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The effect of hypertonic saline dextran solutions on hypoxic pulmonary vasoconstriction in anaesthetised piglets

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The effect of hypertonic saline dextran solutions on hypoxic pulmonary vasoconstriction in anaesthetised piglets. M. Bellezza, F. Kerbaul, L. Roussel, M. Imbert, C. Guidon. ©ERS Journals Ltd 2002.

ABSTRACT: Hypoxic pulmonary vasoconstriction (HPV) is a regulatory mechanism by which blood is diverted from poorly ventilated to better ventilated areas of the lung. The aim of the present study was to assess the extent to which hypertonic saline dextran and dextran solutions modify the magnitude of HPV during isovolumic haemodilution in intact acutely instrumented piglets.

Eighteen large white piglets were anesthetised and assigned to two groups. Mean pulmonary arterial pressure (PAP) and cardiac output (Q), systemic arterial pressure and left arterial pressure (LAP) were measured. A decrease in Q was obtained by reducing venous return. This enabled measurement of transpulmonary pressures (mean PAP minus LAP) at four levels of Q in hyperoxia (inspiratory oxygen fraction (F_{i,O_2})=0.4), then in hypoxia (F_{i,O_2}=0.1) in the two groups before blood soustraction (10 mL·kg^{-1}) and after loading with sodium chloride (NaCl) 7.5% and dextran 6% or with dextran 6% alone. Dextran alone led to a decrease in mean PAP–LAP/Q values, and NaCl with dextran was associated with a significant shift of mean PAP–LAP/Q plots to higher pressures in hypoxia.

Hypertonic saline dextran solution, as replacement fluid in isovolaemic haemodilution increased the magnitude of hypoxic pulmonary vasoconstriction, whereas dextran solution reduced it.

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Fluid expanders are usually used for the resuscitation of intraoperative hypovolaemia or haemorragia. They act on different parts of the cardiovascular system, mainly the heart and vascular resistances. Therefore, the vascular resistance response differs with the solution used and the vascular bed of the organ studied [1, 2].

Hypertonic saline solution (sodium chloride (NaCl) 7.5%) with dextran 6% has been shown to increase volaemia ten-times more than dextran 6% by an osmotic effect (transfer of water from the interstitial to vascular space), this, in turn, increases cardiac output (Q) and decreases systemic vascular resistance [3, 4]. However, the effect of this hypertonic saline and dextran solution on pulmonary circulation remains unknown. Dextran used alone can also reduce pulmonary vascular resistance (PVR) resulting in a reduction of blood viscosity.

Therefore, the effect of these two different plasma expanders on pulmonary vascular circulation was studied, focusing on the hypoxic pulmonary vascular response using pressure (P)/Q relationships in intact anaesthetised piglets submitted to normovolaemic haemodilution. It was hypothesised that these two different plasma expanders would have different effects on hypoxic pulmonary vasoconstriction (HPV), and thereby modify gas exchange. Piglets were chosen because they exhibit the greatest pulmonary vasoconstriction response to hypoxia [5]. In this study, pulmonary haemodynamics were evaluated by multipoint P/Q (mean pulmonary arterial pressure (PAP)–LAP/Q) plots, which provide quantitative characterisation of the PVR/Q relationships [6].

Materials and methods

The study design was reviewed and approved by the animal ethics committee of the La Timone Medical School in Marseille, France. All procedures complied with the Guiding Principles of the Care and Use of Animals of the American Physiological Society.

Animal preparation

After a 12-h fasting period with free access to water, 18 large white piglets (12–15 weeks) were assigned to two groups (group 1: NaCl and dextran, n=9, mean weight 28.2±3.5 kg; group 2: dextran, n=9, mean weight 26.9±2.4 kg).

