PULMONARY ARTERIAL FLOW-PRESSURE CHARACTERISTICS IN DOGS

— Effects of Hypoxia and Nitroglycerin —

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To investigate the effects of hypoxia and nitroglycerin on pulmonary vascular tone, multipoint mean pulmonary arterial flow-pressure (Q-P relationship) plots were constructed by producing stepwise increments of pulmonary flow with a roller pump installed in a right ventricle-pulmonary artery shunt in 12 mongrel dogs under pentobarbital sodium anesthesia. The normal Q-P relationship was convex to the pressure axis when pulmonary flow was 0–0.2 L/min, but it became linear when pulmonary flow was over 0.2 L/min. The slopes and pressure intercepts extrapolated (PAPI) from linear regression fits to the linear parts of the Q-P relationship were determined to compare the effects of hypoxia and nitroglycerin on pulmonary vascular tone. Hypoxic ventilation ($F_{I}O_2$: 0.1) increased the slope from 8.3 ± 3.3 to 12.5 ± 3.6 mmHg/L ($p < 0.01$), with no significant effect on PAPI. Nitroglycerin ($1 \mu\text{g}/\text{min}/\text{kg}$ as a continuous infusion) decreased the slope from 8.9 ± 4.4 to 5.8 ± 2.6 mmHg/L ($p < 0.05$), again with no significant effect on PAPI. The results suggest that hypoxia and nitroglycerin, respectively, increased and decreased incremental pulmonary vascular resistance upstream to the site of pulmonary vascular closure.

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SEVERAL recent studies have employed the Q-P relationship of the pulmonary circulation in order to properly evaluate the direct pulmonary vascular effects of physiological, pathophysiological, and pharmacological stimuli on it,^{1–4} because changes in the Q-P relationship can provide information for separating the active and passive responses of the pulmonary vasculature.⁵ Hypoxia and nitroglycerin is one of the most prominent vasoactive stimulus for the pulmonary vasculature.^{6–9} The changes of the

Q-P relationship during hypoxic ventilation have already been reported in several studies.^{2,3} However, there was no general agreement as to the magnitude of the change in the Q-P relationship induced by hypoxia. Although nitroglycerin is well known to decrease pulmonary artery pressure, there are few studies concerning the effects of nitroglycerin on the Q-P relationship. Our objective in this study was to develop a technique for generating detailed multipoint pulmonary vascular flow-pressure plots in an experimental model to quantify the magnitude of the hypoxic pulmonary vasoconstriction (HPV) response and the active vascular effects of nitroglycerin on the pulmonary

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Fig.1. Diagram of the in situ experimental preparation. The lungs remained in the widely-opened chest cavity of supine dog. Constant pulmonary shunt flows were generated with a roller pump. Arrows indicate the direction of pulmonary shunt flow RAP, pulmonary arterial pressure in the shunt circuit; Q, pulmonary shunt flow; LAP, left atrial pressure; PAW, airway pressure; FO_2 , oxygen fractional concentration; FCO_2 , carbon dioxide fractional concentration; PEEP, positive end-expiratory pressure; RA, right atrium; RV, right ventricle; PA, pulmonary artery; LA, left atrium; LV, left ventricle; Ao, aorta.

circulation.

MATERIALS AND METHODS

Surgical preparation

Twelve mongrel dogs weighing 9–12 kg were anesthetized with sodium pentobarbital (30–35 mg/kg, iv), and placed on positive-pressure ventilation (5 cm H_2O) using a volume-type ventilator and a cuffed endotracheal tube. The respiratory rate was 16–20 breaths/min and the tidal volume was 15–20 ml/kg, and was adjusted to maintain an arterial PCO_2 between 38–42 Torr. Additional intravenous doses of pentobarbital (4–8 mg/kg) were given as necessary to maintain anesthesia and prevent spontaneous respiratory efforts. If metabolic acidosis occurred, it was corrected with a slow infusion of a sodium bicarbonate solution.

