The Effect of Nitroprusside on Pulmonary Edema, Oxygen Exchange, and Blood Flow in Hydrochloric Acid Aspiration

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In canine pulmonary capillary leak induced by intravenous oleic acid, reducing pulmonary wedge pressure (Ppw) reduces pulmonary edema, venous admixture (Qva/Qt), and cardiac output (Qt). The authors tested the possibility that in another canine model of pulmonary capillary leak, that induced by endobronchial instillation of hydrochloric acid, nitroprusside would reduce Ppw and edema without reducing Qt or oxygen delivery (QO_2). In 18 dogs, the authors measured extravascular lung water (EVLW) by thermal-dye dilution and the hemodynamic and gas exchange variables before and at intervals (1, 1.5, 3, and 5 h) after .1 N HCl bronchial infusion. By 1 h, HCl increased EVLW from 175 to 250 ml and Qva/Qt from 11 to 21%. Immediately after the 1-h measurements, the dogs were divided into three equal groups: six controls (C) were maintained with a Ppw of 12 mmHg, while plasmapheresis (P) or nitroprusside (NP) reduced Ppw to 5 mmHg for the next 4 h. EVLW continued to increase to 548 ml in C, but did not increase further in P and NP. Weights of lungs excised at 5 h confirmed that P and NP reduced edema by 50% in 4 h. In C, Qva/Qt increased, but there was no reduction in Qt or QO_2. In contrast, plasmapheresis reduced Qva/Qt, Qt, and QO_2. With nitroprusside, Qt and QO_2 were maintained despite reduced Ppw at 1.5 and 3 h, and Qva/Qt did not decrease as in Group P. We conclude that plasmapheresis-induced reduction in Ppw reduces the pulmonary capillary leak and venous admixture following acid aspiration, but this has the potentially adverse effect of reducing cardiac output and oxygen delivery. Nitroprusside decreases Ppw and edema by a similar amount, but maintains Qt and QO_2. (Key words: Complications: aspiration. Heart: cardiac output. Lung: non-cardiogenic pulmonary edema; respiratory distress syndrome; shunt. Pharmacology: nitroprusside.)

EXTRAVASCULAR LUNG LIQUID (EVLW) can be reduced in canine oleic acid induced non-cardiogenic pulmonary edema by lowering pulmonary capillary wedge pressure (Ppw), and thereby lowering capillary hydrostatic pressure.[1] One approach to treatment of the early, exudative phase of the adult respiratory distress

syndrome (ARDS), therefore, is to maintain the lowest Ppw consistent with an adequate cardiac output.[2,3] The purpose of this study was to determine the effect of lowered Ppw in a different model of non-cardiogenic pulmonary edema, that incited by endobronchial instillation of hydrochloric acid in dogs. In addition to measuring the amount of pulmonary edema present after the animal was exsanguinated, the time course of edema accumulation in treated and untreated groups was followed by thermal-dye dilution technique. One consequence of lowering EVLW by lowering Ppw, however, is a decreased cardiac output (Qt). Since Qt and the effect of venous admixture (Qva/Qt) on arterial oxygen tension (Pa_{O_2}) and concentration (Ca_{O_2}) are the determinants of oxygen delivery ($QO_2 = Qt \times CaO_2$), we sought to reduce Ppw and EVLW without reducing Qt and QO_2. We postulated that sodium nitroprusside might produce this effect.

Methods

ANIMAL PREPARATION

Eighteen mongrel dogs weighing 17.7–32.3 kg (mean: 26.3 kg) were anesthetized with intravenous pentobarbital (30 mg/kg) supplemented as necessary to maintain anesthesia. A tracheostomy was performed and the animals were ventilated in the supine position with a fractional inspired oxygen of 0.6 and tidal volume of 20 ml/kg, using a Bennett air oxygen mixer and Harvard ventilator. The ventilator frequency was adjusted to maintain arterial CO_2 tension between 30 and 40 mmHg.

