Respiratory Gas Tensions of Thoracic Duct Lymph:

An Index of Gas Exchange in Splanchnic Tissues

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STUDIES of respiratory gas tensions in blood have helped clarify the relationship between alveolar ventilation, cardiac output and blood flow through major organs. Ultimately, however, cellular viability depends on microcirculatory dynamics and gas exchange in tissues outside the vascular compartment. Artificial or *in vitro* technics to measure oxygen and carbon dioxide in living tissues are limited. Excision injures tissues or impairs blood supply to cells which then utilize oxygen factitiously from the surrounding atmosphere and accumulate carbon dioxide through continued metabolism.[17] In 1823, Davy[9] estimated extracellular oxygen tension by periodic sampling of an artificial air bubble in the pleural space. With slight modification, the gas pocket is still a popular method for measuring tissue oxygen,[2, 6, 10, 13, 15, 18, 22] but it is not applicable when changes in tissue oxygen are rapid.

The cellular exchange of oxygen and carbon dioxide depends on the gradient of partial pressures of these dissolved gases between plasma and interstitial fluid which governs diffusion of the gases through tissue fluid or lymph. Since interstitial fluid from the splanchnic area is transported mainly by the thoracic duct as lymph,[23] studies were performed in patients and experimental animals to determine whether or not gas tensions of thoracic duct lymph reflect oxygen and carbon dioxide exchange between blood and splanchnic tissues. The effects of variations in splanchnic blood flow, oxygen consumption and pH on PO_2 and PCO_2 in thoracic duct lymph were determined.

Methods

Twenty-two mongrel dogs (10–15 Kg.) were anesthetized with intravenous pentobarbital (24 mg./Kg.). Respirations were controlled with succinylcholine and endotracheal positive pressure ventilation. In some animals supplemental oxygen was administered at constant rate and content. The thoracic duct was exposed in the right chest and cannulated with polyethylene tubing. The spleen was removed and the portal vein was cannulated via the splenic vein. The right atrium, hepatic vein and aorta were cannulated via the femoral vein, the external jugular vein and the femoral artery respectively. Splanchnic blood flow (SBF) was measured by square-wave electromagnetic flow meters on the hepatic and superior mesenteric arteries and recorded on a four-channel direct-writing Grass polygraph. Splanchnic oxygen consumption (SOC) was calculated by the Fick prin-

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ciple: SOC = oxygen content (aorta − hepatic vein ml./L.) × splanchnic blood flow (L./min.). All samples of blood and lymph were collected anaerobically and gas content was measured with an Instrumentation Laboratory gas analyzer utilizing a Clark electrode polarograph,[7, 8] a PCO_2 Severinghaus glass electrode[19] and glass electrode pH meter. PO_2 determinations were corrected for pH and temperature, and oxygen saturation calculated according to the Severinghaus nomogram based on shifts in the oxygen dissociation curve.

Experimental conditions were varied as follows: 1) altering the oxygen content of inspired air using 6%, 10%, and 100% oxygen balanced with nitrogen; 2) changing splanchnic blood flow by induced cardiac standstill, occlusion of the hepatic and superior mesenteric arteries, and rapid hemorrhage to a blood pressure of 40 mm./Hg; 3) altering metabolic activity of splanchnic viscera with intravenous sodium cyanide and glucagon; and 4) observing the Bohr effect or shift of oxygen dissociation curve caused by alkalosis ($NaHCO_3$) and acidosis (NH_4Cl).

Samples of thoracic duct lymph were also obtained from 12 patients undergoing thoracic duct cannulation for diagnostic or therapeutic purposes. The thoracic duct was cannulated in the neck under local anesthesia. Seven patients had cirrhosis of the liver, two severe congestive heart failure, two had rheumatic valvular heart disease without circulatory congestion, and one had hepatic fibrosis and cholestasis with deranged liver functions. Blood samples were obtained from the femoral artery, vena cava or right atrium and at times from the portal vein. These samples and thoracic duct lymph were analyzed for PO_2, PCO_2 and pH in six patients with cirrhosis after intravenous administration of either vasopressin or glucagon, in one patient with severe congestive failure after intravenous administration of metaraminol and in one patient with intrahepatic cholestasis and fibrosis after administration of 100% oxygen by nasal catheter.

