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INFLUENCE OF HYPERTONIC–HYPERONCOTIC SOLUTION AND FUROSEMIDE ON CANINE HYDROSTATIC PULMONARY OEDEMA RESORPTION

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SUMMARY

1. This study aimed at enhancing the clearance of experimental hydrostatic pulmonary oedema in dogs using hypertonic–hyperoncotic solution (HHS) and furosemide.

2. Anaesthetized dogs ($n = 20$) were mechanically ventilated with a positive end-expiratory pressure of 10 cmH_2O (1·0 kPa).

3. Hydrostatic pulmonary oedema was induced by inflating a balloon inserted into the left atrium and simultaneously infusing isotonic saline rapidly. Oedema formation was terminated by deflating the balloon and reducing the infusion rate.

4. Four groups were studied: A, control; B, furosemide; C, HHS and D, HHS + furosemide. HHS, 6 ml kg^{-1}, was given as a bolus injection and furosemide, 1 mg kg^{-1}, intravenously as a bolus followed by an infusion of 0·5 mg kg^{-1} h^{-1}. All dogs were studied for 4 h.

5. Serum osmolarity, plasma colloid oncotic pressure and diuresis in groups C and D (HHS groups) substantially increased; haemoglobin concentration decreased and pulmonary arterial wedge pressure remained constant.

6. Despite the combination of these factors favouring fluid flux from the extravascular to the intravascular compartment, extravascular lung water measured with the double indicator dilution technique decreased no faster in the HHS groups than in the two other groups (from over 26 to approximately 19 ml kg^{-1} in groups A, C and D and to 14·7 in group B (only furosemide)).

7. This was confirmed by postmortem gravimetric measurements of extravascular lung water; A, $11·0 \pm 5·7$; B, $9·7 \pm 3·3$; C, $10·5 \pm 3·1$ and D, $10·6 \pm 1·8$ g kg^{-1}.

8. We speculate that mechanisms other than effective Starling gradients and enhanced diuresis might define a maximal rate of pulmonary oedema clearance.

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INTRODUCTION

Despite considerable improvements in the treatment of acute hydrostatic pulmonary oedema the management of this serious condition remains a challenge for the clinician (O'Brodovich, 1990; Matthay & Wiener-Kronish, 1990). Adequate ventilation, diuretics and supportive care are still the mainstays of therapy. Further progress is hampered by the lack of understanding of the extent and dynamics of fluid shifts between the vascular and the extravascular compartment during formation and resolution of hydrostatic pulmonary oedema. For many years it was believed that the controlling mechanisms were transendothelial Starling gradients. However recently, there is accumulating evidence that other mechanisms such as an active transport mechanism (O'Brodovich, 1990; Matthay & Weiner-Kronish, 1990) and drainage via lymph, pleura and mediastinum (Allen, Drake, Williams, Laine & Gabel, 1987; Staub, 1988; Wiener-Kronish & Matthay, 1988) are involved. Throughout the last decade there has been great interest in the application of hypertonic–hyperoncotic solutions in the treatment of various forms of experimental and clinical hypovolaemic shock conditions (De Fellipe, Timoren, Velasco, Lopes & Rocha-e-Silva, 1980; Mehrkens, Lindner, Ahnefeld & Nonn, 1987; Mullins & Hudgens, 1987; Hands, Holcroft, Perron & Kramer, 1988; Maningas, Mattox, Pepe, Jones, Feliciano & Burch, 1989; Kreimer, Brueckner, Schmidt & Messmer, 1990; Onarheim, Missavage, Kramer & Gunther, 1990). An important effect of these solutions is their pronounced extravascular volume recruitment by establishing osmotic and oncotic gradients across capillary membranes (Kreimeier & Messmer, 1988, 1989; Kreimeier *et al.* 1990). The passage of extremely hyperosmolar blood through the microcirculatory network leads to immediate reduction of the size of erythrocytes, endothelial and perivascular cells (Mazzoni, Borgström, Arfors & Intaglietta, 1988; Kreimeier & Messmer, 1989). Simultaneously the hyperoncotic component effectively retains mobilized fluid in the vascular system by increasing the colloid-oncotic pressure (Smith, Kramer, Perron, Nakayama, Gunther & Holcroft, 1985; Kreimeier *et al.* 1990).

To explore the role and possible limitations of increased Starling forces across pulmonary endothelial membranes of enhancing reabsorption of accumulated hydrostatic oedema in the lung, we studied the effect of an intravenous bolus injection of hyerptonic–hyperoncotic solution in a well-established canine model with acute hydrostatic pulmonary oedema (Frostell, Blomqvist, Wickerts & Hedenstierna, 1990; Blomqvist, Wickerts, Berg, Frostell, Jolin & Hedenstierna, 1991; Wickerts, Blomqvist, Berg, Rösblad & Hedenstierna, 1991; Wickerts, Berg & Blomqvist, 1992).