A Swan-Ganz catheter was inserted via the right external jugular vein and positioned in a branch of the pulmonary artery where pulmonary artery pressures (Ppa) were obtained. Inflation of the balloon yielded Ppw. Positive end-expiratory pressure of 10 cm H_2O was applied when the pulmonary artery catheter was initially positioned to increase the depth of the West Zone I. This favored a position of the catheter tip in a dependent vessel. Confirmation that Zone III conditions prevailed during subsequent measurements of Ppw was obtained by comparison with a simultaneously recorded left ventricular pressure tracing. This was obtained from a saline-filled pig-tail catheter passed via the left common carotid artery to a final position within the left ventricle. These tracings yielded direct determina-

tion of left ventricular end-diastolic pressure (LVEDP) for comparison with Ppw. Correspondence between Ppw and direct measurements of LVEDP was confirmed, even when Ppw was reduced to the lowest levels achieved during these experiments.

A second Swan-Ganz catheter, inserted *via* the right external jugular vein, was positioned in the right atrium and subsequently used for bolus injections of cold indocyanine green dye during measurements of EVLW and Qt. An Edwards lung water catheter (model 96-020-SF) was inserted in the right femoral artery and connected to a densitometer cuvette and syringe pump in series. This detected the thermal and dye indicators which were used to determine EVLW and Qt. A large-bore catheter was inserted into the right femoral vein for volume infusions, blood withdrawal, and red cell infusions.

MEASUREMENTS AND CALCULATIONS

Blood pressure (BP) and heart rate (HR) were obtained from a Statham P231D transducer connected to the femoral artery catheter. Pulmonary vascular pressures were obtained from a second P231D transducer connected to the pulmonary artery catheter. All vascular transducers were referenced to the mid-chest and measurements performed during a 10-s breath-hold at end-expiration. Pressure signals, heart rate, and dye and thermal dilution curves were recorded on a Grass Polygraph.

Measurements of EVLW and Qt were made in triplicate by injecting 10 ml of cold (0°) indocyanine green dye (5 mg) into the right atrium. The thermal and dye indicators were detected downstream by withdrawing blood through the lung water catheter and densitometer cuvette at a rate of 30 ml/min with the syringe pump. An Edwards computer (model 9310) simultaneously determined the mean transit times of both the dye and thermal indicators and the Qt. From these it derived the EVLW.

Mixed venous and arterial blood samples were analyzed for O_2 and CO_2 tensions and pH on a Corning 165-2 analyzer. Hemoglobin (Hgb) values were measured on a Coulter hemoglobinometer and O_2 saturations determined.[4] O_2 contents were then calculated as:

O_2 Content

$$= (.003 \times P_{O_2}) + (Hgb \times O_2 \text{ saturation} \times 1.34)$$

O_2 delivery (QO_2) was determined from simultaneous determination of arterial O_2 content and cardiac output. These values were then expressed per kilogram of body weight.

Venous admixture (Qva/Qt) was calculated as:

$$Qva/Qt = (Cc'O_2 - CaO_2)/Cc'O_2 - CvO_2),$$

where CaO_2 and CvO_2 are the calculated arterial and mixed venous O_2 contents, and $Cc'O_2$ the end capillary O_2 content, estimated from the alveolar gas equation assuming a respiratory quotient of 0.8.

PRETREATMENT PERIOD

After the animals were anesthetized and instrumented, a uniform starting Ppw of 12 mmHg was achieved by volume expansion with an IV infusion of 6% Dextran (molecular weight 75,000), or, in anemic dogs, whole blood from healthy dogs; the total volume infused ranged from .5–1.5 l. Simultaneous arterial and mixed venous blood samples were then drawn for blood gas analysis and hemoglobin (Hgb) determinations. Pre-injury (time 0) measurements of HR, BP, Ppa, and Ppw were recorded. Determinations of EVLW and Qt were then made. These were all repeated at each measurement period in the same order.

Once these baseline measurements were obtained, the dogs were placed in the right lateral position, and the distal trachea was cannulated *via* a side port on the tracheotomy tube. A polyethylene cannula having a plugged end and numerous fenestrations along its distal 2 cm was used, and 0.5 ml/kg of 0.1 N HCl was injected. The cannula was flushed with 10 cc of air. The dog was turned to the left lateral position, and a second injection of 0.5 ml/kg of 0.1 N HCl was made and the cannula flushed.