TABLE 1. *Effect of Changes in Splanchnic Blood Flow and Oxygen Administration on PO_2 (mm. Hg) in Arterial and Venous Blood and Thoracic Duct Lymph. Data Expressed as the Average Maximum Deviation from Control*

Subjects	No.	Procedure	PO_2 Artery	PO_2 Right Atrium	PO_2 Thoracic Duct Lymph
Dogs	3	Control	83	33	51
		I.V. Pentobarbital (cardiac arrest)	+11, −12	−12	−47
Dogs	2	Control	98	38	61
		Ligation of hepatic and superior mesenteric arteries	+5, −10	−8	−53
Dogs	4	Control	110	40	66
		Hemorrhage to B.P. of 40 mm. Hg	+23, −12	+2	−42
Dogs	3	Control	75	42	50
		100% O_2	+500	+25	+75
		10% O_2	−30	−20	−16
		6% O_2	−60	−35	−42
Patient with cholestasis and hepatic fibrosis		Control	68	22	18
		100% O_2*	+108	+9	+60
Patient with severe congestive heart failure		Control*	150	40	32
		Metaraminol*	+8, −30	−18	−9

* 100% O_2 via nasal catheter.

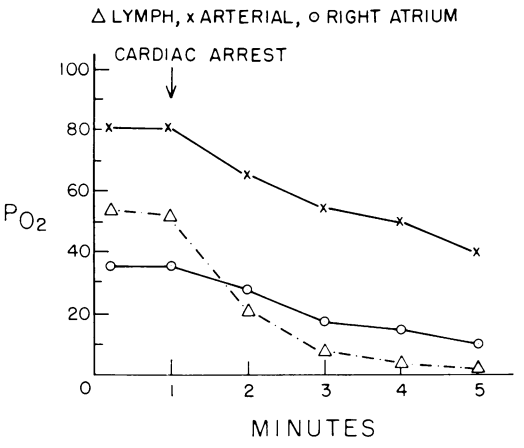

FIG. 1. Effect of induced cardiac standstill in dog on PO_2 in blood and thoracic duct lymph. This figure is representative of three experiments. Thoracic duct lymph PO_2 is normally higher than venous PO_2.

Results

In control samples of thoracic duct lymph PO_2 normally ranged from 55–60 mm./Hg in patients and 45–55 mm./Hg in dogs (contrasted with an earlier report[4]). The peak effects on lymph PO_2 in 12 dogs and two patients after changes in splanchnic blood flow and oxygen administration are shown in Table 1. In five dogs, after either induced cardiac arrest or clamping the hepatic and superior mesenteric arteries, thoracic duct lymph PO_2 progressively decreased with only a moderate diminution in the oxygen content of central venous blood. A similar sequence occurred in four dogs during hemorrhagic shock produced by rapid bleeding to a blood pressure of 40 mm./Hg. Characteristic responses are reproduced in Figures 1, 2, 3.

Varying oxygen composition of inhaled air with 6%, 10% and 100% oxygen with balanced nitrogen for 3–4 minutes in three dogs evoked an immediate (within 20–30 seconds) change in lymph PO_2 which paralleled the change in arterial oxygen tension (Fig. 4). A similar change occurred after 100% oxygen was administered to the patient with hepatic fibrosis and cholestasis.