METHODS

Preparation

This study was approved by the regional animal ethics committee. Twenty mongrel dogs of both sexes, body wt 19–29 kg (mean 22·4 kg), were premedicated with 200–300 mg ketamine and 0·25–0·5 mg atropine I.M. Anaesthesia was induced with 10–20 mg diazepam and 180–300 mg pentobarbitone, and maintained with additional doses of 5–10 mg diazepam and 0·1–0·3 mg fentanyl I.V. Muscular relaxation was achieved and maintained with 1–2 mg pancuronium in intermittent doses throughout the experiment. Any dose of pancuronium was always preceded by additional doses of anaesthetic agents. Electrocardiogram, blood pressures and end-tidal carbon

dioxide concentration were monitored continuously to make sure that the animals were adequately anaesthetized.

The animals were intubated, placed in a supine position and mechanically ventilated with an Erica ventilator (Gambo-Engström AB, Stockholm, Sweden). Tidal volume was 15–20 ml kg^{-1} and respiratory frequency 14–20 breaths min^{-1}. The inspiratory : expiratory ratio was 1 : 2 with an end-inspiratory pause of 0·2–0·4 s. The inspiratory oxygen fraction was 0·5. Normocapnia, defined as arterial carbon dioxide tension (P_{a,CO_2}) 4·5–6·0 kPa, was achieved by adjusting the respiratory frequency, and was monitored continuously by recording the end-tidal carbon dioxide concentration (P_{ET,CO_2}) (Eliza, Gambro-Engström AB, Stockholm, Sweden) and intermittently with arterial blood gas analyses. The ventilator continuously displayed peak and mean airway pressures (P_{max}, P_{mean}) and an internal computer calculated total respiratory system compliance (C_T; expiratory tidal volume divided by end inspiratory pressure minus end-expiratory pressure). The bladder was catheterized for measurement of urinary output. Acidosis, pH less than 7·30, was corrected by intravenous administration of 0·6 M sodium bicarbonate in volumes corresponding to half the calculated base deficit. During formation of oedema 50 ml of 0·6 M sodium bicarbonate was administered to all dogs. Body temperature was maintained at 36–38 °C with electric heating pads.

Catheterization and measurements

A 7F thermistor-tipped pulmonary artery catheter (Swan-Ganz, Edwards Lab, Anasco, Puerto Rico) was introduced into a femoral vein (through a femoral cut-down) and advanced to the pulmonary artery position for pressure recordings, cardiac output measurements and blood sampling. For pressure recordings and blood sampling purposes a short cannula was introduced into the femoral artery through the same cut-down. A 4F fibre-optic thermistor-tipped catheter (Pulsion Medizintechnik, Munich, Germany) was advanced 35–40 cm into the aorta so that the tip of the catheter was close to the aortic root for measurements of extravascular lung water ($EVLW_i$) and central blood volume (CBV). A bolus of 10 ml ice-cold Indocyanine Green dissolved in 5% glucose was injected into the inferior vena cava or right atrium with an automatic temperature-controlled syringe. The temperature was measured in the pulmonary artery and cardiac output (CO) calculated by a computer (Cardiac Output Computer, model 9520A, Edwards Lab., Santa Ana, USA). The mean value of at least three recordings was used for statistical analysis. The same bolus injection was also used for measurements of $EVLW_i$ and CBV. The dilution curves for dye and temperature were recorded from the aortic root with the thermistor-tipped fibre-optic catheter as functions of time by a lung water computer (Partig, System Cold, Munich, Germany). The computer calculated the mean transit time (MTT) for the indicators (dye, temperature) and calculated the total thermal volume (TTV), the central blood volume (CBV) and the extravascular lung water ($EVLW_i$) according to:

$$TTV = CO \times MTT_{temp},$$

$$CBV = CO \times MTT_{dye},$$

$$EVLW_i = TTV - CBV.$$

The temperature of the injectate was corrected for catheter dead space, taking into account the proportions of the catheter lying intravascularly and in room air. Measurements were made at least in triplicate with random distribution of the injections over the respiratory cycle. Mean values were used for statistical analysis. We have previously shown that this Partig-Cold system is without cardiac output dependency (Wickerts, Jakobsson, Frostell & Hedenstierna, 1990).

Arterial mean pressure (MAP), central venous pressure (CVP), pulmonary arterial mean (PAP) and wedge (PCWP) pressures were recorded with transducers (Novatrans TM, Medex Inc., Hilliard, OH, USA) positioned at mid-thoracic level and connected to a recorder (Kontron medical 128 A, Digital Electronics Ltd, UK). Blood gas analyses were made by using standard electrode techniques (ABL 300, Radiometer, Copenhagen, Denmark). Oxygen saturations and haemoglobin concentrations were measured with a haemoximeter (OSM 3, Radiometer, Copenhagen, Denmark) with the capacity to analyse blood from different animals. The arterial to end-tidal carbon dioxide tension difference ($P_{a,CO_2} - P_{ET,CO_2}$) was calculated.

