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Impeded Interstitial Fluid Movement: A Factor in Pancreatic Oedema

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Summary

Pancreatic oedema was induced by physiological saline infused into the superior pancreatico-duodenal artery of 34, chloralose anaesthetized dogs. Both lymph flow from cannulated pancreatico-duodenal lymphatics and intralymphatic pressure in the non-transected ones increased significantly. The increase in pressure may be due to the regional lymph nodes obstructing increased lymph flow. The development of gross pancreatic oedema preceded the peak values of pancreatico-duodenal lymph flow and pressure. This suggested impeded fluid movement along tissue interstices and from tissue interstices into the pancreatic lymphatics. The progression of the oedema ran roughly parallel with the increase in fluid pressure measured by a perforated capsule implanted two weeks earlier into pancreatic tissues supplied by the artery.

The results suggest that both the rise in lymph flow and pressure during the development of oedema in lobular organs like the pancreas are rather the consequences and not the causes of oedema.

Introduction

As established by *Rusznyak* and his coworkers (1), oedema develops, i.e. fluid accumulates in the tissue interstices, when the lymphatic system is unable to transport from the interstitial space the fluid not reabsorbed by the blood capillaries. This concept failed to consider that in lobular organs like the pancreas, the fluid filtrated through capillary endothelium has first to pass fibrous connective tissue capsules, then the extracapsular interlobular connective tissue to reach the lymphatics (2, 3).

Theoretically, if the rate of capillary filtrate formation exceeds the migration rate of interstitial fluid, fluid will necessarily be retained in the interstitial space before entering the lymphatics. This may be called praelymphatic insufficiency of interstitial fluid movement. Oedema due to praelymphatic insufficiency of interstitial fluid movement appears without increase in lymph flow, as in bile-induced acute experimental pancreatitis (4). Another sign of impeded interstitial fluid movement is that oedema may develop earlier than lymph flow reaches its peak. Such impeded fluid movement was demonstrated after the release of experimental acute cardiac tamponade (5) and in pancreatic oedema induced by increasing capillary filtration (6).

Consequently, if oedema develops, it should be elucidated to what extent interstitial fluid movement along tissue interstices is slowed down and/or lymph flow is impeded by the regional lymph nodes (7, 8).

The development of pancreatic oedema is well visible to the naked eye. The lobular structure of the gland permits the implantation between the lobes of a perforated capsule. The pressure within the capsule is believed to reflect interstitial fluid pressure (9, 10).

In this work we studied whether changes in pancreatic interstitial fluid pressure and in pancreatico-duodenal lymph flow and pressure precede or are concomitant to pancreatic oedema formation due to reduced capillary filtrate reabsorption.

Materials and Methods

Thirty-four chloralose-anaesthetized male dogs, with an average body weight of 16 kg, were used in the experiments. A polyethylene cannula was introduced into one duodenal branch of the superior pancreatico-duodenal artery with its tip to the arterial trunk, without disturbing blood flow in it. Evans' blue solution was injected through the cannula to visualize the tissues supplied by the artery and the lymphatics draining them (11). Evans' blue stained physiological saline was infused through the arterial cannula by means of a peristaltic pump:
I to 12 dogs at a rate of 50 ml/min for 10 min,
II to 22 dogs at a rate of 16 ml/min for 60 min.
In 16 dogs, the amount of lymph leaving the cannulated lymphatics draining the pancreatic tissues was measured at 10 min collection periods. In another 12 dogs intralymphatic pressure was continuously measured by electromanometer *via* a polyethylene cannula. With its tip towards the organ this cannula was introduced into one branch of a lymph vessel dividing in a reversed Y-form (8) on its way from the pancreas to the lymph node. Care was taken not to interfere with lymph flow in the other branch and to avoid valves which could disturb pressure measurements. In a further group of 6 dogs, 14 to 16 days before the saline load, a perforated capsule was implanted into pancreatic tissues supplied by the artery and into the subcutaneous tissues under the abdominal wall, under aseptic conditions. (In 2 other dogs, not included in the 34 ones, subcutaneous capsules were used six weeks after implantation.) Only those dogs were included into this study in which neither blood nor pancreatic juice was found in the capsule. The appearance time of visible pancreatic oedema was established by visual observation. At the end of the experiment, in some dogs the oedematous pancreas was fixed by intraarterial 6% neutral formaline infusion for histological examination. The statistical evaluation was performed by analysis of variance followed by the *Friedman, Wilcoxon* tests for values of lymph flow in group I and by the *Dunnett* test for intralymphatic pressure values in group I and data from group II.