During the first hour after instilling HCl, the Ppw was maintained at 12 mmHg with small infusions of 6% Dextran as needed. At the end of this hour (Time = 1 h), the measurements were repeated. These represented the baseline values of the key measurements prior to treatment of the acute lung injury.

TREATMENT PERIOD

The 18 dogs were then randomized into three equal groups, receiving different interventions during the 4-h treatment period. The interventions separating the experimental groups were as follows:

Control group. In this group, the Ppw was maintained at 12 mmHg throughout the 4-h treatment group by intermittent infusion of small amounts of 6% Dextran (50–250 ml).

Plasmapheresis group. In this group, whole blood was removed and spun down in an IEC Centra-7 centrifuge. The plasma was separated off and the pooled red corpuscles reinfused. This procedure was repeated as necessary to achieve, within 30 min, a target Ppw of 5

mmHg. In general, Ppw was reduced within 15 min; thereafter, intermittent plasmapheresis or infusion of 6% Dextran were used to maintain the Ppw at 5 mmHg throughout the remainder of the treatment period.

Nitroprusside group. This group received NP in doses sufficient to reduce mean arterial pressure (MAP) by 25%, a reduction associated with Ppw values no different than those of the plasmapheresis group. This was achieved by progressively increasing the dose of nitroprusside until the desired reduction in MAP was effected. This was accomplished within 30 min, and required final doses of nitroprusside ranging from 3.9–25.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (mean dose 19.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Throughout the remainder of the 4-h treatment period, these dogs were maintained on this dose of nitroprusside.

In all groups, all measurements were repeated at 1.5, 3, and 5 h into the experiment; *i.e.*, 0.5, 2, and 4 h into the treatment period. The dogs were then heparinized (200 units/kg) and exsanguinated. *Via* a midline thoracotomy, the hila were clamped and the right and left lungs excised with care not to lose edema fluid from the airways. Wet weights (WW) and wet weight to body weight (WW/BW) determination of the excised lungs were immediately found on a Sartorius scale. The lungs were then placed in a vacuum oven (Thelco) at 60° C and 400 mmHg of absolute pressure until a constant dry weight (DW) was obtained. Total EVLW determined gravimetrically was calculated as WW − DW; as no technique was used to quantitate residual intravascular blood trapped after exsanguination, this provides a slight overestimate ≐ 2 ml/kg[5], a value quite small in relation to the EVLW of all groups.

STATISTICAL METHODS

Analysis of variance was used to test for differences among the three experimental groups at time 0 and 1 h. When the F-statistic indicated no significant difference among the three groups at both times, a paired Student's *t* test was used to compare the values before and 1 h after acute lung injury for all 18 dogs. To control for variability in the magnitude of lung injury produced prior to treatment, the value of each variable at each treatment period was expressed as the change from the 1-h value. Analysis of variance was then performed upon these values to test for differences among the three groups. When the F-statistic indicated significance, Neuman-Keuls multiple comparison tests were performed to determine which groups differed.

Results

The measurements obtained before HCl showed no significant difference in any variable among the three

TABLE 1. Effect of HCL-induced Pulmonary Edema on Key Variables (Mean ± SD)

	Baseline (Time 0)	1 h after HCl
EVLW (ml)	175 ± 65	250 ± 66*
Qva/Qt (%)	10.8 ± 6.1	21.2 ± 8.0*
Pa_{O_2} (mmHg)	319 ± 36	214 ± 72*
QO_2 (ml · min^{-1} · kg^{-1})	45.4 ± 5.5	39.0 ± 9.5*
Qt (l/min)	7.9 ± 2.3	7.6 ± 1.7
P_{pw} (mmHg)	12.5 ± 0.8	12.3 ± 1.1
P_{pa} (mmHg)	22.3 ± 4.5	22.5 ± 3.2
MAP (mmHg)	147 ± 14	145 ± 15
HR (/min)	160 ± 22	156 ± 22

* $P < .01$ by paired t test.

groups. Similarly, 1 h after HCl instillation, before any treatment, there were no differences among groups. The mean values of key variables for all 18 dogs at time 0 and 1 h are in table 1. In the 1-h interval, the hemodynamic variables did not change significantly. However, lung injury was signalled by increased EVLW and Qva/Qt, and reduced Pa_{O_2} and QO_2.