Venous admixture or shunt fraction (Q_s/Q_t) was calculated from the inspiratory oxygen fraction, arterial and mixed venous blood gases using the standard formula (Berggren, 1942). Colloid oncotic pressure (COP) was measured with an oncometer using a cut-off membrane of 20000 Da (Osmomat

050, Gonotec GmbH, Berlin, Germany). Serum and urine osmolarity were measured using an osmometer (Herman Roebling Meßtechnik, Berlin, Germany.) Haemoglobin concentration (Hb), haematocrit (HCT), white blood cells (WBC), platelets (PLT) and free haemoglobin (free-Hb) were measured by the Coulter principle in an automated haemology analyser (S 8 80, Coulter Electronics Ltd, Luton, Beds). Blood glucose was analysed electrochemically by the glucose-oxidase method (Model 23 AM Glucose Analyzer, Yellow Springs Instrument Co. Inc., Yellow Springs, OH, USA). Sodium and potassium were analysed using ion-selective electrodes (Electrolyte 2, Beckman Instruments, Palo Alto, CA, USA). Total serum protein concentration (TSP) was analysed by a modified Biuret method and serum albumin concentration (Alb) was analysed by a Bromcresol Green binding method (Beckman Clinical System 700, Beckman Instruments, Palo Alto, CA, USA).

Assessment of parameters in the Starling equation

The Starling equation has for many years been used as an expression for the understanding of fluid flux across the capillary membrane (Starling, 1896; Levine, Mellins, Senior & Fishman, 1967; Civetta, 1979):

$$J_v = K_{f,c}\{(P_c - P_t) - \delta(\pi_c - \pi_t)\}, \quad (1)$$

where J_v is described as net volume flow; $K_{f,c}$, capillary filtration coefficient; P_c, capillary hydrostatic pressure; P_t, tissue fluid hydrostatic pressure; δ, capillary membrane reflection coefficient to proteins; π_c, plasma oncotic pressure (colloid oncotic pressure); π_t, tissue fluid oncotic pressure (tissue colloid oncotic pressure). The pulmonary capillary hydrostatic pressure (P_c) cannot be measured reliably, but an estimate is given by the equation:

$$P_c = \text{PCWP} + \gamma(\text{PAP} - \text{PCWP}), \quad (2)$$

where γ is the ratio between the resistance downstream from the exchange vessels and the total pulmonary vascular resistance. This equation is commonly simplified by setting γ at 0·4 (Gaar, Taylor, Owens & Guyton, 1967; Schaeffer, Reniewics, Chilton & Carlson, 1987).

The underlying concept of intravenous HHS administration during the resorption of hydrostatic pulmonary oedema was to increase the oncotic and osmotic components, keeping hydrostatic forces constant, and thus promoting oedema clearance.

Surgical procedures

A thoracotomy was performed by a transverse sternal incision at the Th5–Th6 intercostal space. The left atrium was opened and a 20 charrière sized balloon-tipped catheter (Eschman, Lancing, UK) was inserted and secured by sutures. Following hyperinflation of the lungs, the thorax was closed in layers and made airtight. Intrapleural air and blood were evacuated by suction drainage.

Experimental protocol

Following these preparations, the animals were held at rest for half an hour. After recordings at baseline conditions, hydrostatic oedema was induced by inflation of the left atrial balloon (7–22 ml), and simultaneous rapid intravenous infusion of prewarmed isotonic saline (800–2000 ml, mean 1495 ml). The left atrial balloon inflation was limited to maintaining a systolic arterial pressure of above 80 mmHg (10·7 kPa) at all times. During hydrostatic oedema formation the mean pulmonary artery pressure increased to 30–60 mmHg (4·0–8·0 kPa). When $EVLW_i$ had increased to 25–30 ml (kg body wt)$^{-1}$, the hydrostatic process was terminated by deflating the left atrial balloon and reducing the infusion of fluid to basal rate (5 ml kg^{-1} h^{-1}). A positive end-expiratory pressure (PEEP) of 10 cmH_2O (1·0 kPa) was applied in all animals immediately after left atrial balloon deflation and 5 min later the first recording with oedema was performed (maximum oedema). Following this recording, the animals were divided into four groups with regard to treatment for the hydrostatic oedema and with random allocation to groups. The groups were: A, control; B, furosemide; C, HHS and D, HHS and furosemide ($n = 5$ for all groups). HHS was administered as a single injection of 6 ml (kg body wt)$^{-1}$ in 2 min, preceded by 10 ml of Dextran 1 (Promiten, Kabi-Pharmacia, Stockholm, Sweden) as monovalent hapten. (1000 ml HHS contains 100 g Dextran 60, 1232 mmol Na^+, 1232 mmol Cl^- with an osmolarity of 2465 mosM (Hyperdex, Schiwa GmbH, Glandorf, Germany).) Furosemide (Furix 10 mg ml^{-1}, Benzon Pharma A/S, Hvidovre, Denmark) was administered as an intravenous bolus injection of 1 mg (kg body wt)$^{-1}$ followed by an infusion of 0·5 mg (kg body wt)$^{-1}$ h^{-1}. PEEP was maintained at 10 cmH_2O (1·0 kPa) in all groups.