The effect of changes in pH, oxygen consumption and splanchnic blood flow on

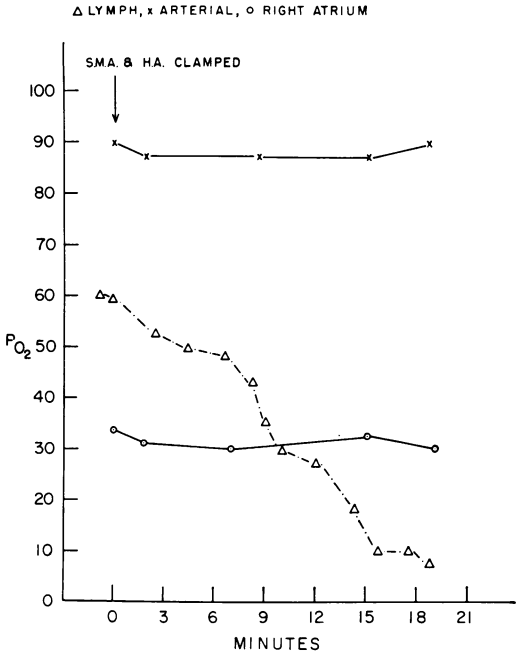

FIG. 2. Effect of ligation of superior mesenteric and hepatic arteries in dog on PO_2 in blood and thoracic duct lymph. This figure is representative of two experiments.

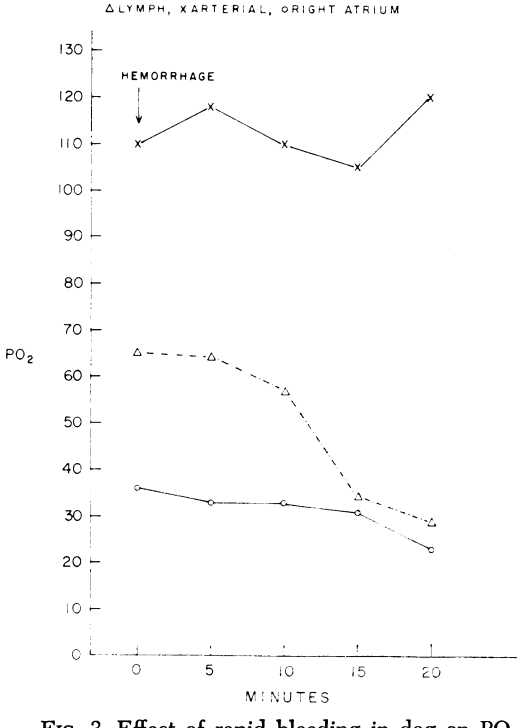

FIG. 3. Effect of rapid bleeding in dog on PO_2 in blood and thoracic duct lymph. This figure is representative of four experiments.

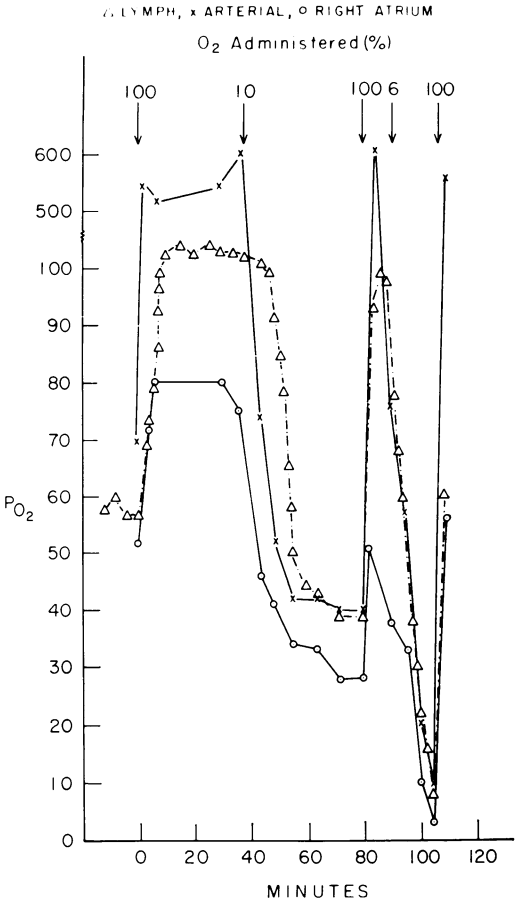

FIG. 4. Effect on PO_2 in blood and thoracic duct lymph in dog after changing the oxygen content of inspired air using 6%, 10%, and 100% oxygen with balanced nitrogen. This figure is representative of three experiments.

