Respiratory Failure in Acute Pancreatitis

A Possible Role for Triglycerides

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Respiratory failure is a frequent complication of acute pancreatitis. Two clinical studies of this association have demonstrated a high incidence of concomitant hypertriglyceridemia. Experimental studies were carried out using an *ex vivo*, isolated, perfused, ventilated, canine pulmonary lobe to evaluate the effects of triglyceride elevations on pulmonary mechanics and gas exchange. Control lobes perfused for a four hour period remained stable. When 5g and 10g of triglyceride were added to the perfusate, the lobes became grossly edematous and hemorrhagic. Intrapulmonary shunting developed (23 and 46%), weight gain occurred (130 and 189g), effective compliance decreased, and the pressure-volume deflation curves became abnormal. Free fatty acid (FFA) levels increased markedly during the perfusion periods. When small quantities of FFA were infused directly into the pulmonary artery, similar changes, but less severe, occurred. These studies demonstrate that triglyceride elevations are capable of adversely affecting pulmonary gas exchange and mechanics. Such changes probably occur secondary to FFA release. These data thus add support to the concept that the respiratory insufficiency that is seen in acute pancreatitis could be mediated through triglyceride elevations.

ALTHOUGH RESPIRATORY INSUFFICIENCY secondary to acute pancreatitis is well recognized, the mechanism for initiation of the respiratory failure is unknown. Two clinical studies[10,17] concerning respiratory failure with acute pancreatitis identified a significant incidence of concomitant hypertriglyceridemia, and it was suggested that the triglyceride elevations might play a role in the pathogenesis of the respiratory insufficiency. The present experiments were carried out to evaluate the effects of elevated triglyceride levels on pulmonary mechanics and pulmonary gas exchange. An isolated, perfused, ventilated canine pulmonary lobe model was utilized for this study.

Experimental Preparation

This preparation has been reported previously.[15] Healthy adult mongrel dogs weighing between 15 and 25 kg were used. Under sodium pentobarbital (30mg/kg) anesthesia, a thoracotomy was performed and the left lower pulmonary lobe was isolated along with its artery, vein and bronchus. After heparinizing the animal, the vessels and bronchus were cannulated and the lobe was removed and placed in a heated humidified chamber. The lobe was suspended from a weight transducer via patches glued onto the pleural surface of the lobe. A Harvard piston type respirator® was used to ventilate the lobe with 100% oxygen. The tidal volume was approximately 2ml/g of lobe weight and the rate 14 per minute. In all lobes the end-expiratory pressure was set at 5cm H_2O throughout the experiment. The perfusate consisted of 800ml of autologous blood to which 6000 units of heparin were added. The autologous blood was pumped into the pulmonary artery cannula by a Sarns roller pump.® The flow rate was increased until the pulmonary artery pressure stabilized at 15mmHg. Flows generally were 2ml/g of lobe weight/minute. Venous blood, collected by a cannula in the pulmonary vein, was deoxygenated in a Bentley infant oxygenator® equilibrated with 95% nitrogen and 5% carbon dioxide. A heat exchanger maintained the temperature at 37° ± 1°. Blood from the oxygenator was then pumped back into the pulmonary artery. Sodium bicarbonate was added as needed to maintain the blood pH in the physiologic range. Lobe weight, arterial, venous, and airway pressures were monitored continuously with Statham p23Db transducers.® Arterial and venous blood samples were analyzed periodically for pH, P_{O_2}, and P_{CO_2} with a Corning blood gas analyzer.® Arterial blood samples were also used for hemoglobin determinations. Intrapulmonary shunting was calculated from the standard

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shunt formula. Effective compliance was calculated according to the following formula:

$$\text{effective compliance} = \frac{\text{Tidal volume (ml)}}{\text{End inspiratory pressure} - \text{end expiratory pressure (cm } H_2O)}$$

At the end of the study the static compliance was determined by performing a standard pressure-volume deflation curve.

Experimental Protocol

All lobes were perfused for at least 30 minutes to allow for stabilization prior to placing them into one of the control or study groups.

Group I: Control (six lobes)

After the period of stabilization, perfusion was continued for four hours. Lobe weight, arterial, venous and airway pressures were recorded every 30 minutes. Samples of arterial and venous blood were drawn at 30 minute intervals for calculation of shunt. Serum free fatty acids (FFA) were determined at time zero and four hours.

