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P. E. Dahl [a]; J. C. Kjæve [a]
[a] Department of Surgery, Institute of Clinical Medicine, University Hospital of North Norway, Tromsø, Norway

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Pulmonary function in rats dying from long-term parenteral nutrition

P. E. DAHL & J. C. KJÆVE

Department of Surgery, Institute of Clinical Medicine, University Hospital of North Norway, Tromsø, Norway

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Infusion of Vamin or Intralipid causes death in a rat model of continuous parenteral nutrition. Morphological investigations have shown vascular injury and thrombus formation in the lungs. In this study, lung function in rats was examined before death due to parenteral nutrition. The rats were fed saline intravenously (group I); 100 mL kg^{-1} day^{-1} (controls); a 7% amino acid-glucose solution (Vamin-Glukos) (group II); 100 mL kg^{-1} day^{-1}, or 20% fat emulsion (Intralipid) (group III); 40 mL kg^{-1} day^{-1}. The infusion was stopped when the condition of the rats deteriorated. In a saline-perfused, isolated lung model, pulmonary arterial pressure (Ppa), transpulmonary pressure (Ptp), endothelial function, measured as inactivation of serotonin (bioassay), and the capillary filtration coefficient (CFC) were determined. Haematological parameters were also evaluated. Constant findings in group II and III were central thrombus formation, anaemia and thrombocytopenia. Ppa increased from 0.7 (0.04) kPa in group I to 1.4 (0.1) kPa and 1.7 (0,1) kPa in groups II and III, respectively ($p < 0.001$). Inactivation of serotonin was reduced to 36% (2) in group II and 37% (2) in group III compared with 74% (5) in group I ($p < 0.002$). CFC increased to 25 mg min^{-1} (5) (group II) and 30 mg min^{-1} (6) (group III) compared with 13 mg min^{-1} (2) in controls ($p = 0.01$). The study shows that major pulmonary hypertension and severe reduction of the endothelial function are present when rats deteriorate after infusion of parenteral nutrition substrates.

Key words: Intralipid; lung injury; rat; thrombosis; Vamin

Per Erling Dahl, Department of Cardiothoracic and Vascular Surgery, University Hospital of Tromsø, NO-9038 RiTø, Norway. Tel. +47 77 626 620, fax. +47 77 626 605, e-mail. per.erling.dahl@unn.no

INTRODUCTION

Sepsis and thrombosis resulting from the central vein catheter are well known complications of long-term parenteral nutrition (TPN) [1–3]. Organ changes caused by the substrates of parenteral nutrition themselves are less readily recognized. However, TPN could cause liver injury, in some instances leading to liver failure [4]. Various organ changes in bone marrow [5] and lungs [6–8] have been reported. Lung emboli, even with fatal outcome, have been thought to originate from catheter thrombosis [9–11]. The mechanisms triggering organ

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changes induced by TPN are not well understood. *In vitro*, both fat solutions and amino acid solutions modify the function of leucocytes and macrophages, which may alter immune function [12, 13].

In contrast to the lack of specific histological changes caused by TPN in humans, we have found that the substrates of TPN induce a granulomatous inflammatory response in rats. The animals die within 40 days. The major organ changes are confined to the liver, spleen and lungs [14–16]. At death the lungs appear stiff, with areas of infarction. The importance of the simultaneous, regular finding of large thrombus formations around the catheter tip is uncertain [17]. In the present study our aim was to evaluate the pathophysiological importance of the lung changes when the animals deteriorate owing to parenteral feeding. The pulmonary arterial pressure and the function of the vascular endothelium were estimated.