The piglets were premedicated with ketamine (20 mg·kg^{-1} *i.m.*), midazolam (0.1 mg·kg^{-1} *i.m.*) and atropine (0.25 mg *i.m.*) and placed in a supine position. Anaesthesia was induced with midazolam (0.1 mg·kg^{-1} *i.v.*), fentanyl (2 μg·kg^{-1} *i.v.*) and maintained

with intravenous infusions of fentanyl (20 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and midazolam (0.1 $mg \cdot kg^{-1} \cdot h^{-1}$). Muscle paralysis was obtained *via* 1 $mg \cdot kg^{-1}$ intravenous vecuronium bromide and maintained with an infusion of vecuronium bromide (2 $mg \cdot kg^{-1} \cdot h^{-1}$) after tracheostomy. The lungs were mechanically ventilated *via* a no.6 cuffed tracheostomy tube (Tracheosoft Lanz^{TM} 101-70 ID 6.0; Malindkrodt Medical, Athlone, Ireland) with a servo ventilator B900 (Siemens, Elema, Sweden) initially set to deliver a inspiratory oxygen fraction (F_{I,O_2}) of 0.4, a tidal volume ~12–15 $mL \cdot kg^{-1}$ and a respiratory rate adjusted to maintain carbon dioxide (CO_2) tension in arterial blood (P_{a,CO_2}) between 4.7–5.2 kPa. No positive end-expiratory pressure was used, but periodic deep inspirations were systematically administered after thoracotomy and at the end of each P/Q relationship to prevent atelectasis. Inspired and expired fractions of oxygen (O_2) and CO_2 were measured using an ULTIMA II^{TM} infrared spectrophotometer (Datex, Helsinki, Finland).

Throughout the experiment, 0.9% NaCl (4 $mL \cdot kg^{-1} \cdot h^{-1}$) was infused into the left internal jugular vein. The temperature was maintained at 38–39°C using an electrical heating pad. Metabolic acidosis, when present, was corrected by slow infusion of triaminolacetate (THAM^{TM}; Roger Bellon Laboratories, Neuilly sur Seine, France). A thermistor-tipped Swan-Ganz catheter (93A-131-7F; Edwards Laboratories, Santa Anna, CA, USA) was inserted into the right internal jugular vein and positioned with reference to right arterial pressure, mean PAP and mean capillary wedge pressure. It was used to measure central core temperature and to perform mixed venous blood sampling. A polyethylene catheter was placed in the abdominal aorta *via* the right femoral artery for systemic arterial pressure (SAP) measurements and arterial blood sampling. A balloon catheter (Redigard^{TM}, 9F 40 mL; St Jude Medical Inc., Cardiac Assist Division, Chelmsford, MA, USA) was advanced into the inferior vena cava through a right femoral venotomy. Inflation of this balloon produced a gradual decrease in Q by reducing venous return. All catheters were inserted through peripheral cut-down.

A left thoracotomy was performed to place a polyethylene catheter (Liddle LAP 17 G 50.6 cm; Research Medical Inc., Salt Lake City, UT, USA) *via* the atrial appendage into the left atrium to monitor LAP. The thoracotomy was hermetically closed, a tube was inserted in the pleural space and connected first to a vacuum pump and then to a water seal as soon as a vacuum was achieved. Thrombus formation along the catheters was prevented by the administration of sodium heparin 100 $UI \cdot kg^{-1}$ *i.v.* just before insertion and 100 $UI \cdot kg^{-1} \cdot h^{-1}$ continuously.