respiratory gases in arterial and venous blood and thoracic duct lymph are shown in Tables 2 and 3. Infusion of large amounts (44 mEq.) of sodium bicarbonate transiently changed splanchnic blood flow and oxygen consumption in three dogs; yet progressive decrease in lymph PO_2 was characteristic. The initial loading dose of bicarbonate caused a temporary rise in blood flow and venous PO_2, widening of the pulse pressure but lowering of the lymph PO_2 (Fig. 5). Acidosis which followed 44 mEq. NH_4Cl intravenously, on the other hand, in three dogs failed to influence splanchnic gas exchange consistently despite pH values as low as 6.9. Only transient alterations in splanchnic blood flow and oxygen consumption, blood gases and lymph gas tensions were observed (Fig. 6).

Characteristic changes in lymph gas tensions in response to variations in splanchnic blood flow and splanchnic oxygen consumption are shown in Figures 7–11. Intravenous sodium cyanide (0.5 mg./Kg.), a cytochrome enzyme inhibitor, raised lymph PO_2 and regional blood flow and lowered PCO_2 (Fig. 7). Intravenous glucagon (0.03 mg./Kg.) which increases oxygen consumption, raised splanchnic oxygen consumption and splanchnic blood flow but lowered lymph PO_2, pH and raised PCO_2 (Fig. 8).

Extremely low values of PO_2 in lymph were occasionally found in patients with

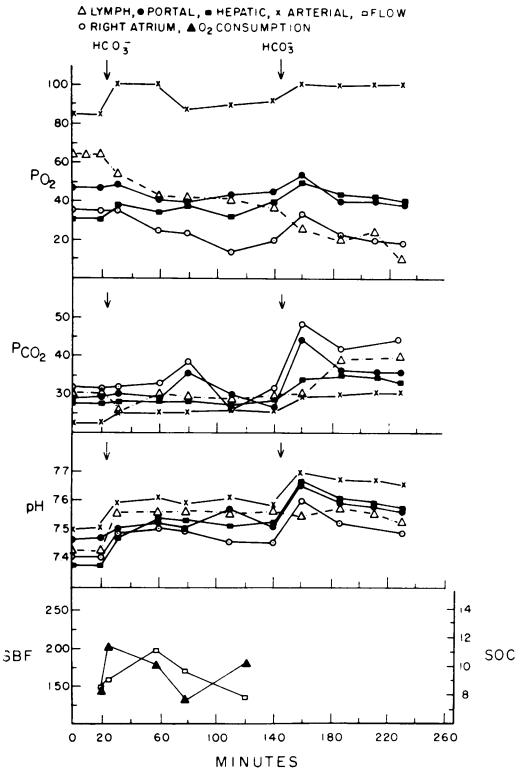

FIG. 5. Effect of sodium bicarbonate administration in dogs on splanchnic blood flow and oxygen consumption on PO_2, PCO_2 and pH in blood and thoracic duct lymph. This figure is representative of three experiments.

TABLE 2. *Effect of Changes in pH on Respiratory Gases (mm. Hg) in Arterial and Venous Blood and Thoracic Duct Lymph. Data Expressed as the Average Maximum Deviation from Control (pre-)*