MATERIALS AND METHODS

The animal model

Male Wistar rats (Møllegaard, Skensved, Denmark) weighing 200–250 g were used for the experiments. The catheterization technique, the procedure for adaptation to the cages and the long-term infusion system have been described in an earlier study [17]. Previously, it has been demonstrated in the same model that normal weight gain is achieved up until some days before death, in animals receiving TPN alone, TPN and pellets, or the separate components of TPN and pellets. The histological changes can already be seen at 20% of the recommended amount of infusion [14, 15]. In a similar model of TPN in rats, it is shown that sufficient weight gain is reached with a caloric daily infusion of 350 kcal kg^{-1}. Giving the animals oral food only in the same model, the daily intake was estimated to 310 kcal kg^{-1} [18]. In the present model, the TPN infusion contained 330 kcal kg^{-1}. The control animals consumed 5 pellets daily. When given TPN, the animals consumed one pellet daily. Hence, the total caloric intake in these animals was 20% higher than the estimated normocaloric intake.

In the present study the separate components of TPN were administered in addition to pellets. The amount of the separate components given corresponded to 100% of recommended TPN infusion in rats and was given continuously throughout the experimental period [14, 15, 18]. The consumption of pellets was not estimated.

Every 12 h the infusion system was disconnected, untwisted and flushed slowly with 0.2 mL saline, and every 6 h the condition of the rats was controlled. The infusion substrates were kept in flexible bags (Viaflex, Travenol laboratories Inc., Deerfield, Ill., USA) and were changed every 3 days during the infusion period. The rats had access to standard pellets (Brood Stock Feed for rats and Mice-R3. Ewos Ltd., Södertälje, Sweden) and fresh water during the entire experimental period.

Substrates

1. NaCl® 0.9 % (Hydro Pharma, Norway).
2. Intralipid® 200 mg mL^{-1} (Kabi, Stockholm, Sweden). 100 mL contains: Soybean oil 20 g; Glycerol 2.3 g. Energy/100 mL: 200 kcal. Osmolality: Isosmolar. pH 7.5.
3. Vamin-Glukos® (Kabi, Stockholm, Sweden). 7% solution of essential amino acids containing 10% glucose. Electrolytes (mM): Na+ 50, K+ 20, Ca++ 2.5, Cl-55. Osmolality: 1350 mosmol. Energy/100 mL: 65 kcal. pH 5.4.

Infusion groups

After the operation the rats were divided into three separate groups and given one of the substrates. The substrates were administrated continuously until the rats were seriously ill, as judged by slow motions and lack of reaction to high-frequency noise. Once this condition had been reached, the rats succumbed within a few hours. The rats infused with saline were killed at the same time as the longest surviving animals in the other two groups.

Group I: Control group. Isotonic saline, 100 mL kg^{-1} bodyweight per 24 h (n=7).

Group II: Vamin-Glukos®, 100 mL kg^{-1} bodyweight per 24 h (n=8).

Group III: Intralipid®, 40 mL kg^{-1} bodyweight per 24 h (n=8).

The isolated lung model and blood sampling

Rats showing signs of deterioration were disconnected from the infusion system and anaesthetized with pentobarbital (Thiopentonnatrium, Nycomed, Norway) 100 mg kg^{-1} bodyweight. A tracheotomy was performed and they were connected to a ventilator (Model 141, Valley Scientific Co. Inc., Medway, Mass., USA). A sternotomy was performed and Heparin 200 U (Nycomed Pharma, Norway) was injected into the left ventricle. One millilitre blood was drawn from the left ventricle, via the apex. Haemoglobin, haematocrit, red blood cell counts, white blood cell counts, and platelet counts were measured. The heart/lung preparation was removed *en bloc*, cannulated through the pulmonary artery and the left ventricle and flushed with Krebs solution via the inlet cannula. The lungs were placed in a humidified perspex chamber at 37°C and perfused in a recirculating system with a Krebs/bicarbonate solution containing 4% bovine albumin [19]. The lung perfusion was performed using a roller pump (2115 Multiperpex, LKB, Bromma, Sweden) at a constant volume inflow (6.5 mL 100 g^{-1} bodyweight) from a reservoir (37°C). The outlet pressure was kept below zero, and the lungs ventilated with 5% CO_2 in air (tidal volume 1.5 mL 100 g^{-1} bodyweight, frequency 70 min^{-1}, PEEP 1.5 cm H_2O). 100 μg Papaverine (NAF, Oslo, Norway) was added to paralyse the vascular bed. The lungs were perfused for 20 min before measurements were taken.