Measurements

Pulmonary, cardiac and systemic pressures were measured using disposable transducers (Pressure monitoring kit; Baxter SA, Maurepas, France) connected to a multichannel monitor (Merlin^{TM}; Hewlett-Packard Inc., Palo Alto, CA, USA). Zero reference was located at midchest, and values were taken at the end of expiration. Cardiac frequency (*f*C) was continuously recorded by three electrocardiographic leads connected to the same monitor. Q was rapidly measured at the end of expiration by thermodilution using injections of 5 mL of 0.9% NaCl at 0°C. Results were analysed by computer. Values correspond to means of at least three measurements after elimination of readings 10% higher or lower than the previous value. Haemodynamic data were sampled every 20 s, digitised and stored on the hard disk of a personal IBM PC/AT (Hewlett Packard Vectra 386 DX 33 and Hewlett Packard software). Arterial and mixed venous pH, partial pressure of CO_2 (PCO_2) and partial pressure of O_2 (PO_2) were immediately measured after drawing the samples using an automated analyser (ABL 500; Radiometer, Copenhagen, Denmark). All blood gas values were corrected according to central temperature. Body surface area (m^2) was calculated as $0.112 \times weight^{2/3}$ (kg) [7, 8].

Protocol

After ensuring steady-state conditions in the two groups for 10 min at an F_{I,O_2} of 0.4 (stable SAP, PAP, LAP, Q, end-tidal CO_2, and *f*C) and before blood soustraction, the first four-point P/Q plot was generated in 20 min: the first point corresponding to basal Q, followed by one point for each incremental inflation of the vena cava balloon (three points). Each point of P/Q plot construction took 5 min. A similar four-point P/Q plot was constructed at a F_{I,O_2} of 0.12 for 30 min, when O_2 tension in arterial blood (P_{a,O_2}) reached 5.3–6.7 kPa. Previously reported stimulus/response curves for HPV in intact anaesthetised ventilated piglets have shown that the whole-lung hypoxic pressor response is undetectable if F_{I,O_2} >0.3 and maximal when F_{I,O_2}=0.12 [7]. Similar plots were generated at F_{I,O_2}=0.4 and F_{I,O_2}=0.12 after blood soustraction (10 $mL \cdot kg^{-1}$) and loading with NaCl 7.5% with dextran 6% (1 $mL \cdot kg^{-1}$; group 1) or with dextran 6% alone (10 $mL \cdot kg^{-1}$, group 2) [9]. At each step of the study and for each level of Q, measures of haemodynamic parameters (SAP, LAP, PAP, *f*C, arterial and mixed venous blood gases were performed.

At each step of this study (baseline, dextran, dextran with NaCl) in hyperoxia and in hypoxia, 5 mL of blood was collected in dry tubes and centrifuged at 4000 $t \cdot min^{-1}$. Plasma was frozen at -80°C until the end of the study. Osmolalities were also measured with an osmometer (Microosmomètre 3 MO; Radiometer, Copenhagen, Denmark).

Statistical analysis

Individual PAP–LAP/Q plots appeared to be linear, so a linear regression analysis (least-square method) was used to compute slopes. Q was considered to be the independent variable and P as the dependent variable. To obtain composite P/Q plots, pressures interpolated from the regression analysis from individual piglets were averaged at 0.5 $L \cdot min^{-1} \cdot m^{-2}$ intervals of Q from 2.5 to 4.5 $L \cdot min^{-1} \cdot m^{-2}$. Blood gases and

haemodynamic data were analysed in each group by analysis of variance for serial measurements. When the significance of a factor was $p<0.05$, a Bonferroni *post-hoc* test was performed to compare specific situations. Comparison of osmolalities in each group were performed by paired t-tests. Data are presented as mean±SD.

Results

Stepwise inflation of the balloon catheter in the inferior vena cava induced variations in Q. Mean values ranged from 1.8–5.4 $L \cdot min^{-1} \cdot m^{-2}$ (tables 1 and 2). The PAP–LAP/Q relationships were linear in all experimental conditions, before and after infusion of hypertonic saline dextran solutions. Correlation coefficients were always >0.8 (table 3).

At the lowest Q, blood gases mainly changed *via* a decrease in mixed venous P_{O_2} (tables 1 and 2).

Effect of sodium chloride with dextran

Hypoxia caused a pronounced acceleration of f_C ($p<0.05$) after loading with the NaCl and dextran solution. Other haemodynamic values were not significantly modified.