Fig.1 illustrates the surgical procedures and the perfusion circuit. After a central thoracotomy and pericardiotomy were performed using sterile surgical techniques, a cannula was inserted into the right ventricle

Fig.2. Actual tracings of pulmonary arterial pressure in the shunt circuit (PAP), pulmonary shunt flows (Q), and mean left atrial pressure (LAP) at different flow rates recorded during room air ventilation.

through an incision in the right atrial appendage and connected to the inflow side of the perfusion roller pump. Then the right pulmonary artery was cannulated through a small incision in the pulmonary artery trunk using a silicon tube. This cannula was connected to the outflow of the wind kessel and bubble trap which contained 5–8 ml of air to damp flow pulsations. After the perfusion pump, a wind kessel and electromagnetic flowmeter (Nihon Koden Co., Tokyo) were connected in series, the right pulmonary artery was ligated to make an independent shunt circuit from the pulmonary circulation and this circuit was perfused with autologous blood using the roller pump (pulmonary shunt flow). The procedures were performed with the heart still beating and the circulation still functioning under normal physiological conditions. A femoral cutdown was performed for cannulation of the femoral artery and to allow drug administration via the femoral vein. For measurement of the left atrial pressure, a polyethylene catheter was also placed into the left atrial appendage. Sodium heparin (50 U/kg) was administered intravenously to prevent clot formation and the same dose was given every hour thereafter. Temperature was maintained at 37–38 °C by means of an electrical heating pad.

Physiological measurements

Pulmonary arterial pressure in the shunt

Fig. 3. Multipoint plot of pulmonary arterial pressure in the shunt circuit (PAP) versus pulmonary shunt flow (Q) for a single dog during room air ventilation (Q-P relationship). The Q-P relationship is generally linear and is well described by the respective regression equation.

circuit (PAP) as well as the left atrial and aortic pressures were measured from the implanted catheters attached to a P23Db Statham transducer. All pressures in this study were measured at the hydrostatic level of the center of the right atrium. Pulmonary shunt flow (Q) was measured with an electromagnetic flowmeter. Inspired and expired gas concentrations were monitored continuously using a mass-spectrometer (MGA 1100B; Perkin Elmer Medical Instruments, Pomona, California). Atrial blood gases were measured with an IL1303 blood gas analyzer (Instrument Laboratory Inc., Lexington).

Experimental measurements

After ensuring steady-state conditions had been reached, multipoint pulmonary arterial flow-pressure relationship (Q-P relationship) plots were constructed by making stepwise changes of Q using the roller pump and measuring PAP. The range of Q was from 0 L/min to about 1.0 L/min and each stepwise increment was about 0.1 L/min. The Q-P relationship was first determined for room air ventilation and then for hypoxic ventilation ($F_{I}O_2=0.1$) in 7 animals to evaluate the effect of HPV on the pulmonary circulation. In 8 dogs, the Q-P relationship was determined both for room air ventilation and following the intravenous administration of nitroglycerin ($1 \mu\text{g}/\text{min}/\text{kg}$) to evaluate the

Fig. 4. The control state and the changes in pulmonary arterial pressure in the shunt circuit (PAP) produced by hypoxia. Hypoxia caused an increase in PAP at every level of pulmonary shunt flow (Q), except when Q was 0 L/min. Values are the means $\pm$ SE. $n=7$

effect of vasodilator.

Data analysis

Actual tracings of PAP, Q, and left atrial pressure recorded with room air ventilation are shown in Fig. 2. From the values obtained with each increment in Q, PAP was plotted as a function of Q. The linearity of the individual Q-P relationship was visually assessed throughout the range of pressures and flows studied. To compare the effects of nitroglycerin and HPV, least-squares regression analysis was used to compute the slopes and extrapolated pressure intercepts (PAPI) for the linear part of each Q-P relationship as shown in Fig. 3, and the results were presented as the mean $\pm$ SD. Student's t-test for paired comparisons was used to assess the effects of hypoxia and nitroglycerin on baseline hemodynamics.

RESULTS

The pulmonary arterial Q-P relationship

Pulmonary shunt flow was manipulated between values of 0 to about 1 L/min. With room air ventilation and a shunt flow of 0 to 0.2 L/min, the Q-P relationship was convex to the pressure axis, but it became linear when pulmonary flow was over 0.2 L/min. Under control conditions, the slope was $8.61 \pm 3.83 \text{ mmHg}/\text{L}/\text{min}$ and PAPI was $12.5 \pm 4.29 \text{ mmHg}$. Pulmonary pressure was

Fig. 5. Effect of hypoxia on the Q-P slope [left] and PAPI [right]. Each symbol identifies one dog. Hypoxia increased the slope significantly ($p < 0.01$), but it had no effect on PAPI.

Fig. 6. The control state and the changes in pulmonary arterial pressure in the shunt circuit (PAP) produced by the intravenous administration of nitroglycerin. Nitroglycerin caused a decrease in PAP at every level of pulmonary shunt flow (Q). Values are the means $\pm$ SE. $n = 8$

not 0 mmHg, but was 5.79 ± 3.44 mmHg, at a flow rate of 0 L/min. Left atrial pressure was almost constant during the changes in flow and seemed to have no effect on the P-Q relationship.