Group II: 5 g Triglyceride Infusion (five lobes)*

After the period of stabilization, 50ml of a 10% triglyceride emulsion were added to the perfusate, and the perfusion was continued for four hours. After the addition of triglyceride, the concentration in the perfusate was calculated to be 1000 mg/dl. Serum triglyceride concentrations were determined periodically during the four hour perfusion and remained stable. The values were falsely high, however, because the high glycerin content in the emulsified fat solution makes the standard laboratory method of determining triglyceride concentration invalid. The lobes were monitored in a fashion identical to the Group I controls.

Group III: 10g Triglyceride Infusion (five lobes)

After the period of stabilization, 100ml of a 10% triglyceride emulsion were added to the perfusate and the perfusion was continued for four hours. After the addition of triglyceride the concentration in the perfusate was calculated to be 2000 mg/dl. The lobes were monitored in a fashion identical to the Group I controls.

Group IV: Rapid Infusion of Oleic Acid† (five lobes)

After the period of stabilization, 1 ml of oleic acid was infused into the arterial line over a five minute period, and then the perfusion was continued for four hours. The lobes were monitored in a fashion identical to the Group I controls.

Group V: Slow Infusion of Oleic Acid (five lobes)

After the period of stabilization, one ml of oleic acid was infused into the arterial line over a 60 minute period, and then the perfusion was continued for three hours. The lobes were monitored in a fashion identical to the Group I controls.

Group VI: Mineral Oil Infusion (five lobes)

After the period of stabilization, 1ml of mineral oil was infused into the arterial line over a five minute period, and then the perfusion was continued for four hours. The lobes were monitored in a fashion identical to the Group I controls.

Results

Group I: Control

The gross appearance of the control lobes remained normal during the four hour perfusion. Weight gain during the perfusion was minimal (Table 1). Mean pulmonary artery pressure was stable (Table 2). No significant intrapulmonary shunting developed during the perfusion period (Table 3). Although effective com-

* Soybean Oil 10.0g, Phospholipids 1.2g, Glycerin 2.25g per 100ml: Cutter Laboratories, Inc., Berkeley, California.

† Oleic Acid 4 mM per 1ml: Mallinckrodt Chemical Works, New York, New York.

TABLE 1. *Weight (g) During Perfusion*

Group / Hour	Control	Triglyceride (5g)	Triglyceride (10g)	Oleic Acid 1ml (5 min.)	Oleic Acid 1ml (1 hour)	Mineral Oil 1ml
0	67.3 ± 6.1	76.6 ± 6.1	58.8 ± 3.4	68.4 ± 2.7	66.4 ± 5.2	64.2 ± 4.1
1	71.8 ± 5.5	83.0 ± 6.6	69.4 ± 4.8	83.6 ± 6.2	73.4 ± 8.1	68.8 ± 5.5
2	72.8 ± 5.9	96.4 ± 11.0	86.8 ± 8.3	110.8 ± 14.1*	91.4 ± 7.8	69.8 ± 6.1
3	73.8 ± 4.9	206.6 ± 55.4*	247.0 ± 65.2*	129.8 ± 17.7*	117.0 ± 11.9*	74.2 ± 7.0
4	79.5 ± 5.5			158.6 ± 21.3*	139.4 ± 15.7*	79.2 ± 10.1

Mean ± 1 S.E. *Unpaired t-test, $p < 0.05$.

TABLE 2. *Pulmonary Artery Pressure (mmHg)*

Group / Hour	Control	Triglyceride (5g)	Triglyceride (10g)	Oleic Acid 1ml (5 min)	Oleic Acid 1ml (1 hour)	Mineral Oil 1ml
0	13.0 ± 1.1	13.0 ± 1.0	12.8 ± 1.1	12.4 ± 0.6	11.6 ± 1.3	12.1 ± 1.4
1	11.1 ± 0.8	12.7 ± 1.3	14.0 ± 1.7	12.3 ± 0.5	12.3 ± 1.5	11.6 ± 1.0
2	10.8 ± 0.7	15.3 ± 3.5	14.9 ± 0.8*	12.3 ± 0.5	13.2 ± 1.7	11.4 ± 0.8
3	10.7 ± 0.6	24.4 ± 9.4	27.2 ± 6.6*	12.4 ± 0.6	13.1 ± 1.7	11.7 ± 0.7
4	11.0 ± 0.5			14.1 ± 2.2	15.2 ± 2.7	12.0 ± 0.9

Mean ± 1 S.E. *Unpaired t-test, $p < 0.05$.

pliance dropped moderately during the four hour run, pressure-volume deflation curves performed at the end of the perfusion were within the normal range (Tables 4 and 5). FFA levels were unchanged at the end of the perfusion (Table 6).