Acute normovolemic haemodilution significantly reduced haemoglobin and did not induce a significant rise of osmolalities either in hyperoxia or in hypoxia. In hyperoxia, loading with NaCl and dextran did not cause a significant shift of the P/Q relationship. In hypoxia, this solution induced an upward shift of the P/Q relationship when compared to hypoxia baseline vasoconstriction (fig. 1a). Comparison of variation in the hypoxic pressor response ((PAP–LAP) at $F_{i,O_2}=0.12$ minus (PAP–LAP) at $F_{i,O_2}=0.4$ for all levels of Q) without and then with NaCl with dextran (fig. 1b) showed a significant increase after infusion of NaCl with dextran.

Effects of dextran

In hyperoxia and in hypoxia, LAP, PAP and mean Q increased after filling with dextran, but osmolality was not modified. Acute normovolemic haemodilution significantly decreased haemoglobin in hyperoxia and in hypoxia. Loading with dextran did not cause a significant shift of the P/Q relationship ($p=0.06$).

In hypoxia, dextran caused a progressive downward shift of the P/Q relationship when compared with hypoxia baseline ($p=0.02$) (fig. 2a). Variation in the hypoxic pressor response ((PAP–LAP) at $F_{i,O_2}=0.12$ minus (PAP–LAP) at $F_{i,O_2}=0.4$ for all levels of Q) showed a significant decrease after filling with dextran (fig. 2b).

Table 1. – Effects of sodium chloride (NaCl) with dextran on haemodynamic and blood gas data

	Q	Hyperoxia		Hypoxia	
		Baseline	NaCl/dextran	Baseline	NaCl/dextran
SAP mmHg	HQ	126±7	113±8	112±8	102±8
	LQ	72±7	77±10	50±3	61±7
LAP mmHg	HQ	7±1	8±1	9±1	9±1
	LQ	6±1	7±1	6±1	6±1
f_C beat·min^{-1}	HQ	142±12	136±15	141±12	154±11$^{\#}$
	LQ	160±15	179±14	158±17	183±11$^{\#}$
Q $L \cdot min^{-1} \cdot m^{-2}$	HQ	4.1±0.3	3.8±0.3	3.9±0.3	3.8±0.3
	LQ	2.1±0.4	1.9±0.3	2.0±0.2	1.8±0.2
PAP mmHg	HQ	20±1	20±2	33±3¶	38±2$^{\P,\#}$
	LQ	15±1	14±2	23±4	25±4
P_{a,O_2} kPa	HQ	37±4	37±4.5	4.8±0.3¶	5.7±0.4$^{\P,\#}$
	LQ	27.6±4.7	24.1±2.7	5.6±0.4¶	5.6±0.4¶
P_{a,CO_2} kPa	HQ	5.2±0.1	5.5±0.3	5.0±0.1	5.2±0.3
	LQ	5.3±0.3	4.4±0.1	4.9±0.3	4.7±0.3
pH	HQ	7.46±0.02	7.38±0.02$^{\#}$	7.44±0.02¶	7.40±0.02
	LQ	7.43±0.02	7.38±0.02$^{\#}$	7.37±0.03¶	7.38±0.02
Venous P_{O_2} kPa	HQ	6.5±0.5	6.0±0.4	3.7±0.4¶	2.9±0.3¶
	LQ	3.9±0.6	3.1±0.4	1.7±0.2 ¶	1.8±0.1¶
Haemoglobin g·dL^{-1}	HQ	9.2±0.4	8.1±0.6$^{\#}$	9.0±0.4	7.8±0.6$^{\#}$
	LQ	9.0±0.7	7.9±0.7$^{\#}$	9.2±0.6	8.0±0.7$^{\#}$
Osmolality mOsm·L^{-1}		298±3	286±14	292±18	286±19
PVR $mmHg \cdot min \cdot m^2 \cdot L^{-1}$	HQ	3.2±0.2	3.2±0.2	6.2±0.4¶	7.6±0.4¶
	LQ	4.3±0.3	3.8±0.3	8.5±0.5¶	10.3±0.4¶