Subject	No.	Agent	Sample	PO_2 Pre	PO_2 Post	PCO_2 Pre	PCO_2 Post	pH Pre	pH Post
Dogs	3	NH_4Cl	Artery	100	−12	22	−2	7.42	−0.52
			Right Atrium	30	+3, −4	29	+15	7.39	−0.53
			Hepatic Vein	40	−10	25	+8	7.42	−0.53
			Portal Vein	39	+15	27	+8	7.40	−0.62
			Thoracic duct lymph	43	+12	25	+15	7.40	−0.51
Dogs	3	$NaHCO_3$	Artery	99	+20	26	+8	7.52	+0.21
			Right Atrium	27	+7, −3	34	+16	7.41	+0.14
			Hepatic Vein	36	+8, −7	33	+13	7.50	+0.15
			Portal Vein	46	+7, −8	32	+14	7.44	+0.14
			Thoracic duct lumph	52	−33	34	+5	7.46	+0.07

advanced hepatic disease (Fig. 9) and in those with severe congestive heart failure. In five patients with cirrhosis, 20 units of vasopressin administered intravenously over 10-minute periods produced a fall in PO_2 and pH and a rise in PCO_2 in lymph (Fig. 10). In one patient with cirrhosis glucagon caused a fall in lymph PO_2 similar to that in experimental animals (Fig. 11).

Discussion

Fifty years ago Starling specifically emphasized the role of lymph in tissue gas exchange: "The physical diffusion of oxygen and carbon dioxide between capillaries and cells involves not only passage across capillary endothelium and cell wall but through intervening tissue fluid or lymph. Dissociation of oxygen from hemoglobin at the arteriolar end of the capillary de-

TABLE 3. *Effect of Agents Altering Splanchnic Blood Flow and Splanchnic Oxygen Consumption on Respiratory Gases (mm. Hg) and pH in Arterial and Venous Blood and Thoracic Duct Lymph. Data Expressed as the Average Maximum Deviation from Control (pre-)*

Subjects	No.	Agent	Splanchnic Blood Flow (ml./min.) Pre	Splanchnic Blood Flow (ml./min.) Post	Splanchnic O_2 Consumption (ml. O_2/min.) Pre	Splanchnic O_2 Consumption (ml. O_2/min.) Post	Sample	PO_2 Pre	PO_2 Post	PCO_2 Pre	PCO_2 Post	pH Pre	pH Post
Dogs	2	NaCN	165	+168	10.8	−6.2							
							Artery	85	+10	22	−6	7.46	+0.02, −0.03
							Right Atrium	29	+6	29	−9	7.42	+0.01, −0.04
							Hepatic	38	+17	25	+2, −6	7.44	−0.04
							Portal Vein	37	+11	25	−3	7.45	+0.03, −0.06
							T.D. lymph	48	+22	31	−17	7.45	+0.03, −0.06
Dogs	2	Glucagon	195	+380	11.6	+9.8							
							Artery	90	−15	27	−4	7.45	−0.04
							Right Atrium	38	−13	29	+6	7.40	−0.09
							Hepatic Vein	41	+5, −5	25	+3	7.42	+0.02, −0.06
							Portal Vein	36	+25, −5	30	+2, −5	7.40	+0.04, −0.02
							T.D. lymph	52	−23	24	+14	7.39	+0.03, −0.12
Patient with Cirrhosis	1	Glucagon					Artery	62	−3	26	+3	7.50	−0.06
							Right Atrium	35	+2, −2	22	+8	7.48	−0.03
							T.D. lymph	36	−18	24	+10	7.46	−0.03
Patients with Cirrhosis	5	Vaso-pressin					Artery	66	+4, −7	29	+9	7.46	+0.05, −0.09
							Right Atrium	32	−4	30	+11	7.39	+0.03, −0.09
							Portal Vein*	40	−10	25	+2	7.29	+0.03, −0.03
							T.D. lymph	41	−21	33	+9	7.48	+0.01, −0.12

* Samples obtained from umbilical vein in two patients.