Measurements

Pulmonary arterial pressure (Ppa) and the transpulmonary pressure (Ptp) were continuously recorded (Transducer: AE 840, AME, Horten, Norway). The lungs were suspended in a weight transducer (FT 30C, Grass Instruments, Quincy, Mass., USA). The microcirculatory permeability was estimated by measuring the capillary filtration coefficient (CFC). The CFC was determined by raising the outlet pressure from the lungs by 0.4 kPa for 5 min. CFC was taken as weight increase per minute during the last three minutes.

It is known that serotonin is extensively cleared by the pulmonary endothelium of rat lungs during the first passage through the lungs [20]. Clearance of serotonin in the lungs was determined using the superfusion bioassay technique [21]. The venous effluent was pumped to superfuse a strip of rat stomach, known to be sensitive to serotonin, and then returned to the reservoir by gravity. Contractions of the stomach strip were measured on an isometric force transducer (FT 30C, Grass Instruments); 150 ng serotonin dissolved in 0.3 mL saline was injected on the arterial side of the lungs. The serotonin *not* cleared by the lungs then superfused and caused contraction of the bioassay tissue. This contraction was measured and calibrated with various amounts of serotonin applied directly to the venous effluent.

The transducers were connected to a Beckmann polygraph (R500A) with a preamplifier (9853A) and an amplifier (411) (Beckmann Instruments, Schiller Park, Ill., USA).

Statistics

The results are presented as the mean (SEM). The Kruskal–Wallis test supplied with the Wilcoxon test was used to evaluate statistical differences between groups. The correlation between CFC, Ppa and serotonin clearance regardless of substrate infusion was evaluated by means of simple regression analysis; $p < 0.05$ was considered significant.

RESULTS

One rat that was given saline was excluded because of catheter obstruction and one rat receiving Vamin-Glukos was excluded because of catheter leakage. The rats in the saline group were healthy throughout the infusion period. The animals in groups II and III were fit until the last 4 or 5 days before death. The time to deterioration of the animals in the other two groups and the incidence of thrombosis extending into the right side of the heart are reported in Table I. The lungs in groups II and III rats were stiff and heavy and revealed a varying number of dark spots on the surface.

Blood measurements

Infusion with Vamin-Glukos or Intralipid caused a 50% reduction of haemoglobin, and an

TABLE I. Days of infusion and number of animals with central thrombus formation in rats dying after infusion of Vamin-Glukos® or Intralipid® compared with infusion of saline.

Group	Days	Incidence of thrombus formation
Saline (n = 6)	38 (5)	0
Vamin-Glukos® (n = 7)	36 (4)	6
Intralipid® (n = 8)	24 (3)	7
P-value	NS	

The results are means (SEM).

even more impressive reduction in the number of platelets compared with saline infusion.

There were no significant differences in the number of leucocytes (Table II).

Lung measurements

Ptp was significantly increased in groups II and III compared with group I. Ppa was doubled in lungs exposed to Vamin-Glukos or Intralipid compared to lungs exposed to saline, regardless of the vascular bed being paralysed by Papaverine. This was paralleled with a 50% reduction in serotonin clearance in groups II and III compared to group I. The increase in CFC measured in groups II and III was significant compared with that in group I (Table III).

TABLE II. Haemoglobin, haematocrit, red blood cell counts, white blood cell counts and platelet counts in rats dying after infusion of Vamin-Glukos® (group II) or Intralipid® (group III) compared with infusion of saline (group I).