Data are presented as mean±SD, n=9. Q: cardiac output; HQ and LQ: highest and lowest cardiac output respectively; SAP: systemic arterial pressure; LAP: left arterial pressure; f_C: cardiac frequency; PAP: pulmonary arterial pressure; P_{a,O_2}: oxygen tension in arterial blood; P_{a,CO_2}: carbon dioxide tension in arterial blood; P_{O_2}: partial pressure of oxygen; PVR: pulmonary vascular resistance; Significant difference $^{\#}$: $p<0.05$ between baseline and NaCl with dextran at the same level of Q; ¶: $p<0.05$ between hyperoxia and hypoxia at the same step.

Table 2. – Effects of dextran on haemodynamic and blood gas data

	Q	Hyperoxia		Hypoxia	
		Baseline	Dextran	Baseline	Dextran
SAP mmHg	HQ	116±6	106±3	91±8¶	102±7
	LQ	65±6	78±8	56±8¶	57±5
LAP mmHg	HQ	7±1	10±1#	7±1	9±1#
	LQ	5±1	6±1#	4±1	6±1#
f_C beat·min^{-1}	HQ	126±9	126±9	140±11¶	137±11¶
	LQ	130±11	144±15	163±11¶	171±11¶
Q L·min^{-1}·m^{-2}	HQ	4.4±0.4	5.4±0.5	4.1±0.4	5.4±0.5¶
	LQ	2.1±0.2	2.6±0.3	2.2±0.3	2.6±0.2
PAP mmHg	HQ	18±1	22±1#	37±2¶	39±2¶
	LQ	11±1	13±1#	19±1¶	19±1¶
P_{a,O_2} kPa	HQ	29±1.3	31.7±4.5	5±0.4¶	5.2±0.4¶
	LQ	29.6±2.7	32.4±4.9	5.3±0.4¶	5.9±0.4¶
P_{a,CO_2} kPa	HQ	5.2±0.3	4.9±0.1	4.7±0.1	4.9±0.1
	LQ	4.7±0.1	4.4±0.3	4.7±0.1	4.4±0.1
pH	HQ	7.43±0.01	7.40±0.01#	7.44±0.10¶	7.39±0.01#,¶
	LQ	7.45±0.01	7.41±0.01#	7.40±0.01¶	7.36±0.02#,¶
Venous P_{O_2} kPa	HQ	6.1±0.3	6.3±0.3	3.3±0.4¶	2.5±0.4¶
	LQ	4.5±0.5	4.1±0.4	2.3±0.1¶	2.3±0.1¶
Haemoglobin g·dL^{-1}	HQ	8.0±0.2	5.3±0.4#	9.0±0.4	6.2±0.5#
	LQ	9.0±0.4	5.7±0.4#	9.4±0.5	7.0±0.7#
Osmolality mOsm·L^{-1}		269±16	287±11	255±23	263±32
PVR mmHg·min^{-1}·m^2·L^{-1}	HQ	2.5±0.1	2.2±0.2	7.3±0.5¶	5.6±0.4¶
	LQ	2.9±0.2	2.7±0.3	6.8±0.5¶	5.5±0.4¶

Data are presented as mean±SD, n=9. Q: cardiac output; HQ and LQ: highest and lowest cardiac output respectively; SAP: systemic arterial pressure; LAP: left arterial pressure; f_C: cardiac frequency; PAP: pulmonary arterial pressure; P_{a,O_2}: oxygen tension in arterial blood; P_{a,CO_2}: carbon dioxide tension in arterial blood; P_{O_2}: partial pressure of oxygen; PVR: pulmonary vascular resistance. Significant difference #: $p<0.05$ between baseline and dextran at the same level of Q; ¶: $p<0.05$ between hyperoxia and hypoxia at the same step.