Subsequently, oedema resorption was studied over the period of 240 min. Eight recordings were carried out in each animal; baseline, maximum oedema (0 min), 15, 30, 60, 120, 180 and 240 min after maximum oedema. Measurements of haemodynamics, pulmonary mechanics, gas exchange, $EVLW_i$, CBV, COP, serum osmolarity, protein concentrations, electrolytes, Hb, HCT, WBC and platelets were carried out at all eight recordings. Free haemoglobin in serum (haemolysis) was analysed at baseline, maximum oedema and at 30 min. Blood glucose was analysed at baseline, maximum oedema, 120 and 240 min. Diuresis was measured hourly during oedema resorption and samples were taken for analyses of urine osmolarity, sodium and potassium content. After the animal was killed, the lungs were removed for analysis of extravascular lung water by gravimetric technique ($EVLW_g$).

Gravimetric procedures

At the end of the experiment, blood was analysed for water content, haemoglobin content and haematocrit. The dogs were killed by injecting an overdose of pentobarbitone and potassium chloride, and the lungs were clamped within 2–3 min. Postmortem analysis of extravascular lung water ($EVLW_g$) was carried out with correction for residual blood within the lungs as described by Pearce *et al.* (Pearce, Yamashita & Beaell, 1965) and with modification in ultracentrifugation according to Selinger *et al.* (Selinger, Bland, Demling & Staub, 1975). The lungs were weighed and homogenized in an equal weight of ion-free water in a blender. The well-stirred homogenate was centrifuged at 30000 *g* at +5 °C for 1 h (Beckman L5-50B Ultracentrifuge, Beckman Instruments, Palo Alto, CA, USA) to obtain a clear supernatant. Haemoglobin content in the supernatant was analysed and weighed samples of lung homogenate, whole blood and supernatant were analysed for water content by drying at +85 °C to constant weight (> 72 h). Calculations and formulae have been presented in a previous study (Frostell, Blomqvist & Wickerts, 1987*b*).

Statistics

Results are presented as mean values ± standard deviation. Statistical analyses between groups were performed using analysis of variance (ANOVA) for unpaired data. Statistical analyses within the groups were performed with analysis of variance (ANOVA) for repeated measurements. Differences were considered significant at 95% significance level with a multiple comparation test, Fisher's least significant difference method (PLSD test).

RESULTS

All animals remained haemodynamically stable during oedema development, and had comparable elevations in $EVLW_i$ (see Fig. 1). Recorded haemodynamic and laboratory parameters were also comparable in all groups when maximum oedema was reached (see Tables 1 and 2).

Fifteen minutes after the bolus injection of HHS, colloid oncotic pressures in groups C and D (HHS groups) were elevated ($P < 0{\cdot}05$–$0{\cdot}001$) by means of 3·3 and 5·1 mmHg respectively, and remained increased throughout the study (see Fig. 2*A*). Simultaneously, serum osmolarity in both HHS groups (C and D) was increased ($P < 0{\cdot}001$) at 15 min, from approximately 303 to 326 mosM, and remained elevated for the 4 h period (see Fig. 2*B*). Pulmonary arterial mean and wedge pressures were not statistically different among the groups. Immediately after the HHS injection the pulmonary capillary hydrostatic pressure (P_c) was transiently higher in the HHS groups (C and D) compared to the control group (A). Group B (only furosemide) had a higher P_c throughout the study compared to the control group, even before the administration of furosemide (see Table 1). Pulmonary vascular resistance decreased after the administration of HHS (see Table 1). HHS increased cardiac output, with group C (only HHS) showing a more pronounced increase compared to group D (HHS + furosemide). Central blood volume increased transiently after HHS

administration in groups C and D (see Table 1). In addition we observed a substantial increase in diuresis ($P < 0.05$) in group C compared to the control group and even more pronounced ($P < 0.01$) when furosemide was added in group D (see Fig. 3).

Oedema clearance

Despite significant differences in factors favouring oedema reabsorption in the HHS groups (C and D), $EVLW_i$ did not decrease more in groups C and D than in the

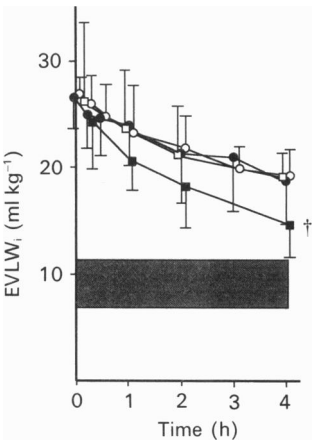

Fig. 1. Extravascular lung water ($EVLW_i$) measured by the double indicator dilution technique. Baseline value indicated as a shaded area represents a pooled mean value ± S.D. ($n = 20$) and the remaining data are given as mean values ± S.D. within each group. Group A (□) = control, $n = 5$; group B (■) = furosemide, $n = 5$; group C (○) = HHS, $n = 5$; group D (●) = HHS + furosemide, $n = 5$. † Group B (furosemide) is significantly lower compared to groups A and C ($P < 0.05$).

control group (A, see Fig. 1). In group B (only furosemide) the reduction in $EVLW_i$ was significantly ($P < 0.05$) greater compared to groups A and C. The gravimetric measurements of extravascular lung water were A = 11·0 ± 5·7, B = 9·7 ± 3·3, C = 10·5 ± 3·1 and D = 10·6 ± 1·8 g kg^{-1}.