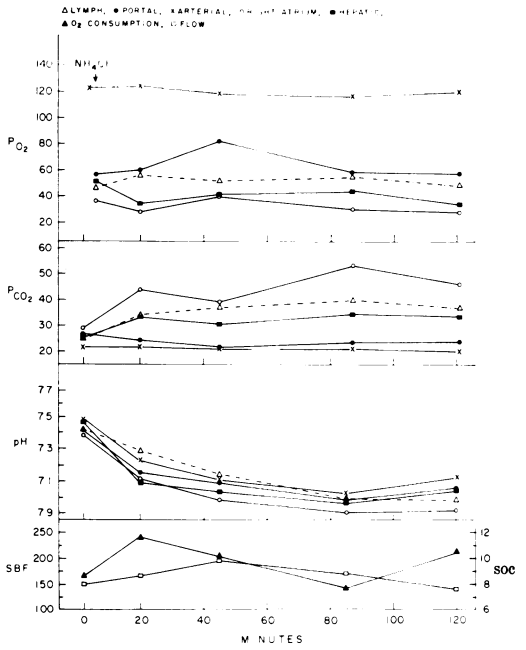

FIG. 6. Effect of ammonium chloride administration in dog on splanchnic blood flow and oxygen consumption on PO_2, PCO_2 and pH in blood and thoracic duct lymph. This figure is representative of three experiments.

pends on lowering of the partial pressure of oxygen in plasma at that point. The extent of this lowering is directly determined

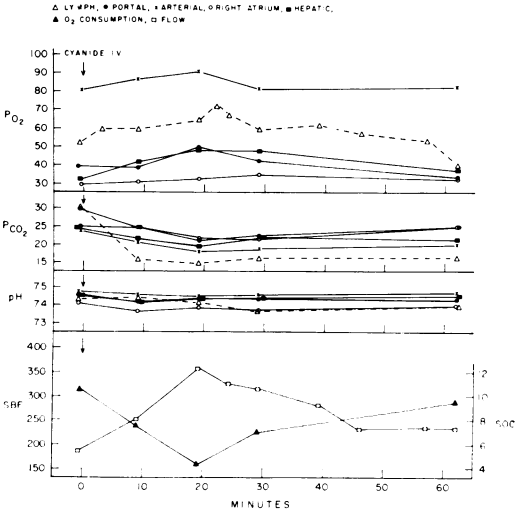

FIG. 7. Effect of sodium cyanide administration in dog on splanchnic blood flow and oxygen consumption on PO_2, PCO_2 and pH in blood and thoracic duct lymph. This figure is representative of two experiments.

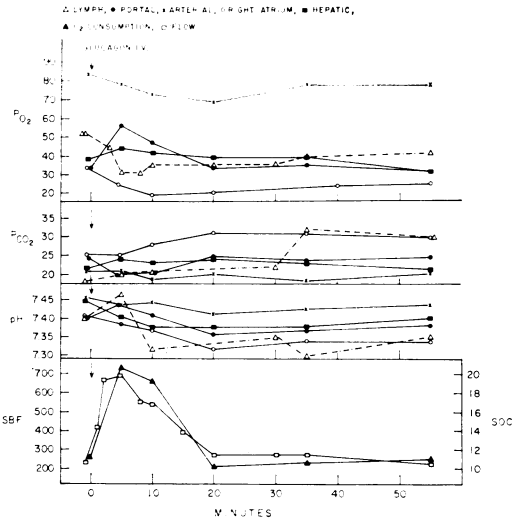

FIG. 8. Effect of glucagon administration in dog on splanchnic blood flow and oxygen consumption on PO_2, PCO_2 and pH in blood and thoracic duct lymph. This figure is representative of two experiments.

by the gradient of dissolved oxygen between capillary plasma and interstitial fluid." [21]

It is generally recognized that the primary factors regulating tissue oxygen tension include arterial oxygen content, rate of capillary blood flow, arteriovenous shunts,