Results

I. A 50 ml/min saline load for 10 min increased pancreatico-duodenal lymph flow (Fig. 1). It was found to be significantly higher ($p < 0.05$) than the control value even 20 min after stopping saline load. Simultaneously to the increase in lymph flow, a significant rise occurred in the intralymphatic pressure of a pancreatico-duodenal lymph vessels ($p < 0.01$). Pressure decreased gradually after stopping intraarterial saline load (Fig. 2).

II. A 16 ml/min saline load for 60 min significantly increased pancreatico-duocenal lymph flow ($p < 0.01$); the peak was reached 40 min after beginning saline infusion (Fig. 3). Before intraarterial saline infusion, the pressure in a pancreatico-duodenal lymphatic was 6.1 ± 0.77 S.E. mmHg. The pressure reached its peak, 12.38 ± 2.05 mmHg, significantly different from the control value ($p < 0.01$), after 40 min saline load (Fig. 4).

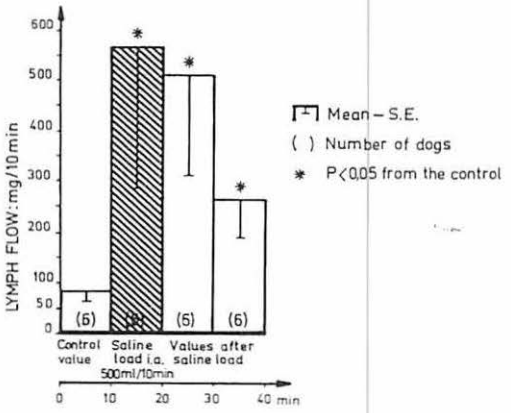

Fig. 1. 500 ml/10 min saline load into the superior pancreatico-duodenal artery significantly increased pancreatico-duodenal lymph flow even 20 min after stopping intraarterial saline load.

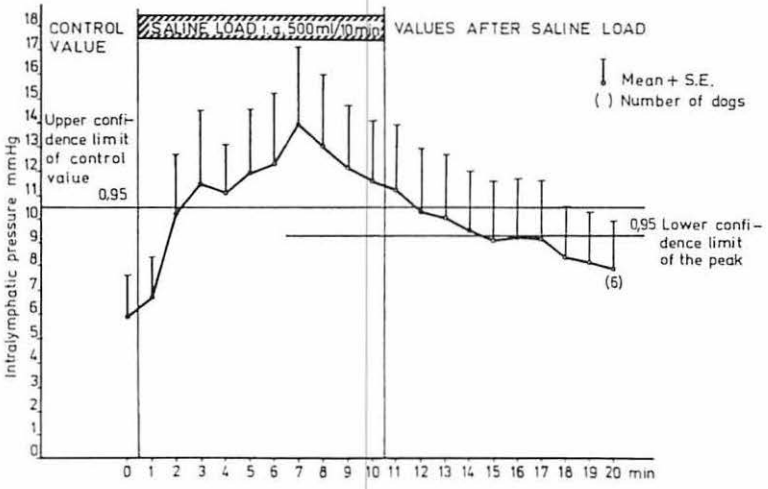

Fig. 2. Increased intralymphatic pressure after 500 ml/10 min intraarterial saline load.

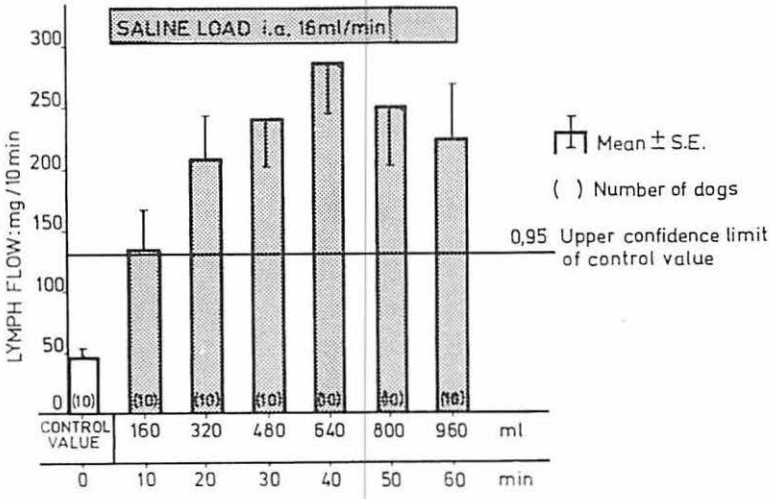

Fig. 3. 16 ml/min intraarterial saline load for 60 min significantly increased pancreatico-duodenal lymph flow reaching its maximum 40 min after beginning saline load.