Gas exchange and lung mechanics

There were no major differences among the four groups regarding gas exchange and lung mechanics. Oedema formation was accompanied by a pronounced decrease in P_{a,O_2} from approximately 35 to 16 kPa in all groups. Oxygenation improved during the course of the experiment and P_{a,O_2} normalized in all groups within 2 h. Respiratory system compliance was similarly reduced in all groups and remained so despite reduced oedema and normalized oxygenation in all animals.

Laboratory parameters

Blood glucose was unchanged and remained within normal limits during the study. Serum potassium was significantly ($P < 0.05$–0.01) lower (0·5 mM) in group D (HHS + furosemide) compared to group C (HHS). The total losses of electrolytes in the urine during the 4 h period expressed in mmol (kg body wt)$^{-1}$ were sodium 13·9 ± 2·3 and potassium 1·5 ± 0·3 in group D and sodium 6·0 ± 0·9 and potassium

TABLE 1. Effects of hypertonic–hyperoncotic solution (HHS) alone and in combination with furosemide on cardiac output (CO), mean arterial pressure (MAP) and capillary hydrostatic pressure (P_c), pulmonary vascular resistance (PVR) and central blood volume (CBV)

	Group	CO (ml kg^{-1} min^{-1})	MAP (mmHg)	P_c (mmHg)	PVR (kdyn × (s cm^{-5}) kg^{-1})	CBV (ml kg^{-1})
Baseline	A	134 ± 33	86 ± 18	9·8 ± 1·2	3·1 ± 1·0	18·9 ± 2·1
	B	126 ± 15	129 ± 33‡	13·8 ± 2·6‡	4·6 ± 1·2‡	18·0 ± 3·1
	C	124 ± 15	95 ± 9	10·4 ± 1·2	3·5 ± 1·0	17·1 ± 1·6
	D	134 ± 8	84 ± 9	11·7 ± 2·1	2·9 ± 0·7	20·6 ± 1·7†
0 min	A	136 ± 14	79 ± 13	13·3 ± 1·0*	5·6 ± 0·2	19·3 ± 2·7
	B	136 ± 11	100 ± 16‡	16·4 ± 2·5* ‡	5·0 ± 0·8	18·5 ± 1·4
	C	130 ± 34	71 ± 12*	15·8 ± 2·2*	4·8 ± 1·8	17·5 ± 2·3
	D	144 ± 29	67 ± 8*	17·6 ± 2·5*	4·6 ± 1·0*	21·5 ± 1·9†
15 min	A	102 ± 22*	64 ± 11	13·7 ± 1·8	6·6 ± 1·2	17·6 ± 2·3
	B	88 ± 22*	109 ± 21	17·2 ± 3·5‡ (2)	7·5 ± 1·8 (2)	16·3 ± 1·5*
	C	187 ± 18* ‡	99 ± 9*	17·7 ± 1·8* ‡	3·5 ± 0·6‡	21·4 ± 1·8* ‡
	D	173 ± 17* ‡	100 ± 8*	18·2 ± 2·0‡	4·2 ± 1·1‡	22·6 ± 1·5‡
60 min	A	103 ± 15	84 ± 20*	14·0 ± 1·5	7·3 ± 1·2	16·6 ± 1·8
	B	68 ± 21* ‡	105 ± 16‡	18·6 ± 1·5‡	14·4 ± 7·6‡	13·8 ± 2·7* ‡
	C	129 ± 10* ‡	86 ± 9*	15·8 ± 1·7 (1)	5·5 ± 0·8	17·4 ± 1·4*
	D	104 ± 12* †	84 ± 7	16·2 ± 1·3	6·6 ± 1·3	16·9 ± 1·5*
120 min	A	91 ± 9	87 ± 16	14·6 ± 1·6	9·1 ± 2·8	16·2 ± 2·0
	B	73 ± 16	103 ± 22	19·0 ± 4·4‡	14·9 ± 5·5‡	13·4 ± 1·1‡
	C	116 ± 17‡	93 ± 10	16·2 ± 1·8	6·7 ± 1·7	16·8 ± 1·7
	D	87 ± 16†	81 ± 8	15·8 ± 1·5	8·8 ± 1·6	16·2 ± 1·9
240 min	A	98 ± 13	88 ± 16	16·8 ± 2·8*	10·0 ± 1·8	16·9 ± 3·1
	B	76 ± 18‡	101 ± 21	17·7 ± 3·3	15·8 ± 7·1‡	14·9 ± 1·4
	C	104 ± 20	89 ± 11	16·2 ± 1·4	8·2 ± 1·6	17·3 ± 1·7
	D	79 ± 11†	83 ± 8	16·6 ± 1·9	10·9 ± 2·8	15·5 ± 1·2

P_c = PCWP + 0·4 (PAP − PCWP). PVR = 79·92 (MAP − PCWP)/CO kg^{-1}. Values are presented after preparations (baseline), after the oedema-producing process had been terminated and before administration of HHS and/or furosemide at maximum oedema (0 min) and 15, 60, 120 and 240 min after HHS and/or furosemide had been given. Data are presented as mean values ± S.D.