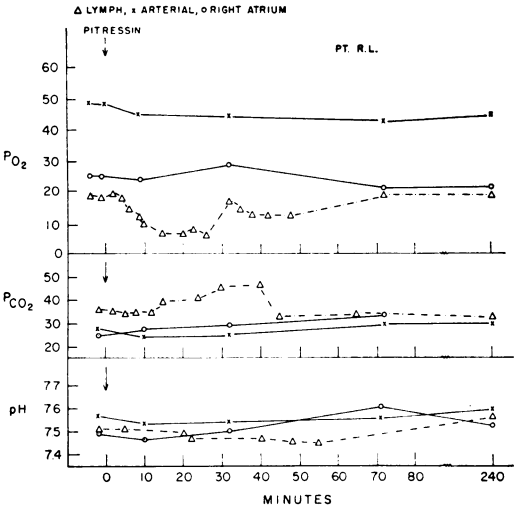

FIG. 9. Effect of vasopressin administration with advanced hepatic cirrhosis on PO_2, PCO_2 and pH in blood and thoracic duct lymph. Note low control level of lymph PO_2 which rapidly approaches zero.

tissue oxygen consumption and the dissociability of hemoglobin.[12, 14] Increased arterial oxygen content, increased capillary blood flow, decreased oxygen consumption and a shift of the oxygen dissociation curve to the right (Bohr effect) tend to raise tissue oxygen tension. Conversely, decreased arterial oxygen content, decreased capillary blood flow, increased oxygen consumption or a shift of the oxygen dissociation curve to the left tend to lower tissue oxygen tension. Diversion of capillary blood flow through arteriovenous shunts may reduce or eliminate gas exchange at the cellular level. Each of these variables exerts its influence on tissue gas tensions by altering the plasma-interstitial fluid gas gradient.

The data presented in this study demonstrate that factors known to alter splanchnic tissue oxygen tension influence thoracic duct lymph oxygen tension in a predictable manner. Reduction of blood flow in experimental animals by induced cardiac arrest, rapid hemorrhage or interruption of major splanchnic arteries produces splanchnic tissue or lymph "hypoxia" by restricting the amount of oxygen reaching capillaries. Changes in oxygen content in inhaled air regulate the supply of available oxygen carried in arterial blood and there-

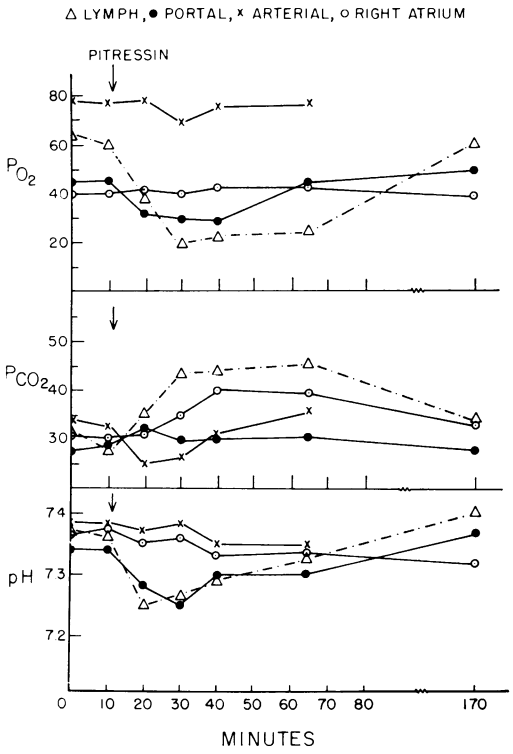

FIG. 10. Effect of vasopressin administration in patient with hepatic cirrhosis on PO_2, PCO_2 and pH in blood and thoracic duct lymph. Lymph PO_2 falls below right atrial and portal vein PO_2.