Effect of HPV on the pulmonary circulation

Administration of a hypoxic gas mixture decreased the PaO_2 from 93.8 ± 11.7 Torr to 38.8 ± 5.23 Torr, while the PaCO_2 and pH remained unchanged. The effect of hypoxic ventilation was to produce an elevation in

pulmonary arterial pressure over the range of flows studied. Left atrial pressure was almost constant. Consequently, the Q-P relationship was shifted upward (Fig. 4), but the linearity of the Q-P relationship was preserved during hypoxia. The slope before hypoxic ventilation was 8.3 ± 3.3 mmHg/L/min and 12.5 ± 3.6 mmHg/L/min after hypoxic ventilation ($p < 0.01$). PAPI before hypoxic ventilation was 11.9 ± 5.1 mmHg and 11.9 ± 5.8 mmHg/L/min after hypoxic ventilation. This change was not significant (Fig. 5). Thus, the increase in the Q-P relationship resulted from an increase in the slope and seemed to indicate clearly active pulmonary vasoconstriction.

Effect of nitroglycerin on the pulmonary circulation

Left atrial pressure was almost constant. Nitroglycerin caused a downward shift of the Q-P relationship, but its linearity was also preserved during the continuous infusion of this agent (Fig. 6). The slope before nitroglycerin infusion was 8.9 ± 4.4 mmHg/L/min and 5.8 ± 2.6 mmHg/L/min after the infusion ($p < 0.05$). The PAPI before nitroglycerin infusion was 13.1 ± 3.7 mmHg and it was 11.9 ± 4.8 mmHg/L/min after the infusion. This change was not significant (Fig. 7). The change of the slope showed the active vasodilatory effect of nitroglycerin on the pulmonary circulation.

Fig.7. Effect of nitroglycerin on the Q-P slope [left] and PAPI [right]. Each symbol identifies one dog. Nitroglycerin decreased the slope significantly ($p < 0.05$), but it had no effect on PAPI.

DISCUSSION

Determination of the nature of pulmonary hemodynamics under normal conditions is important to help in understanding the pathophysiological changes of the pulmonary circulation in patients with cardiopulmonary disease and to evaluate the effects of pharmacological agents. It has been recognized previously that analyzing the Q-P relationship is one of the most important methods for studying the pulmonary circulation.¹⁰ There have been several studies published concerning the Q-P relationship.^{1,8,10-14} These studies generally showed that the Q-P relationship of the pulmonary circulation was linear over the physiological range of flow, while when flow was very low ($Q < 0.2$ L/min in our study) it became convex to the pressure axis (Fig. 3). In some reports, the Q-P relationship was not found to pass through the origin.^{1,11,13} There have been many hypotheses about the cause of the convex part of the Q-P relationship and it has generally been ascribed to either the recruitment of vessels or the distensibility of vessels.^{15,16} The concept of critical closing pressure^{12,17} was also introduced to explain why the Q-P relationship was convex and did not pass through the origin.^{1,8,18} However, the most important finding in these studies is that the Q-P relationship is linear over the physiological range of flow, indicating that pulmonary vascular tone is nearly constant

under normal conditions.¹⁹

Pulmonary vascular resistance (PVR) is calculated as the mean pulmonary pressure minus the pulmonary capillary wedge pressure, or as the mean left atrial pressure divided by the cardiac output, and is believed to represent the tone of the pulmonary vasculature. It has also been considered that as pulmonary arterial pressure increased there was a rapid reduction of the PVR.²⁰ Thus, there is a discrepancy between the Q-P relationship and the PVR calculated for the physiological range of flow. Graham et al¹ recently emphasized that this phenomenon is a pure artifact of the calculation of PVR, because the Q-P relationship in the pulmonary circulation is not linear and does not pass through the origin. Thus, to evaluate the pulmonary vascular tone using PVR is misleading in many clinical and experimental circumstances. A change of this so-called resistance does not necessarily indicate a change of vasomotor tone in the pulmonary vasculature. Accordingly, in this study we computed Q-P slopes (equivalent to the vascular resistance) and extrapolated pressure intercepts (PAPI, equivalent to the resistance-weighted mean of the critical closing pressure of the entire pulmonary vascular bed) for each linear segment of the Q-P relationship to obtain a representation of pulmonary vascular tone.