Group II: 5g Triglyceride Infusion

Following the addition of triglyceride these lobes became grossly edematous and hemorrhagic. Weight gain was massive and three perfusions had to be stopped after only three hours because all the perfusate had been absorbed by the lobe (Table 1). Pulmonary artery pressure doubled and intrapulmonary shunting increased from 6.5 to 23% during the three hour perfusion period (Tables 2 and 3). Effective compliance decreased moderately and the pressure-volume deflation curve was markedly depressed (Tables 4 and 5). FFA concentration rose markedly during the perfusion period (Table 6).

Group III: 10g Triglyceride Infusion

Following the addition of triglyceride, these lobes became edematous and hemorrhagic and weight gain was massive (Table 1). Only two of the five lobes completed the planned four hour perfusion. The remaining three lobes developed massive pulmonary edema and hemorrhage and the perfusion had to be terminated because of the loss of perfusate. Mean pulmonary artery pressure doubled and intrapulmonary shunting increased from 8.4 to 45.8% during the three hour perfusion (Tables 2 and 3). Effective compliance decreased markedly (Table 4). FFA concentration became markedly elevated during the perfusion (Table 6).

Group IV: Rapid Oleic Acid Infusion

Following the five minute oleic acid infusion these lobes became edematous and atelectatic, but were less hemorrhagic than the triglyceride-infused lobes. The lobe weight more than doubled (Table 1), but all five lobes could be continued for the entire four hour perfusion. Pulmonary artery pressure rose only slightly (Table 2). Intrapulmonary shunting increased from 5.9 to 13.0% (Table 3). Effective compliance decreased and the pressure-volume deflation curve was markedly depressed (Tables 4 and 5). Serum FFA concentration tripled during the perfusion (Table 6).

Group V: Slow Oleic Acid Infusion

Following the one hour oleic acid infusion these lobes also became edematous, atelectatic and hemorrhagic. Lobe weight doubled (Table 1). Pulmonary artery pressure rose only slightly (Table 2) and shunting increased from 5.5 to 16.7% (Table 3). Effective compliance and pressure volume deflation curves were significantly depressed (Tables 4 and 5). FFA concentration more than doubled during the perfusion (Table 6).

Group VI: Mineral Oil Infusion

The appearance of these lobes grossly remained normal during the entire perfusion. Weight gain was

TABLE 3. *Intrapulmonary Shunt (%)*

Group / Hour	Control	Triglyceride (5g)	Triglyceride (10g)	Oleic Acid 1ml (5 min)	Oleic Acid 1ml (1 hour)	Mineral Oil 1ml
0	7.2 ± 0.5	6.5 ± 1.0	8.4 ± 0.9	5.9 ± 0.8	5.5 ± 0.9	4.8 ± 0.6
1	6.6 ± 0.7	7.7 ± 1.7	11.5 ± 4.7	5.5 ± 0.8	5.5 ± 0.7	4.3 ± 0.5
2	7.4 ± 0.4	20.1 ± 9.6	22.2 ± 9.6	9.4 ± 2.5	12.6 ± 5.7	5.8 ± 0.9
3	6.7 ± 0.3	23.0 ± 8.1	45.8 ± 12.1*	10.2 ± 3.9	13.4 ± 5.9	4.9 ± 0.1
4	6.3 ± 0.2			13.0 ± 4.6	16.7 ± 7.0	4.8 ± 0.5

Mean ± 1 S.E. *Unpaired t-test, $p < 0.05$.

TABLE 4. *Effective Compliance (ml/cmH_2O)*

Group / Hour	Control	Triglyceride (5g)	Triglyceride (10g)	Oleic Acid 1ml (5 min)	Oleic Acid 1ml (1 hour)	Mineral Oil 1ml
0	24.0 ± 5.0	24.0 ± 2.8	23.3 ± 2.8	23.3 ± 2.9	23.7 ± 1.2	22.0 ± 1.3
1	20.3 ± 3.5	21.9 ± 3.2	19.2 ± 2.8	16.3 ± 1.7	17.8 ± 1.9	19.5 ± 0.7
2	19.4 ± 4.7	21.9 ± 3.2	17.5 ± 1.7	14.0 ± 1.9	16.6 ± 2.4	18.1 ± 0.6
3	19.4 ± 4.6	18.5 ± 4.6	12.4 ± 1.9	13.5 ± 2.0	15.2 ± 2.4	16.6 ± 0.6
4	17.3 ± 3.6			12.4 ± 1.9	14.9 ± 2.2	14.7 ± 0.5

Mean ± 1 S.E.

minimal (Table 1), pulmonary artery pressure was stable (Table 2), and no intrapulmonary shunting developed (Table 3). Effective compliance fell but the pressure-volume deflation curves were within normal limits (Tables 4 and 5). FFA concentrations did not change during the perfusion (Table 6).