Table 3. – Slopes and correlation coefficients of the composites transpulmonary vascular pressure divided by cardiac output (P/Q) plots

	Slope mmHg·L^{-1}·min^{-1}·m^{-2}	Correlation coefficient
Hyperoxia		
Baseline	2.00±0.27	0.86±0.04
Dextran	1.90±0.49	0.81±0.06
Baseline	2.24±0.38	0.80±0.07
NaCl/dextran	3.76±1.50	0.87±0.05
Hypoxia		
Baseline	9.20±1.70*	0.94±0.01
Dextran	7.40±1.18*	0.92±0.01
Baseline	5.59±1.52*	0.86±0.04
NaCl/dextran	6.61±0.60*	0.87±0.06

Data are presented as mean±SEM, n=18 piglets; NaCl: sodium chloride. *: $p<0.05$ for comparison of slope at inspiratory oxygen fraction (F_{i,O_2})=0.4 *versus* slope at F_{i,O_2}=0.12 in the same step.

Discussion

This study was designed to assess the effects of hypertonic saline dextran and dextran solutions on the magnitude of HPV during isovolaemic haemodilution in intact acutely instrumented piglets. Hypertonic saline dextran solution, as replacement fluid in isovolaemic haemodilution, increased the magnitude of HPV, whereas dextran alone reduced it.

Piglets where chosen because they exhibit one of the greatest pulmonary vasoconstriction responses to hypoxia [5] and previous experiments have demonstrated linear P/Q relationships [7]. However, HPV shows a large interindividual and interspecies variability relative to vascular reactivity [10] Therefore, no statistical comparison was performed between the two groups at baseline as the hypoxic pressor response was more marked in the dextran group than in the NaCl with dextran group (fig. 1a and 2a).

In the current study, pulmonary vasomotor tone was evaluated by the generation of multipoint P/Q plots. This technique was developed by LODATO *et al.* [6] in conscious dogs, and has been used for different inspired O_2 concentrations. P/Q relationships allow discrimination of vasoactive from passive mechanical effects on the pulmonary circulation. This approach has been shown to be superior to isolated PVR calculations, which do not take into consideration PVR variations with respect to Q [11]. However, it has a number of limitations including systemic hypotension, changes in blood gases and changes in zonal conditions of the lung. This technique has already been used in mammals to test anaesthetic effects [12, 13] and physiological or metabolic manipulations on HPV [7, 14].

Hypovolemic hypotension is a common surgical problem during extensive surgical procedures and usual resuscitative measures include blood components, colloids and isotonic crystalloid solutions.