Though this idea is theoretically sound, it is difficult to actually obtain a multipoint

Q-P relationship in the clinical experimental situation without affecting the pulmonary vasculature itself. Recently, Lodato et al² used graded IVC constriction to generate multipoint Q-P relationship plots in the conscious dog. However, though there was little damage to the pulmonary circulation produced by their method, only five points were obtained to construct the Q-P relationship. Our experimental preparation used in this study has two advantages for the construction of Q-P relationship plots. First, a true multipoint plot (every 0.1 L/min of pulmonary flow) could be obtained. Second, there was little damage to the pulmonary vasculature, because pulmonary blood flow was not stopped during setting up of the experimental circuit.

Pulmonary arterial Q-P relationship

The shape of the Q-P relationship obtained was almost the same as that found in former studies performed on isolated lungs^{1,13} and intact conscious dogs² but our Q-P relationship had a slightly steeper slope and a higher PAPI (range: 6.82–19.47 mmHg) than previously reported in spontaneously breathing dogs. The reason for this discrepancy is not clear, but the cause of this difference may be due to factors such as differences in surgical manipulations, the suppression of the normal pulsatility of pulmonary circulation or the changes of pH, mixed venous PO₂, neurohumoral activity and activation of the baroreflex influence on pulmonary vascular tone. However, previous studies have indicated that small changes in pH and PCO₂ would have little, if any, effect on the pulmonary vasomotor tone.²¹

Hypoxia

It has become apparent that HPV is one of the most prominent mechanisms that acts as a vasoconstrictor in the pulmonary vasculature. We could not determine the mechanism of HPV in our experimental model. However, we could quantify the magnitude of HPV using the changes of the Q-P relationship. It was found that PAP was elevated at every level of Q, except at extremely low flow rates ($Q < 0.1$ L/min), and the more that Q increased, the greater was the degree of PAP elevation. This increase in

the Q-P relationship was mainly the result of an increase in the steepness of its slope. (The slope before hypoxic ventilation was 8.3 ± 3.4 mmHg/L/min and it was 12.5 ± 3.6 mmHg/L/min after hypoxic ventilation, showing an average increase of 68.5% (Fig. 5)).

Concerning the site of vasoconstriction during HPV, the increase in the Q-P slope may be taken to indicate the constriction of perfused pulmonary vessels and/or the complete closure of some of the vessels previously perfused during normoxia, and the increase of PAPI may be explained as representing an increase in the "critical closing pressure" of the pulmonary vessels? Accordingly, our results indicated that the main site of HPV in the pulmonary circulation was different from that producing "critical closing pressure".

Our finding that only the Q-P slope was increased by HPV appears to differ from that of a previous study² in which hypoxia affected the Q-P relationship by producing variable increases in both the slopes and PAPI. This difference could be due to the effects of the artificial perfusion systems used or some other methodological differences (e.g., open chest vs. closed chest, or spontaneous vs. mechanical ventilation).

Nitroglycerin

Nitroglycerin is one of the most potent vasodilators that is widely used to treat many pulmonary hypertensive states and decrease pulmonary arterial pressure. But it is also well known that nitroglycerin also acts on systemic vessels to decrease venous return and so decrease pulmonary arterial pressure. In addition, pulmonary arterial pressure may vary spontaneously by as much as 22% under normal conditions and by 36% in patients with pulmonary hypertension.²² Thus, though the proof that nitroglycerin dilates a constricted pulmonary vasculature was obtained previously, the extent to which nitroglycerin actively dilates the pulmonary vessels is uncertain. The unique feature of our study was the use of the Q-P relationship to assess the effect of nitroglycerin. We found that during the continuous administration of nitroglycerin ($1 \mu\text{g}/\text{min}/\text{kg}$), the Q-P relationship shifted downwards. As the main cause of this change was a decrease of the

slope (the average decrease was 31.0% after nitroglycerin), it demonstrated the direct action of nitroglycerin on the pulmonary vascular bed, because the Q-P slope appears to represent the vascular resistance itself. Thus, we were able to demonstrate a specific vasodilatory effect of nitroglycerin on the pulmonary vasculature that was independent of any effect on cardiac output. It would seem to be possible to compare the effects of other vasodilators accurately by using the Q-P slope.

It is also interesting that nitroglycerin decreased the Q-P slope but no effect on the PAPI. This seems to show that nitroglycerin acted at a special site in the vasculature. Analyzing the Q-P slopes may help to find one of the mechanisms by which vasodilators act on the pulmonary vascular bed.

In conclusion, in our experimental model the Q-P relationship of the pulmonary vasculature was linear over the physiological range of flows studied, but when flow was very low it became convex to the pressure axis. We also found that HPV increased and nitroglycerin decreased the slope of the Q-P relationship without affecting PAPI. We believe that our experimental model can be utilized to investigate and to quantify the effects of various physiological and pharmacological interventions on pulmonary vascular tone.

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