Group A = control, $n = 5$; group B = furosemide, $n = 5$; group C = HHS, $n = 5$; group D = HHS + furosemide, $n = 5$.

* Significantly different from preceding value ($P < 0·05$).

† Significant difference between groups C and D ($P < 0·05$).

‡ Significantly different from control (group A) ($P < 0·05$).

(1) One missing value.

(2) Two missing values.

TABLE 2. Effects of hypertonic–hyperoncotic solution (HHS) alone and in combination with furosemide on serum sodium, total serum protein (TSP), serum albumin (Alb), haemoglobin concentration (Hb) and white blood cells (WBC)

	Group	Sodium (mM)	TSP ($g\ l^{-1}$)	Alb ($g\ l^{-1}$)	Hb ($g\ l^{-1}$)	WBC ($10^9\ l^{-1}$)
Baseline	A	144±1	40±1	28±3	118±5	5·9±3·6
	B	146±3	46±4	30±2	113±2	6·6±0·2
	C	145±1	45±3	29±2	122±8	5·6±2·2
	D	145±2	43±5	28±2	114±6	8·7±3·9
0 min	A	143±1	30±10	19±2	92±4	3·5±2·8
	B	147±4	40±11	22±0	95±1	5·2±0·2
	C	145±4	28±5*	18±5*	90±5*	3·5±1·4*
	D	146±3	29±6*	19±3*	88±11*	6·2±2·3
15 min	A	145 (1)	29±2	21±1	104±6	3·8±3·3
	B	147±1	38±1	26±1	107±7	6·1±0·0
	C	158±5*	22±3*	15±2*	74±12*	4·3±2·0
	D	155±4*	23±3*	16±3*	78±8*	6·7±1·9
30 min	A	143±1	29±1	20±1	113±7	4·2±3·9
	B	146±5	42±1	27±0	117±6	7·2±0·6
	C	155±5	22±4	14±3	80±8	4·3±1·0
	D	156±6	26±5	17±3	85±13	7·0±2·2†
60 min	A	146±1	30 (1)	21±1	115±15	5·8±5·6
	B	144 (1)	44±1	29±1	133±0	8·8±0·8
	C	157±8	24±5	16±3	86±8	5·0±1·6
	D	154±2	30±5	20±3†	105±14*†	9·4±3·7†
120 min	A	145±0	31±1	21±0	119±7	7·4±6·7
	B	146±4	41 (1)	30±4	146±9	11·1±2·4
	C	163±6 (2)	26±5	17±3	94±4	6·1±1·8*
	D	155±4	34±6	22±3	120±6*†	11·6±4·3*†
180 min	A	148±6	32±0	22±1	119±4	9·1±7·4
	B	146±1	45±6	28±5	146±13	13·0±4·7
	C	155±5	26±5	17±4	98±5	8·2±2·3*
	D	154±3	33±6	22±3	126±11†	13·3±4·3†
240 min	A	146±4	31±0	22±1	123±5	10·4±7·6
	B	146±4	43±6	26±1	142±16	13·7±7·4
	C	154±3	27±5	17±3	104±6	9·2±3·0*
	D	153±2 (1)	34±7	22±3†	130±16†	15·3±5·4

Values are presented after preparations (baseline), after the oedema-producing process had been terminated and before administration of HHS and/or furosemide at maximum oedema (0 min) and 15, 30, 60, 120, 180 and 240 min after HHS and/or furosemide had been given. Data are presented as mean values±S.D. Comparative statistics are only made within and between groups C and D. Group A = control, $n = 2$; group B = furosemide, $n = 2$; group C = HHS, $n = 5$; group D = HHS+furosemide, $n = 5$.

* Significantly different from preceding value ($P < 0·05$).

† Significant difference between groups C and D ($P < 0·05$).

(1) One missing value.

(2) Two missing values.

0·8±0·1 in group C. Leucocytes and platelets decreased in all groups during oedema formation (Table 2). Free haemoglobin was 0·4 $g\ l^{-1}$ at baseline, 0·5 $g\ l^{-1}$ during maximum oedema before HHS was given and decreased to 0·3 $g\ l^{-1}$ 30 min after HHS was given ($n = 10$; groups C and D).