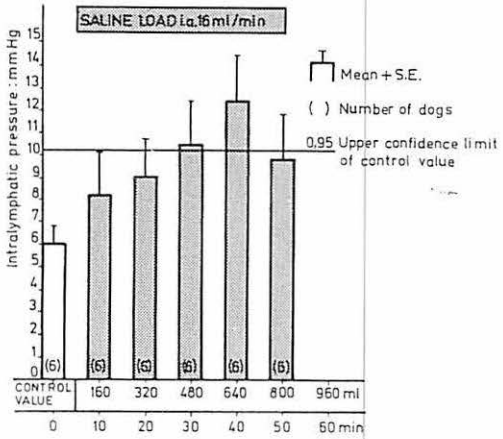

Fig. 4. 16 ml/min intraarterial saline load for 60 min significantly elevated intralymphatic pressure reaching its maximum 40 min after saline load.

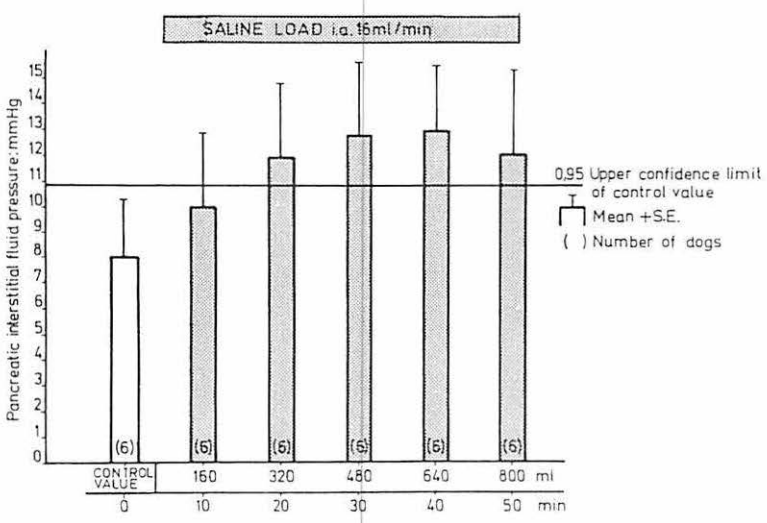

Fig. 5. 16 ml/min intraarterial saline load for 60 min significantly elevated intrapancreatic interstitial (intracapsular) fluid pressure reaching its peak value 40 min after saline load.

Mean pressure in the lumen of pancreatic capsule was 8.0 ± 2.27 mmHg; saline load increased the pressure in the pancreatic capsule significantly ($p < 0.01$). The pressure peaked at 12.92 ± 2.53 mmHg after 40 min (Fig. 5). Saline load increased also subcutaneous interstitial pressure from 1.0 ± 0.40 mmHg to 2.1 ± 0.64 mmHg ($p < 0.05$) which significantly differed from pancreatic interstitial pressure ($p < 0.05$).

As shown on Fig. 6, pancreatic oedema first appeared between 15 to 20 min of intraarterial saline infusion, preceding the appearance of peak values both in lymph flow and intralymphatic pressure by 20 min. Oedema formation progressed roughly parallel with the rise of the pancreatic interstitial pressure.