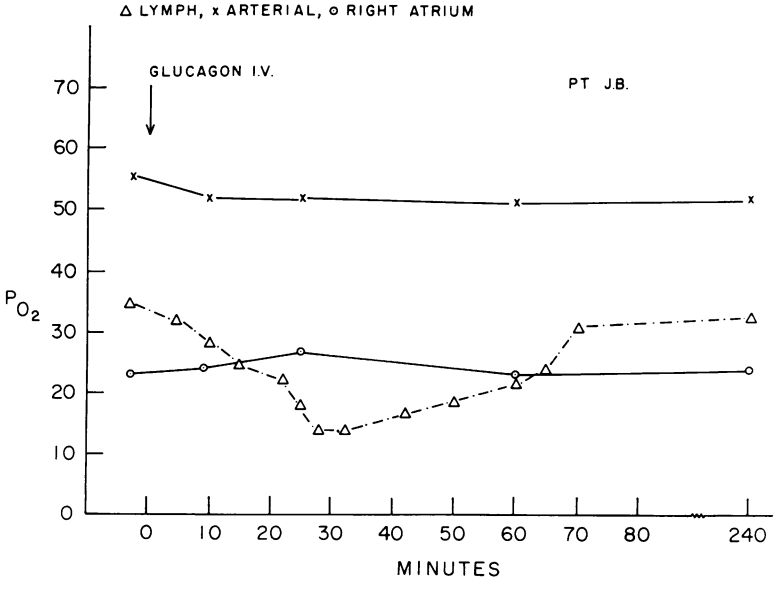

FIG. 11. Effect of glucagon administration in patient with hepatic cirrhosis on PO_2, PCO_2 and pH in blood and thoracic duct lymph.

by alter lymph PO_2. Administration of sodium cyanide inhibits oxygen consumption by interfering with oxidative phosphorylation which accompanied by an increase in regional blood flow from vasodilatation, raises PO_2 and lowers PCO_2 in lymph. Administration of sodium bicarbonate tends to lower lymph PO_2 by diverting capillary blood flow through arteriovenous shunts as suggested by an increase in blood flow, venous PO_2 and pulse pressure (*vide supra*), and perhaps by a shift in the oxygen dissociation curve to the left. Acidosis following intravenous ammonium chloride, however, does not lead to significant changes in blood or lymph gas tensions.

The effect of increased splanchnic oxygen consumption on splanchnic tissue gas tensions is difficult to assess because an autoregulatory rise in blood flow occurs during increased functional activity.[1, 20] Patients with hepatic disease are limited in their ability to compensate for increased splanchnic oxygen consumption with a rise in splanchnic blood flow.[5, 16] Instead, increased cellular activity is offset by a wider extraction of oxygen content (aortic-hepatic vein) a derangement which limits the availability of oxygen to splanchnic tissues. Thus, when splanchnic oxygen consumption rises a diminution in tissue PO_2 is likely to occur. After administration of glucagon, a hormone capable of almost doubling the splanchnic oxygen consumption in cirrhosis,[16] thoracic duct lymph PO_2 decreases.

Administration of vasopressin to patients with hepatic disease results in a decrease of lymph PO_2 and pH and a rise in PCO_2. Metaraminol administration in congestive heart failure similarly results in a diminution in lymph PO_2. These potent vasoconstrictive drugs, in all likelihood, favor anaerobic metabolism by raising arteriolar resistance thereby reducing capillary blood flow. Moreover, in patients with severe hepatic disease or congestive heart failure, PO_2 of lymph may already be as low as 14–35 mm. Hg. Although reduction of hepatic blood flow could account for a low PO_2 in splanchnic interstitial fluid in these conditions, in cirrhosis there may be, in addition, a mechanical block to diffusion of oxygen secondary to parenchymal fibrosis analogous to the alveolar-capillary block in pulmonary interstitial fibrosis. When 100% oxygen was administered to a patient with marked hepatic dysfunction a prompt rise in arterial and lymph PO_2 occurred. This response resembles that in the dog[3] and suggests that administration of oxygen to such patients may increase tissue oxygen tension toward normal levels and provide more oxygen for parenchymal cells.

Summary

Samples of thoracic duct lymph from dogs and patients were analyzed for PO_2, PCO_2 and pH under experimental conditions that were varied by altering pH, splanchnic blood flow, splanchnic oxygen consumption and the PO_2 of inspired air. Evidence was obtained which indicated that changes in gas tensions of thoracic duct lymph provide direct information concerning alterations in gas exchange in splanchnic tissues. This technic may be useful in unraveling some of the poorly understood problems of tissue oxygenation in hemorrhagic shock, cirrhosis and congestive heart failure.

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