HEMODYNAMICS

Figure 1 shows the effect of the interventions on pulmonary vascular pressures. In the controls, Ppa and Ppw remained unchanged through the experiments. An immediate decline in Ppw occurred in the plasmapheresis group, as per the experimental design. The same decline in Ppw occurred in the nitroprusside-treated dogs. In both groups, the Ppw remained at 5 through the end of the experiment. A similar decline in
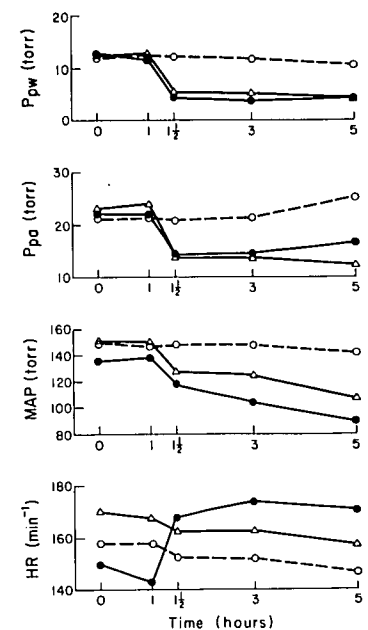

FIG. 1. Mean values of hemodynamic variables in three groups (open circle = control; closed circle = NP; triangle = P) at five measurement times. The change from the pretreatment (1 h) values of all pressures was significantly different (*P* < .05) in the plasmapheresis and nitroprusside groups than in group C at 1.5, 3, and 5 h. The change in heart rate from 1 h was significantly different in NP than in the other two group at 1.5, 3, and 5 h (*P* < .05).
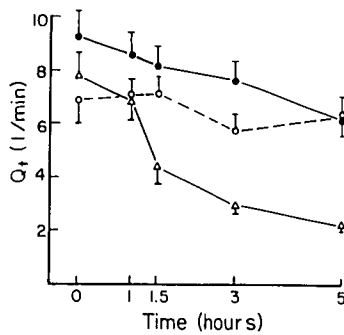
FIG. 2. Mean values (±SEM) of Qt of the three groups (see fig. 1 for symbols) at five measurement points. The change from the 1-h value in P is significantly different from control (*P* < .05) at 1.5, 3, or 5 h, and different from NP at 1.5 and 3 h.

FIG. 3. Mean values (±SEM) of EVLW measured by thermal dye dilution technique in three groups (see fig. 1 for symbols) at five measurement times. There were no differences among groups at time 0 and 1 h. The change from the 1-h values was significantly different in the treated (NP and P) dogs than in the control dogs (*P* < .05) at 1.5 and 5 h.

Ppa occurred in both treated groups. MAP decreased by 22% in the nitroprusside dogs at 1.5 h (0.5 h after nitroprusside intervention). Plasmapheresis-treated dogs had a similar decrease of 15% at 1.5 h. Both groups tended toward a lower MAP by the end of the study. Controls showed no change in MAP. Heart rate remained unchanged in the plasmapheresis and control animals, but increased approximately 20% in the nitroprusside-treated group and remained at that level. The change from 1 h was different from both of the other groups at all measurement periods.

Cardiac output did not change with time in the control group (fig. 2). In group P, Qt decreased by 37% when Ppw was lowered at 1.5 h, and continued to decrease to less than half of the pre-treatment values by the end of the study. In contrast, the cardiac output of the nitroprusside group did not decrease significantly when Ppw was lowered at 1.5 h, and it remained approximately constant until 5 h when there was a statistically significant (*P* < .05, paired *t*) decrease of 1.4 l/min from the 3-h value. Accordingly, there was a significant difference between groups P and NP in their change in Qt at 1.5 and 3 h from 1-h values.