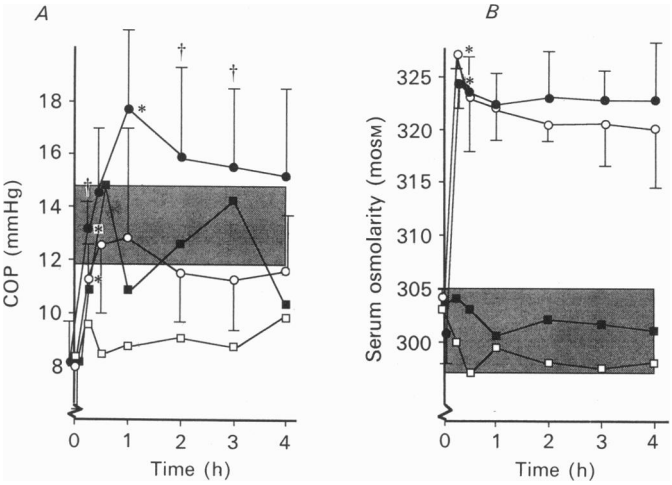

Fig. 2. Colloid oncotic pressure (COP; *A*) and serum osmolarity (*B*). Baseline value indicated as a shaded area represents a pooled mean value ± S.D. ($n = 14$) and the remaining data are given as mean values ± S.D. within each group (no standard deviation is plotted in groups A and B). Group A (□) = control, $n = 2$; group B (■) = furosemide, $n = 2$; group C (○) = HHS, $n = 5$; group D (●) = HHS + furosemide, $n = 5$. * Significantly different from preceding value ($P < 0{\cdot}05$). † Significant difference between groups C and D ($P < 0{\cdot}05$).

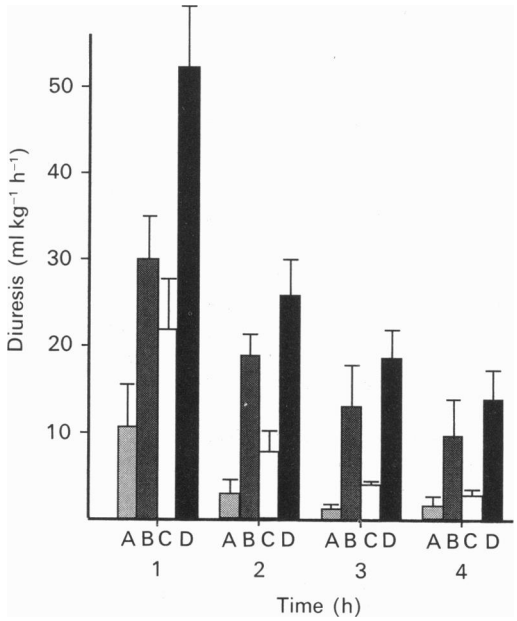

Fig. 3. Diuresis expressed in ml per kg body wt per hour during the 4 h study. Data are given as mean values ± S.D. within each group. Groups: control (A), furosemide (B), HHS (C) and HHS + furosemide (D).

DISCUSSION

The major finding of this study was that rapid intravenous administration of hypertonic–hyperoncotic solution in canine hydrostatic pulmonary oedema did not influence the rate of reabsorption of oedema despite changes in parameters favouring oedema clearance. In addition, enhanced diuresis by the combination of HHS and intravenous furosemide did not increase oedema reduction.

Effects of HHS bolus injection

The rapid bolus injection of HHS led to marked and sustained increases in serum osmolarity and colloid oncotic pressure (π_c). That total systemic net volume flow (J_v) in fact became negative, and the fact that fluid influx actually occurred is evidenced by a significant increase in plasma volume (increased central blood volume and marked decreases in haemoglobin and protein concentrations). All these findings have previously been well documented in hypovolaemic conditions (Smith *et al.* 1985; Hands *et al.* 1988; Kreimeier *et al.* 1990). Simultaneously, except for a short transient increase immediately following administration of HHS, P_c remained unchanged. The fact that increased cardiac output and plasma volume influenced P_c to only a minor degree can be explained by the well-known effect of HHS of decreasing systemic and pulmonary vascular resistances (Auler, Pereira, Gomide-Amaral, Stolf, Jatene & Rocha e Silva, 1987). Several different phenomena can explain this reduction in vascular resistance by HHS. An instant effect of HHS is a shrinkage of erythrocytes and endothelial cells (Mazzoni *et al.* 1988; Mazzoni, Borgström, Intaglietta & Arfors, 1990) as well as active vasomotion possibly due to osmotic changes in the water content of the smooth muscle cell (Gazitúa, Scott, Chou & Haddy, 1969). In the lungs, hyperosmolarity causes a precapillary dilatation but a postcapillary constriction (Bø, Hauge & Nicolaysen, 1971).

The initial plasma volume expansion was only transient, as demonstrated by the fact that already after 60 min (group C) and 30 min (group D) respectively the central blood volume had returned to or below pre-HHS injection values. The osmotic sodium load alone led to an immediate osmotic diuresis which was markedly enhanced by the combination with furosemide. Increased diuresis did not severely affect serum potassium balance. In addition, no signs of intravascular haemolysis or adverse pulmonary effects were observed as a result of the HHS dose used in this study.

