pressures. *Circ. Res.*, **22**: 1–10.
- KURAMOTO, K. and RODBARD, S. (1962) Effects of blood flow and left atrial pressure on pulmonary venous resistance. *Circ. Res.*, **11**: 240–246.
- LAWSON, W. H., Jr., DUKE, H. N., HYDE, R. W., and FORSTER, R. E. (1964) Relationship of pulmonary arterial and venous pressure to diffusing capacity. *J. Appl. Physiol.*, **19**: 381–386.
- LINDEN, R. J. (1987) The function of atrial receptors. In: *Cardiogenic Reflexes*, ed. by HAINSWORTH, R., MCWILLIAM, P. N., and MARY, D. A. S. G., Oxford University Press, New York, pp. 18–39.
- LLOYD, T. C., Jr. and SCHNEIDER, A. J. L. (1969) Relation of pulmonary arterial pressure to pressure in the pulmonary venous system. *J. Appl. Physiol.*, **27**: 489–497.
- MASERI, A., CALDINI, P., HARWARD, P., JOSHI, R. C., PERMUTT, S., and ZIERLER, K. L. (1972) Determinants of pulmonary vascular volume. Recruitment versus distensibility. *Circ. Res.*, **31**: 218–228.
- MURPHY, M. F. and FISHMAN, A. P. (1988) Pulmonary disorders produced by cardiac disease. In: *Pulmonary Diseases and Disorders*, 2nd ed., ed. by FISHMAN, A. P., New York, McGraw-Hill, Vol. 2, pp. 1103–1126.
- RABIN, E. R. and MEYER, E. C. (1960) Cardiopulmonary effects of pulmonary venous hypertension with special reference to pulmonary lymphatic flow. *Circ. Res.*, **8**: 324–335.
- SADA, K., SHIRAI, M., and NINOMIYA, I. (1985) X-ray TV system for measuring microcirculation in small pulmonary vessels. *J. Appl. Physiol.*, **59**: 1013–1018.
- SADA, K., SHIRAI, M., and NINOMIYA, I. (1987) Effects of prostaglandin $F_{2\alpha}$ and prostacyclin on pulmonary microcirculation in the cat. *J. Appl. Physiol.*, **62**: 1124–1132.
- SANGER, P. W., ROBICSEK, F., TAYLOR, F. H., MAGISTRO, R., and FOTI, E. (1959) Observations on pulmonary vasomotor reflexes. *J. Thorac. Surg.*, **37**: 774–782.
- SHIRAI, M., SADA, K., and NINOMIYA, I. (1986) Effects of regional alveolar hypoxia and hypercapnia on small pulmonary vessels in cats. *J. Appl. Physiol.*, **61**: 440–448.
- SHIRAI, M., SADA, K., and NINOMIYA, I. (1987) Nonuniform effects of histamine on small

- pulmonary vessels in cats. *J. Appl. Physiol.*, **62**: 451-458.
- SHIRAI, M., SADA, K., and NINOMIYA, I. (1988) Diameter and flow velocity changes in small pulmonary vessels due to microembolization. *J. Appl. Physiol.*, **65**: 288-296.
- SHOUKAS, A. A. (1975) Pressure-flow and pressure-volume relations in the entire pulmonary vascular bed of the dog determined by two-port analysis. *Circ. Res.*, **37**: 809-818.
- SOBIN, S. S., INTAGLIETTA, M., FRASHER, W. G., and TREMER, H. M. (1966) The geometry of the pulmonary microcirculation. *Angiology*, **17**: 24-30.
- VAN BOGAERT, A. and TOSETTI, R. (1963) Experimental pulmonary hypertension. *Br. Heart J.*, **25**: 771-783.
- WALLENSTEIN, S., ZUCKER, C. L., and FLEISS, J. L. (1980) Some statistical methods useful in circulation research. *Circ. Res.*, **47**: 2-9.
- WEST, J. B., DOLLERY, C. T., and NAIMARK, A. (1964) Distribution of blood flow in isolated lung; Relation to vascular and alveolar pressures. *J. Appl. Physiol.*, **19**: 713-724.