Discussion

Respiratory failure can accompany any serious acute intra-abdominal disorder. Abdominal distention with elevated diaphragms and a reduced respiratory excursion; splinting from abdominal and lower chest pain; intravenous fluid overload; and an increased oxygen demand can all play a role in the development of respiratory insufficiency. Undoubtedly some of the respiratory problems that develop in acute pancreatitis can be attributed to these factors. However, it is generally accepted that the respiratory complications accompanying acute pancreatitis are too severe to be explained by these mechanisms.[7,8] In addition, Ranson et al.[13] demonstrated that over half of all patients presenting with acute pancreatitis develop arterial hypoxemia during the first 48 hours after admission. These reports have suggested to many investigators that some specific mechanism, which is not present in equally ill patients with other abdominal disorders, influences pulmonary mechanics and gas exchange in acute pancreatitis. One theory proposes that phospholipase A is liberated into the blood stream along with other pancreatic enzymes during an acute attack, and that phospholipase A causes respiratory injury. Conceivably, phospholipase A could destroy surfactant, which is a phospholipid, resulting in widespread atelectasis and respiratory insufficiency. In a small series of patients Zieve and Vogel[19] found elevated serum levels of phospholipase A in acute pancreatitis. In a laboratory study, Morgan and others[11] demonstrated that the intravenous administration of phospholipase A resulted in respiratory failure in dogs. Subsequently, however, Bolooki and others[2] demonstrated no alteration in pulmonary surfactant or elevation of serum phospholipase A in dogs with experimental pancreatitis. Unfortunately, there are virtually no clinical data to support or refute this theory.

Two reports of small series of patients with acute pancreatitis and respiratory failure noted a significant incidence of concomitant hypertriglyceridemia. Kellum and colleagues[10] reported that two of four patients with pancreatitis and respiratory failure had hypertriglyceridemia, and Warshaw and others[17] identified the association in five of seven patients. Hypertriglyceridemia is not an unusual finding in an alcoholic patient.[3,5,9] The triglyceride elevations are probably induced by alcohol ingestion. It has recently been proposed on the basis of both clinical[6] and experimental[14] data that the hypertriglyceridemia might actually be the intermediary between alcoholic intake and the episode of acute pancreatitis. The pathogenic mechanism proposed involves the release of free fatty acids (FFA) in the pancreas by the lipolysis of triglyceride by pancreatic lipase. By injuring acinar cells or capillary membranes, FFA could initiate the episode of pancreatitis.[12] This same mechanism could in part be responsible for the pulmonary injury that frequently occurs during an attack of pancreatitis. Ashbaugh and Uzawa[1] have demonstrated that the injection of FFA into the pulmonary artery of a dog results in respiratory failure. It is possible that in some patients with acute pancreatitis and hypertriglyceridemia, the triglycerides are lipolyzed in sufficient quantities in the lung to liberate enough FFA to cause significant pulmonary injury. Surfactant destruction and/or injury to capillary–al-

TABLE 5. *Pressure-volume Deflation (% Volume/the Lobe Volume at 40 cmH_2O)*

40 cm H_2O	Control	Triglyceride (5 & 10g)	Oleic Acid (5 min & 1 hr)	Mineral Oil
	100	100	100	100
30	97.3 ± 0.3	96.3 ± 0.3*	96.0 ± 0.9	97.7 ± 0.3
20	93.9 ± 0.9	89.0 ± 0.6*	88.8 ± 1.7*	92.7 ± 0.9
15	88.2 ± 1.2	80.0 ± 1.5*	76.5 ± 1.8*	86.0 ± 3.0
10	78.3 ± 1.7	63.3 ± 2.7*	56.0 ± 3.2*	71.7 ± 3.2
5	59.4 ± 1.6	44.3 ± 3.2*	35.8 ± 2.9*	54.0 ± 2.3
0	13.8 ± 2.3	11.7 ± 2.2	11.8 ± 2.4	17.0 ± 1.5

Mean ± 1 S.E. *Unpaired t-test, $p < 0.05$.