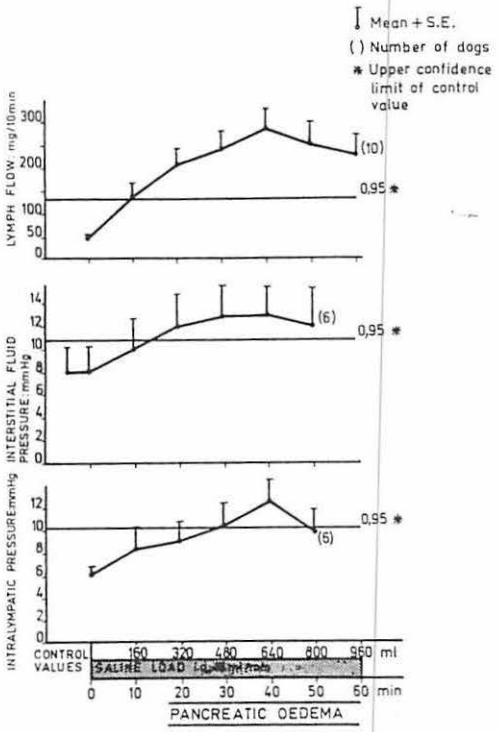

Fig. 6. Parallelism in change of lymph flow, intralymphatic and interstitial (intracapsular) fluid pressure during intraarterial saline load. Their peak values were reached already in the oedematous state of the pancreas.

Discussion

Blood flow through the superior pancreatico-duodenal artery amounts to 22-26 ml/min in dogs (12). Saline dilutes the blood flowing through the gland and reduces its oncotic pressure. This, in turn, decreases the reabsorption of the fluid filtrated through the extremely-thin, continuous, fenestrated endothelium of pancreatic blood capillaries (13, 14); so interstitial fluid accumulates and visible oedema will develop. Since the protein concentration of the augmented interstitial fluid also diminishes, fluid will enter the pancreatic capsule as long as the protein concentration in intracapsular fluid will equal that in the surrounding interstitial fluid. Thus, fluid accumulation in the capsule will elevate intracapsular pressure. After reaching an equilibrium, the pressure inside the capsule reflects rate of fluid removal from the space surrounding the capsule. Pancreatico-duodenal lymph flow elevated gradually. However, it reached its peak value, an average sixfold increase over control values, already in the oedematous state of the gland.

As observed, more lymph leaves spontaneously the dissected pancreatico-duodenal lymphatics during the contractions of the duodenum. During intraarterial saline load, e.g. during oedema formation, the duodenal contractions become more frequent and marked.

Lymphatic pressure increases parallel with the rise in lymph flow; the rise of pressure may be due to resistance of the lymph system to increased lymph flow. Lymph nodes were found to obstruct increased lymph flow (7) and the rise was not due to elevated pressure either in the thoracic duct or in the left subclavian vein (8). We have to assume that the rise in lymphatic pressure during the formation of pancreatic oedema must have been evoked by increased lymph flow through the flow resisting peripancreatic lymph nodes. The resistance of the regional lymph nodes to elevated lymph flow may be a fluid pressure- and volume regulating factor slowing down the sudden return of tissue fluid into blood circulation.

The fact that pancreatic oedema, provoked by increasing capillary filtrate formation and reducing capillary filtrate reabsorption, developed earlier than both pancreatico-duodenal lymph flow and pressure would reach their peak values, suggests the impeded pancreatic interstitial fluid movement. Namely, the lymphatics in the pancreas are situated in the interlobular connective tissue septa and in the vicinity of interlobular arteries and veins (15). The impeded movement of interstitial fluid towards pancreatico-duodenal lymphatics may be caused by the swelling of connective tissue gel owing to the large quantity of capillary filtrate (9).

Surprisingly, positive basal pressure was measured inside the pancreatic capsule two weeks after its implantation. The positive pressure inside the capsule might be a consequence of some inflammation surrounding the capsule. Considering that protein concentration difference in fluids from capsules implanted in the canine hind paw region for less than one month and in

those from capsules implanted for longer than one month was found to be only 0.3 g/100 ml (10), this assumption seems unlikely. Other data show that e.g. in the kidneys interstitial pressure is still positive (9) as we found in the pancreas. It can be safely stated that the gradual rise of intracapsular pressure during saline load reflects growing accumulation of the interstitial fluid. This latter induces an increase in lymph flow (16, 17), however, from the pancreas after a delay. After having reached its peak, the interstitial pressure decreased, indicating that beyond the maximum, the rise of interstitial pressure and that of interstitial fluid volume cease to run parallel (18).

It has been generally accepted that oedema develops when the lymph circulation cannot transport the fluid entering the interstitial space: "As long as the lymph channels are able to carry off the filtrated fluid, oedema cannot arise. The appearance of oedema indicates in this case also an insufficiency of the lymph circulation" (1). On the contrary, we suggest that oedema of the lobular organs like the pancreas may be due to impeded interstitial fluid movement rather than to the insufficient drainage of accumulating interstitial fluid by the lymphatics.

Acknowlegement

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