Pulmonary vascular resistance (PVR) increased in all groups (table 2). The increase in the P group was significantly larger than in the other two groups. Systemic vascular resistance (SVR) doubled in P by 5 h. At 5 h,
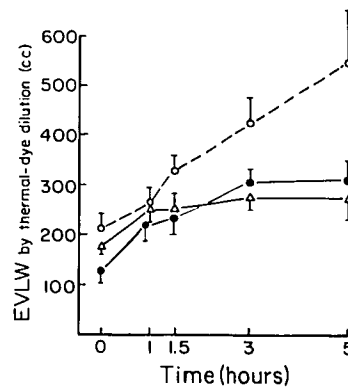
however, SVR was unchanged in C and NP. At 1.5 and 3 h, it had decreased in NP from 17.0 mmHg/l/min to 14.4 and 13.6, respectively.

PULMONARY EDEMA

Measurements with EVLW by thermal dye dilution technique in group C increased linearly with time throughout the experiment (fig. 3). By 5 h, there was an increase of 285 cc from the 1-h value. In contrast, EVLW did not increase after Ppw was reduced in both the plasmapheresis- and nitroprusside-treated groups; the increases in EVLW between 1 and 5 h were only 23 ± 78 ml in group P and 84 ± 58 ml in group NP. These changes from the 1-h value were both significantly less (*P* < .05) than the change in the controls.

These results were confirmed by the gravimetric estimates of edema in the lungs excised from the exsanguinated dogs (table 3). Both WW/BW and WW/DW indices confirmed considerable edema in all groups, compared to corresponding values in normal dogs.[5] There was no difference between the P and NP groups by either WW/BW or WW/DW measurements, but both groups were different from untreated controls. Gravimetric EVLW showed a similar pattern. When these gravimetric estimates were plotted against the 5-h

TABLE 2. Effects of Treatments on Pulmonary and System O_2 Exchange and Vasoconstriction (mean ± SD)

	Control		Plasmapheresis		Nitroprusside	
	1 h	5 h	1 h	5 h	1 h	5 h
Pa_{O_2} (mmHg)	225 ± 91	163 ± 100	220 ± 45	287 ± 28	199 ± 85	242 ± 92
Hgb (g%)	9.2 ± 1.9	8.8 ± 2.5	10.5 ± 2.5	14.9 ± 3.5	9.4 ± 1.8	10.5 ± 2.0
QO_2 (ml·min^{-1}·kg^{-1})	35.0 ± 8.0	27.2 ± 3.7	38.8 ± 9.5	20.9 ± 6.9	46.1 ± 9.3	36.8 ± 3.9
Pa_{CO_2} (mmHg)	36 ± 6	35 ± 4	35 ± 4	33 ± 5	33 ± 3	26 ± 8
pHa	7.33 ± .06	7.30 ± .04	7.35 ± .07	7.34 ± .06	7.34 ± .06	7.39 ± .05
PVO_2 (mmHg)	56 ± 10	45 ± 8	58 ± 8	44 ± 8	59 ± 11	58 ± 9
SVR (mmHg/l⁻·min⁻¹)	21.5 ± 4.3	22.1 ± 4.5	22.1 ± 4.5	45.3 ± 11.9	17.0 ± 4.5	16.1 ± 4.3
PVR (mmHg/l⁻·min⁻¹)	1.29 ± .58	2.20 ± .90	1.66 ± .31	4.26 ± 1.6	1.23 ± .54	2.15 ± 1.05
VO_2 (ml/min)	186 ± 37	196 ± 43	193 ± 66	163 ± 39	172 ± 9	157 ± 8

TABLE 3. Pulmonary Edema Measurements at 5 h (mean ± SD)

	Thermal Dye EVLW (g)	Gravimetric			
		EVLW (g)	WW/BW (g/kg)	WW/DW	DW/BW (g/kg)
Control	548 ± 248	655 ± 124	26.1 ± 3.6	9.03 ± 1.27	2.90 ± .29
P	277 ± 104*	434 ± 100*	18.3 ± 2.8*	7.43 ± .36*	2.47 ± .42
NP	314 ± 77*	317 ± 91*	14.9 ± 2.4*	6.48 ± 1.50*	2.34 ± .23*
Normal dogs	175 ± 65†		8.6 ± 1.4‡	4.64 ± .23‡	1.86 ± .31‡

* Different from control, $P < .01$.
† Value of all dogs at time 0.