Group	Hb g/L	Hct %	RBC 10^9 L^{-1}	WBC 10^9 L^{-1}	Platelets 10^9 L^{-1}
I (n = 6)	15.4 (0.2)	45 (2)	6.3 (0.2)	4.4 (0.5)	690 (22)
II (n = 7)	6.3 (0.7)*	28 (3)*	4.2 (0.4)*	6.0 (0.5)	189 (29)*
III (n = 8)	6.9 (0.6)*	28 (2)*	4.3 (0.3)*	8.3 (1.9)	127 (17)*
P-value	0.002	0.002	0.002	0.07	0.001

Hb = Haemoglobin; hct = haematocrit; RBC = red blood count; WBC = white blood count.
The results are means (SEM).
*Denotes different from group I.

TABLE III. Pulmonary arterial pressure, capillary filtration coefficient, serotonin inactivation and transpulmonary pressure in rats dying after infusion of Vamin-Glukos® (group II) and Intralipid® (group III) compared with infusion of saline (group I).

Group	Ppa (KPa)	CFC (mg/min)	5-HT (%)	Ptp (KPa)
I (n = 6)	0.7 (0.04)	13 (2)	74 (5)	0.6 (0.04)
Range	0.6–0.8	8–17	60–85	0.5–0.8
II (n = 7)	1.4 (0.1)*	25 (5)*	36 (2)*	1.0 (0.06)*
Range	1.1–1.8	8–43	30–50	0.8–1.3
III (n = 8)	1.7 (0.1)*	30 (6)*	37 (3)*	1.0 (0.04)*
Range	1.3–2.1	17–56	30–50	0.9–1.3
P-value	0.001	0.01	0.002	0.001

Ppa = Pulmonary arterial pressure; CFC = capillary filtration coefficient; 5-HT = serotonin activation; Ptp = transpulmonary pressure.
The results are means (SEM).
*Denotes different from group I.

A correlation was found between increased Ppa and reduction of serotonin clearance (Spearman's $r_s = -0{,}768$, $p < 0.01$) and increased Ppa also was correlated to increased CFC (Spearman's $r_s = 0.446$, $p = 0.043$). Increased CFC was correlated to reduction in serotonin clearance (Spearman's $r_s = -0.530$, $p = 0.013$).

DISCUSSION

Functional and morphological changes in lungs after parenteral nutrition, mainly after lipid infusion in children, have been reported. The morphological alterations particularly described are fat accumulations in the smaller lung vessels and capillaries [6–8]. Even hypertonic, lipid-free solutions have been shown to create lung oedema, interstitial inflammation and thrombosis of small pulmonary arterioles in rabbits [22].

Reports on alterations in gas exchange and pulmonary haemodynamics after TPN are limited to consequences of increased ventilation owing to increased CO_2 production. Addition of glucose to the TPN solutions creates increased CO_2 production and O_2 consumption, thus increasing ventilatory requirements. Adding a fat emulsion as energy source seems to produce a more positive trend, at least in patients with respiratory failure [23].

It has been demonstrated that fast Intralipid infusion gives a transient rise in pulmonary arterial pressure [24]. No acute haemodynamic effects were found in critically ill patients during infusion of 500 mL Intralipid [25]. After long-term infusion of TPN in pigs, haemodynamic effects have been reported [26].

The present model of TPN infusion in rats has shown a granulomatous inflammation in liver, spleen and lungs. The organ changes were observed irrespective of the age of the rats, or whether the infusion was given via the jugular vein, the hepatic portal vein or via the thoracic duct [14–16, 27, 28]. The organ changes in rats were observed with 25% of the recommended normocaloric TPN regimen [18]. The changes were still present, but to some lesser extent 36 days after discontinuing the infusion [14, 15]. The total substrate infusions in this study are in accordance with previous recommendations of TPN infusions in rats [15, 18].