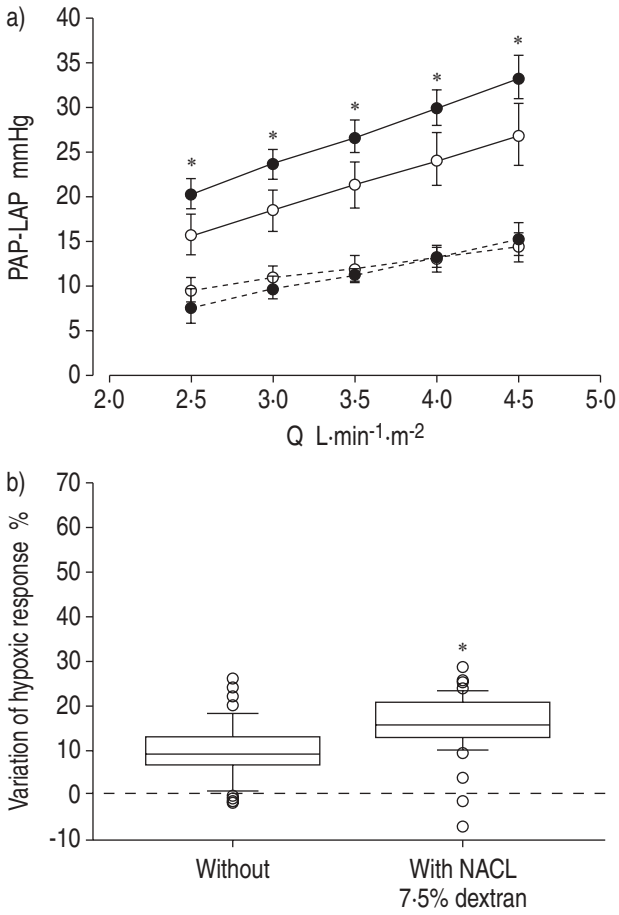

Fig. 1. – a) Extrapolated plots of pulmonary arterial pressure–left arterial pressure (PAP–LAP) *versus* cardiac output (Q) in hyperoxia (inspiratory oxygen fraction (F_{i,O_2})=0.4; ---) and in hypoxia (F_{i,O_2}=0.12; —), before (●) and after blood soustraction and filling with sodium chloride (NaCl) and dextran (○). Data are presented as means±SEM, n=9 piglets. *: $p<0.05$ for comparison of plots in hypoxia. b) Comparison of hypoxic pressor response ((PAP–LAP) at F_{i,O_2}=0.12 minus (PAP–LAP) at F_{i,O_2}=0.4 for all levels of Q) without and then with NaCl and dextran. Box plots show isolated values and 10th, 25th, 50th, 75th, and 90th percentiles. #: p= 0.0058.

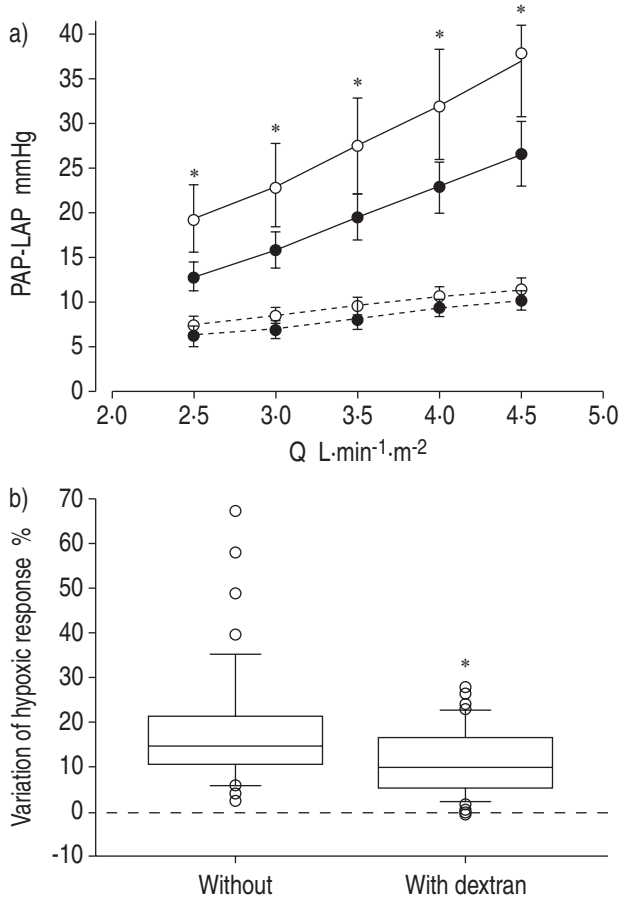

Fig. 2. – a) Extrapolated plots of pulmonary arterial pressure–left arterial pressure (PAP–LAP) *versus* cardiac output (Q) in hyperoxia (inspiratory oxygen fraction (F_{i,O_2})=0.4; ---) and in hypoxia (F_{i,O_2}=0.12; —), before (●) and after blood soustraction and filling with dextran alone (○). Data are presented as mean±SEM, n=9 piglets. b) Comparison of hypoxic pressor response ((PAP–LAP) at F_{i,O_2}=0.12 minus (PAP–LAP) at F_{i,O_2}=0.4 for all levels of Q) without and then with dextran alone. Box plots show isolated values and 10th, 25th, 50th, 75th, and 90th percentiles. #: p< 0.0001.