‡ Values obtained from reference 5.

values of thermal-dye EVLW, most values for groups C and P lay below the line of identity (fig. 4), indicating an underestimation by thermal-dye technique for these groups. However, the values for NP lay close to the line of identity. DW/BW ratios showed higher values in all groups than in normal dogs. In group C, DW/BW was 2.91, and this was higher than the values of either treated group.

PULMONARY AND SYSTEMIC OXYGEN EXCHANGE

After 1 h, pulmonary venous admixture continued to increase in the control group (fig. 5), and a further
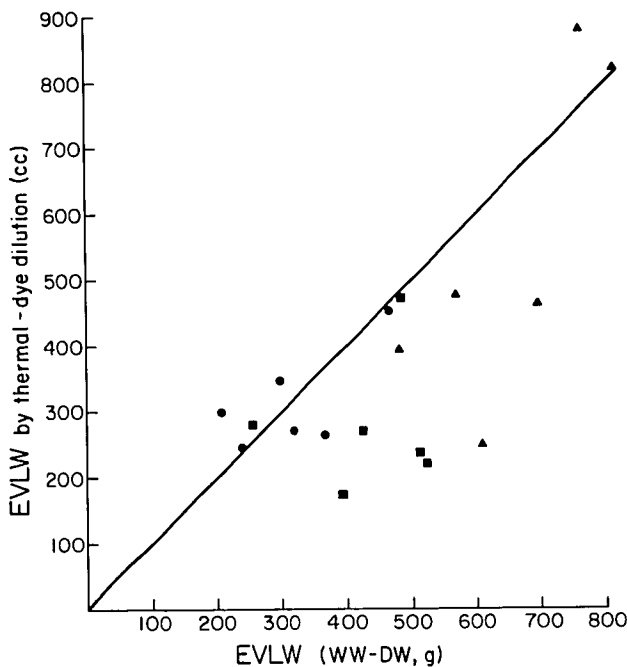

FIG. 4. Comparison of EVLW as measured by thermal dye dilution technique (ordinate) and gravimetric methods (abscissa) in six dogs in each of three groups (circle = NP; square = P; triangle = C). The line of identity is drawn. Thermal dye dilution consistently underestimated EVLW in P and C, but not in NP. Note that residual intravascular blood cause a small overestimate (average 40 gr) of gravimetric EVLW.

increase in Qva/Qt (%) of 5.3 was found by 5 h. In contrast, there was an immediate decrease in Qva/Qt in group P at 1.5 h, which persisted until 5 h when Qva/Qt (%) was 13.5 less than the 1-h value. These changes from 1-h values were significantly different from those in the control group at 1.5, 3, and 5 h. In group NP, Qva/Qt did not change at 1.5 or 3 h. Accordingly, this group had a similar Qva/Qt to group C and a greater Qva/Qt than group P ($P < .05$) at 3 h. By 5 h, Qva/Qt in group NP decreased by 7.9 from the 3-h value ($P < .05$, paired t). This Qva/Qt was significantly different from that of the control group.

Pa_{O_2} (table 2) continued to decrease in the control group after 1 h, but increased in P. Pa_{O_2} did not change in group NP at 1.5 h (a decrease of 5 mmHg) and 3 h (a decrease of 18 mmHg). However, at 5 h, there was an increase of 43. The change from the 1-h to the 5-h values in both experimental groups were significantly different than control. Despite an elevated Pa_{O_2}, oxygen delivery (QO_2) fell significantly in the P group ($P < .05$). By 5 h, there was a fall of 18 cc $\cdot$ min$^{-1} \cdot$ kg^{-1} from the pretreatment value. In contrast, NP showed no fall at 1.5 or 3 h, so the change in O_2 delivery was significantly different ($P = .01$) between NP and P at 3 h. However, in the NP group at 5 h, there was a fall of 9 cc $\cdot$ min$^{-1} \cdot$ kg^{-1} from the 1-h value; this was similar to the fall of 8 cc $\cdot$ min$^{-1} \cdot$ kg^{-1} at 5 h in group C. The values of PvO_2 showed significant reductions in the C and P groups, but none in NP (table 2).