The lung changes are further characterized by a severe vascular inflammation with occluding thrombosis and damage to the endothelial lining. Both Intralipid and Vamin induced severe vascular changes, making it sometimes difficult to identify the original structure of the vascular bed [15]. In rats given Intralipid, fat droplets were a constant finding in the lung vessels. Changing the route of infusion to the portal vein or the thoracic duct caused fewer organ changes of the liver and spleen [27, 28]. However, the inflammatory responses in the lung vessels were almost unaltered compared to infusion in the jugular vein. The possibility that the death of the rats was caused by deterioration of lung function has therefore been investigated.

Cell studies have revealed a huge accumulation of activated lung macrophages after a short period of TPN infusion of the animals [17]. A concomitant activation of blood phagocytes did not take place. After 12 days of infusion with Intralipid or Vamin-Glukos, a moderate increase of Ppa and reduction of serotonin clearance occurred [29]. Extending the investigation until death of the animals caused severe pulmonary hypertension and reduction of serotonin clearance. The changes were similar with Intralipid and Vamin-Glukos infusion. Despite paralysing the vascular bed with Papaverine, the pulmonary perfusion pressure increased. This indicates that the pulmonary hypertension was due to structural changes of the vascular bed rather than vasoconstriction.

The rise in Ptp reflects the combined effect of airway resistance and dynamic lung compliance. Macroscopically, the lungs were wet and heavy, indicating a gross oedema. In addition, previous histological examinations have revealed a thickening of the alveolar septa. These findings are probably the main causes of the increased Ptp.

Serotonin is removed from the circulation by the pulmonary endothelial cells in an energy-dependent process. The hormone is then inactivated intracellularly [20]. From previous studies in this model we know that the amount of serotonin injected is well below the capacity of rat lungs to remove serotonin in the first passage through the lungs [30]. In another animal model it has been shown that exclusion of one lung reduced serotonin clearance by only 13% [31]. The capacity of the lung to handle serotonin depends on the function of the endothelial cells and available surface area of the vascular bed. CFC depends on capillary

hydrostatic pressure, the permeability of the endothelial surface, and the perfused surface area. In the present study the major reduction of serotonin clearance suggests that a larger part of the lungs was not perfused. If the reduction was caused by damage to the vascular endothelium only, a much more impressive increase in the CFC would have been expected. This is in keeping with lung function after 3 and 12 days' infusion of the substrates, showing a consistent reduction of serotonin clearance only [29].

To what extent the substrates injured the endothelial lining is difficult to assess as long as larger parts of the vascular bed were probably occluded owing to an inflammatory reaction and thrombosis. The lung response to sepsis or embolization is characteristically a permeability oedema caused by endothelial injury. Neither histological examinations nor prior studies of lung function after short-term TPN infusion are in keeping with sepsis or embolization as the initial cause of lung injury. On the contrary, the present study is in concert with previous studies suggesting that the main lung injury is caused by a granulomatous inflammation associated with severe vasculitis. Bearing in mind the regular findings of central thrombus formation and occluding thrombosis in the vascular bed, it is likely that embolization or thrombosis in lungs already injured by vasculitis exaggerates the lung injury and causes deterioration of lung function.

Catheter sepsis is the most frequent, severe complication in humans receiving long-term TPN. Adults have a septic episode every two to three years, which occurs even more frequently among children receiving TPN [32].

Lethal thromboembolic complications in lungs have been reported in children receiving TPN [11]. Liver injury induced by TPN is frequent and may cause liver failure and death. Microscopic examination of the liver has revealed an unspecific inflammation around the bile ducts [32].

The severe, specific, inflammatory changes in the lungs and liver of rats have not been reported in humans. However, TPN induces similar changes in pigs [33]. Although specific granulomatous inflammation has not been documented in humans, it is still possible that TPN induces an inflammatory reaction in both liver and lungs of humans, rendering the organs more susceptible to thromboembolic disease and other specific complications.

In conclusion, long-term infusion of Vamin-Glukos or Intralipid in rats causes severe lung injury. The lung injury is probably initiated by vasculitis associated with a granulomatous inflammation. Secondary thromboembolic disease may exaggerate the initial insult to the lungs.

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