TABLE 6. *FFA (μM/dl)*

Group / Hour	Control	Triglyceride (5g)	Triglyceride (10g)	Oleic Acid 1 ml (5 min)	Oleic Acid 1 ml (1 hour)	Mineral Oil 1 ml
0	58 ± 6	57 ± 8	62 ± 11	75 ± 6	59 ± 13	54 ± 8
1				150 ± 11	73 ± 10	62 ± 11
4	62 ± 4	530 ± 87*	486 ± 85*	225 ± 12*	140 ± 21*	71 ± 18

Mean ± 1 S.E. *Unpaired t-test, $p < 0.05$.

veolar membranes induced by FFA release could provide a vehicle through which respiratory insufficiency develops.

The present work was carried out to study the effects of elevated triglyceride levels on pulmonary mechanics and gas exchange. Use of the *ex vivo*, isolated, perfused, ventilated canine pulmonary lobe allowed evaluation of the influence of the lipid elevation on pulmonary function in the absence of other systemic influences. The control lobes remained stable throughout the four hour perfusion period. Weight gain was minimal, pulmonary arterial pressure was stable, and no significant intrapulmonary shunting developed. Effective compliance did decrease moderately during the experiment, but the mean pressure-volume deflation curve at the end of the perfusion was normal. This confirms our prior experience which has demonstrated the stability and reproducibility of this preparation.[15,16] When triglyceride was added to the perfusate, oxygen exchange and pulmonary mechanics both deteriorated. Both 5 and 10g of triglyceride produced significant shunting, a fall in effective compliance, and depression of pressure-volume deflation curves. This quantity of triglyceride results in blood concentrations well within the range of triglyceride elevations seen clinically with pancreatitis.[3–5] FFA concentrations became markedly elevated during the four hour perfusion, signifying that triglyceride hydrolysis released glycerol and FFA. The FFA concentrations at the end of the four hour perfusion were essentially the same whether 5 or 10g of triglyceride were added. This implies that there was a great triglyceride substrate excess in both groups. In support of this is the fact that there were no statistically significant differences in terms of oxygen exchange and pulmonary mechanics between the 5 and 10g triglyceride lobes.

When a small quantity of FFA (oleic acid) was infused into the pulmonary artery in the absence of triglyceride, the same sequence of events occurred. The lobes gained weight, intrapulmonary shunting developed, and compliance fell. The magnitude of the changes was less than with the triglyceride, but this was presumably related to the dose of oleic acid infused. The FFA concentration in the perfusate rose during the perfusion, but not to as high level as with the triglyceride infusion. Since oleic acid is not readily soluble in blood and tends to form oil droplets, mineral oil was infused in five lobes as a control. Mineral oil also served in part as the control for the inert glycerin that is contained in the infused triglyceride solution. No significant changes in gas exchange or pulmonary mechanics followed the mineral oil infusion.

These results suggest that elevated triglyceride levels in acute pancreatitis could provide a mechanism for initiation of respiratory failure. Damage appears to depend upon the lipolysis of triglyceride with the release of FFA. When unbound to albumin, FFA are toxic to tissues and could injure the capillary–alveolar membrane and increase permeability.[12] The resultant increase in interstitial and intra-alveolar water, manifest by lobe weight gain, could decrease pulmonary compliance and reduce gas exchange. This mechanism of injury to the capillary–alveolar membrane also appears responsible for the physiologic responses seen in other models of respiratory failure.[15,16]

Since there are many clinical situations in which hypertriglyceridemia is present without pulmonary problems, there must be an additional factor in some patients with acute pancreatitis that triggers lipolysis and the local release of FFA in the pulmonary circuit. The lung is rich in lipoprotein lipase[18] which may be activated by a circulating factor released by the pancreas during a severe attack. In our isolated pulmonary lobe model, heparin is added to the perfusate to avoid clotting in the oxygenator and blood pump. Heparin is a potent activator of lipoprotein lipase and thus in our model lipolysis is initiated by this means. In the clinical situation another strong mechanism of lipoprotein lipase activation in the lung would obviously be necessary. Clinically, if one stimulates in a hyperlipemic patient lipoprotein lipase systemically with a small dose of heparin, the triglyceride will clear with the release of FFA, but pancreatitis or pulmonary injury does not occur. Apparently it is the local release of very large quantities of FFA rapidly in the pancreas or lung that results in injury.

In a series of patients presenting to this hospital with acute pancreatitis, 38% had serum triglyceride elevations.[3] Most of these patients did not develop pulmonary insufficiency. The presence, however, of

hypertriglyceridemia in combination with a mechanism for lipoprotein lipase activation in the lung, could provide a mechanism to explain the development of pulmonary insufficiency in some patients with severe acute pancreatitis. The present work demonstrates that the lipolysis of triglyceride with FFA release is capable of causing pulmonary injury, and adds supportive evidence for this concept.

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