Hypertonic crystalloid solutions such as NaCl (7.5%) have been effective in the treatment of hypovolemic shock [15, 16]. The most striking features of resuscitation with hypertonic saline are the effectiveness and the speed of very small volumes. Reduction in volume infusion could subsequently reduce the large positive fluid balances and oedema associated with usual resuscitation regimens. The combination of a hyperoncotic colloid, such as dextran, with NaCl has been proposed to sustain the beneficial effects of hypertonic saline on cardiovascular function [2] and to lower the volumes of colloid required.

Acute isovolaemic anaemia has been shown to alter pulmonary gas exchange, possibly through attenuation of HPV in the atelectatic lung [17]. Hypothetical mechanisms for the effect of haemodilution on blood flow to the hypoxic lung include decreased blood viscosity on microcirculatory flow (rheological effect) or the accumulation of mediators causing inhibition of HPV, involving the endothelium derived relaxant factor nitric oxide [18]. However, in intact hyperoxic lungs, isovolaemic anaemia enhanced gas exchange as a result of favourable changes in pulmonary blood flow distribution when 6% hetastarch was used [19]. The results of the present study did not differ substantially, and other possible explanations for the reduction of HPV response in the dextran group were considered.

Dextran solutions are known to improve rheological blood properties due to their low viscosity in combination with haemodilution. Changes in blood viscosity and low haematocrit [20, 21] influence the magnitude of hypoxia-induced PAP decrease. Haemoglobin levels were lowered after dextran infusion. The rheological properties of dextran and a low haematocrit may explain the impairment of HPV in the dextran group. Metabolic situations, such as acidosis or alkalosis, could therefore modify the HPV response [22]. However, in the current study, no

significant variation of pH and P_{a,CO_2} were observed in the dextran group.

The main determinant of HPV is P_{a,O_2}, although P_{O_2} in mixed venous blood (P_{v,O_2}) may also play an important role in HPV [23]. In this study, decreases in P_{v,O_2} were only observed at a low Q, but no significant difference was found between baseline and dextran infusion.

Some factors, such as catecholamines, which can modify Q, may also act on HPV [24]. However, although no catecholamines were used in this study, no variations in *f*C or SAP were found before or after dextran infusion.

An increase in LAP has been shown to reduce vascular reactivity to hypoxia [14]. In this group of animals, LAP increased after dextran infusion in hypoxia. This could be one factor explaining the decreased hypoxic trans-PAP response in this group.

The present results suggest that an enhancement of HPV was observed after infusion with the hypertonic saline and dextran solution. This can not simply be explained by a reduction of viscosity. Metabolic factors did not vary and osmolality did not increase significantly after infusion of hypertonic saline with dextran. In previous studies, a rise in osmolality has been shown to lower PVR [2, 25], which appears to contradict the results of the present study. However, previous studies focused on microcirculation rather than on vascular resistances and did not consider hypoxia [2]. Moreover, variations in osmolality observed in the present study were nonsignificant and may not be enough to influence vasomotricity.

LAP and Q were not modified after perfusion with saline with dextran when compared to baseline. However, during hypoxia, there was a *f*C increase, which may be related to a baroreflex stimulation, this stimulation could therefore have induced a pulmonary vasoconstriction. One other explanation for enhanced HPV with hypertonic saline could be related to the increase of vascular smooth muscle tone due to a higher intracellular Ca^{2+} concentration, as has been shown in the myocyte [26].

The characteristics of hypertonic sodium chloride administered with dextran solution as a replacement fluid in isovolaemic haemodilution allows the use of small infusion volumes with an enhancement of hypoxic pulmonary vasoconstriction. The mechanism of this beneficial enhancement of HPV is still unknown, and could be due to an increase in vascular smooth muscle tone associated with a higher intracellular ionised calcium concentration. Further *in vitro* studies could help to elucidate the subcellular mechanism that involves the neurohumoral system.

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