An important difference in lymphatic flow in any of the groups is unlikely since central venous pressure and all other vascular pressures were similar and there were no differences in airway pressures among the four groups. Thus, the factors that may affect fluid clearance by the lymphatic system (Drake, Adcock, Scott & Gabel, 1982; Drake, Scott & Gabel, 1983; Laine, Allen, Katz, Gabel & Drake, 1986; Frostell, Blomqvist, Hedestierna, Halbig & Pieper, 1987*a*) appeared to be similar in all four groups.

Interpretation of our findings

Despite significant differences in factors favouring oedema reabsorption in both HHS groups compared to control group A, $EVLW_i$ clearance was not facilitated by HHS injection. This was also confirmed by the gravimetric EVLW showing no significant differences between the groups. The greater reduction of $EVLW_i$ in the

furosemide group B was in accordance with our previous finding that furosemide improves hydrostatic pulmonary oedema clearance, probably by increasing the colloid oncotic pressure (Wickerts *et al.* 1991). For some reason this was not seen when furosemide and HHS were combined.

There are a number of mechanisms influencing the lung fluid balance when PEEP is applied. (a) Increased lung volume reduces interstitial fluid pressure in the perivascular interstitial space and thereby increases fluid filtration (Bø, Hauge & Nicolaysen, 1977; Gee & Williams, 1979; Bshouty, Ali & Younes, 1988). (b) Increased alveolar pressure leads to a decreased filtration from alveolar capillaries (Bø *et al.* 1977; Gee & Williams, 1979; Bshouty *et al.* 1988). (c) Changes in perfused area or alterations in distribution of pulmonary blood flow (Goldberg, Mitzner & Batra, 1977; Dueck, Wagner & West, 1977; Hasinoff, Ducas & Prewitt, 1988). (d) Obstruction of lymphatic drainage (Pilon & Bittar, 1973; Van der Zee, Cooper, Hakim & Malik, 1986; Haider, Schad & Mendler 1987*a*, *b*; Frostell *et al.* 1987*a*). (e) Redistribution of fluid from the alveolar to the interstitial compartment (Paré, Warringer, Baile & Hogg, 1983; Malo, Ali & Wood, 1984). It is impossible from just a theoretical discussion to anticipate the net influences of PEEP on EVLW. It is also conceivable that the mechanisms cited above are operating in a different manner and are of varying importance during different phases of pulmonary oedema. In a model similar to this with hydrostatic pulmonary oedema during resorption we have previously shown that PEEP retards the resorption of oedema (Blomqvist *et al.* 1991). It is possible that PEEP *per se* may limit clearance even when it is favoured by other factors, such as the Starling gradients, but one of the aims of this study was just to see if it was possible to overcome the disadvantages of PEEP on oedema clearance by adding HHS and furosemide.

There are several possible explanations for the lack of beneficial effect of HHS injection with or without furosemide on pulmonary oedema clearance.

1. There was a significant increase in pulmonary blood flow after HHS administration which by recruitment and expansion of pulmonary capillaries might have increased the filtration area and thus net fluid filtration (J_v). However, this increased pulmonary blood flow does not necessarily counteract oedema reduction in a situation where oncotic and osmotic gradients favour fluid influx. Furthermore, an adverse effect of elevated lung tissue perfusion in group C (HHS) seems unlikely, since the reduction in cardiac output in group D (HHS + furosemide) to the same level found in the control group A did not lead to enhanced reduction of extravascular lung water content.

2. A substantial proportion of the oedema fluid might not be accessible to the capillary membrane and therefore not immediately reabsorbed.

3. The major determinant for reabsorption of pulmonary oedema might be a rate-limited active mechanism, as recently suggested (O'Brodovich, 1990; Matthay & Wiener-Kronish, 1990), which cannot be increased further by optimizing intravascular factors favouring fluid absorption. This mechanism is shown to be an active transport of sodium by type II epithelial cells (Cheek, Kim & Crandall, 1989). Fluid can be cleared from the alveolar space in intact adult lung against a colloid oncotic pressure of approximately 70 cmH_2O (Matthay, Berthiaume & Staub, 1985). β_2-Adrenergic stimulation increases sodium flux (Crandall, Heming, Palombo & Goodman, 1986) and clearance of airspace fluid (Berthiaume, Staub & Matthay, 1979;

Saumon, Basset, Bouchonnet & Crone, 1987); cAMP can also increase fluid clearance (Saumon *et al.* 1987).

In summary, this study adds further evidence that increased colloid oncotic pressure and serum osmolarity as well as maximized diuresis *per se* or in combination cannot enhance canine hydrostatic pulmonary oedema clearance rate despite constant hydrostatic pressures. We speculate that factors other than effective Starling gradients and enhanced diuresis such as an active transport mechanism might define the maximal rate of oedema clearance.

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