QO_2 decreased in P, despite an increase in hemoglo-
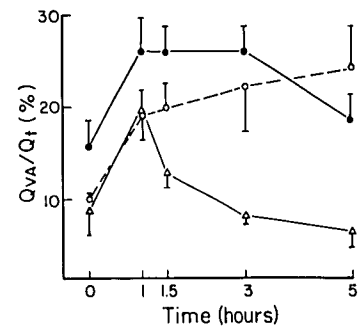

FIG. 5. Mean values (±SEM) of Qva/Qt of the three groups (see fig. 1 for symbols) at the five measurement times. The change from 1 h in P was significantly different from control at 1.5, 3, and 5 h ($P < .05$) and from NP at 3 h.

bin concentration, which was unchanged in the other two groups. The increase in hemoglobin concentration from the 1-h value in P was significantly different than in NP and C (table 2). Values of *p*H and p_{CO_2} were not significantly different among the groups.

Discussion

EXTRAVASCULAR LUNG WATER

Extravascular lung water declined by all methods of measurement when a decrease in pulmonary capillary wedge pressure was produced. The effects of the decreased hydrostatic pressure produced by lowering Ppw with nitroprusside or plasmapheresis has been previously reported in the canine oleic acid model of noncardiogenic pulmonary edema.[2] This study found similar results in a different model of ARDS.

This study also describes the time course of the effects of a lowered Ppw on EVLW. The utility of using indocyanine green and cold indicators for following the development of pulmonary edema is clear. Although EVLW continued to increase linearly with time in the control dogs, the lowering of the Ppw in both experimental groups led to an immediate halt in further edema accumulation. Gravimetric methods of measuring EVLW confirmed the thermal-dye dilution technique results. These results are consistent with the cause of the decreased edema being decreased hydrostatic pressure; the decrease in Ppw led to an immediate decrease in pulmonary leak.

The formation of pulmonary edema can be predicted from the Starling equation:[1]

$$Q = k[(Pmv - Ppmv) - \sigma(\pi mv - \pi pmv)],$$

where Q is net filtration rate, k is the liquid conductance of the microvascular barrier, P is hydrostatic pressure in the microvascular (mv) lumen and in the perimicrovascular (pmv) interstitial fluid, σ is the reflection coefficient (representing the relative resistance of the barrier to protein leakage), and π is the oncotic pressure. The proteinaceous edema produced in the HCL aspiration model is presumably secondary to changes in k and σ.[6,7] The Starling equation predicts the results of this study; even in edema characterized by normal hydrostatic pressure, a decrease in hydrostatic pressure should result in less fluid accumulation. Whether the mean pulmonary capillary pressure is best reflected by the Ppw or other parameters,[8] the decreased Ppw and Ppa produced in this study clearly resulted in decreased capillary hydrostatic pressure.

The thermal dye dilution technique may underestimate EVLW in HCl-induced pulmonary edema.[9] In this study, the technique did underestimate EVLW in the control and plasmapheresis dogs. In contrast, there was a more accurate estimation of EVLW in dogs treated with nitroprusside. Although this may make it impossible to compare directly the accurate values of EVLW among the various treatments while the animals are alive, the direction of change within each group is validly revealed. Furthermore, the underestimation was not large, as determined by comparison with gravimetric methods at 5 h. One possible explanation for the differences in underestimation of EVLW among the groups is that nitroprusside blocked hypoxic vasoconstriction to allow access to all edema by the cold injectate, with complete diffusion of the temperature indicator. Incomplete diffusion of a temperature indicator has been previously documented; pulmonary embolization leads to a consistent underestimation of EVLW when edema is abundant.[10] When the cold is not able to equilibrate with all edematous units, whether secondary to hypoxic vasoconstriction or embolization, underestimation of EVLW would occur. One would thus expect that the direct dilation effects of NP would lead to a more accurate and higher estimation of EVLW by thermal-dye dilution in NP-treated dogs, as compared to controls. These considerations support the conclusions drawn in this study; EVLW did not increase after NP was initiated.

RELATIONSHIP OF PULMONARY EDEMA, OXYGEN EXCHANGE AND BLOOD FLOW

Our data demonstrated that pulmonary venous admixture varies with cardiac output when edema is stable. When Qt fell with plasmapheresis at 1.5 h, Qva/Qt decreased; yet, when Qt was maintained by nitroprusside, Qva/Qt did not change. When cardiac output decreased between 3 and 5 h in group NP with no interval change in EVLW, pulmonary venous admixture also decreased. This relationship between Qt and Qva/Qt in canine oleic acid edema[11] and in patients[12] with ARDS has been attributed to redistribution of increased pulmonary blood flow toward edematous lung units. This, in turn, could be explained by the reduction of hypoxic vasoconstriction in edematous lung units by increased mixed venous P_{O_2} or by preferential recruitment of pulmonary vessels in edematous areas by the increased Ppa associated with greater cardiac output.[11-14] Although the increase in Qva/Qt on nitroprusside can be explained by the associated increase in cardiac output, our data do not exclude an additional and direct pulmonary vasoactive effect of nitroprusside in increasing Qva/Qt, as has been reported in other canine[15,16] and clinical studies.[3,17] Indeed, the better

and higher *in vivo* estimate of EVLW in our NP group may be attributed to such a vasoactive effect. While this effect did not appear to be important in this study, it is conceivable that other vasodilators might maintain cardiac output at reduced Ppw and EVLW without this potential adverse effect.[18]

While a low Ppw was associated with decreased cardiac output in the plasmapheresis group, at this same Ppw nitroprusside maintained the cardiac output at both the 1.5- and 3-h measurements. This improved cardiovascular function may be secondary to reduced resistive afterload;[2,14,19] SVR (mmHg/l/min) decreased on NP to 13.6 at 3 h, but increased to 40.5 at the same time in group P. Cardiac output may also have been maintained by changes in left ventricular compliance, with a greater end-diastolic volume and preload at the same Ppw, as demonstrated in patients with congestive heart failure[20] and ARDS.[21] Contractility, on the other hand, is not affected by NP.[22] Direct measurements of pressure and volume need to be done to determine if the effects on Qt in canine HCl acid aspiration are secondary to cardiac or systemic effects. Presumably, the decrease in cardiac output at the same Ppw between 3 and 5 h in NP is due to reversal of these beneficial effects of nitroprusside. Conceivably, the relatively high doses of nitroprusside caused toxic cyanide levels by 5 h.[23] Yet potential cyanide toxicity is quite unlikely by our 3-h measurements,[23] when the favorable effects of nitroprusside on EVLW and Qt were quite evident. We contend that the demonstrated therapeutic effects of nitroprusside may be obtained at lower, non-toxic doses.

We conclude that nitroprusside and plasmapheresis have the benefit of reducing pulmonary edema, probably by a decreased capillary hydrostatic force caused by lower pulmonary vascular pressures. Despite an increased hematocrit, the hemodynamic effects of plasmapheresis are potentially harmful to the extent that associated reduction in both cardiac output and oxygen delivery reduce O_2 consumption.[24] However, nitroprusside therapy reduced edema without reducing cardiac output. Note that the effect of sodium nitroprusside on hypoxic pulmonary vasoconstriction had little effect on Pa_{O_2} because the associated increase in cardiac output and mixed venous O_2 content (see table 2 at 5 h) caused no more arterial hypoxemia when venous admixture was 20% with nitroprusside than when Qva/Qt was 7% with plasmapheresis[11,13,14,25] (fig. 5 at 5 h). In both groups, edema was reduced compared to the untreated controls yet O_2 delivery with nitroprusside was about twice that in the plasmapheresis group. Accordingly, nitroprusside therapy is one way to minimize low pressure pulmonary edema induced in dogs by HCl as-

piration (as well as by intravenous oleic acid[2]) while maintaining adequate oxygen delivery. To the extent that similar effects of non-toxic doses of nitroprusside occur in ARDS of diverse etiologies,[3] these model studies suggest an approach to the cardiovascular management of the early exudative stage: seek the lowest pulmonary wedge pressure compatible with adequate oxygen delivery. Such treatment may shorten the duration of ventilation and intensive care and so reduce the attendant complications. Of course, this approach requires a clinical trial to ensure that these benefits are clinically significant and that other more important complications do not ensue.

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