Hypertonic Saline Hydroxyethylstarch Restores Right Ventricular-Arterial Coupling after Normovolemic Hemodilution in Piglets

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ABSTRACT

Background: Normovolemic hemodilution is known to inhibit hypoxic pulmonary vasoconstriction. How the coupling between the pulmonary arterial (PA) circulation and the right ventricle (RV) is affected by normovolemic hemodilution and by the composition of replacement solutions remains unknown. Therefore, the effects of isotonic and hypertonic saline hydroxyethylstarch solutions on the pulmonary circulation and RV, in control and hypoxic conditions, were compared.

Methods: Anesthetized piglets (n = 14) were equipped with manometer-tipped catheters in the RV and main PA and an ultrasonic flow probe around the main PA. The pulmonary circulation was assessed by pressure-flow relations and vascular impedance, RV afterload by effective arterial elastance (Ea), RV contractility by end-systolic elastance (Ees), and RV-PA coupling by the Ees/Ea ratio. Measurements were done in control (F_{IO_2} 0.40) and hypoxic (F_{IO_2} 0.12) conditions before and after acute normovolemic hemodilution with either 20 ml/kg isotonic saline hydroxyethylstarch (hydroxyethylstarch 130/0.4 6% in NaCl 0.9%, Voluven, Fresenius-Kabi, Sevres, France) or 5 ml/kg hypertonic saline hydroxyethylstarch (hydroxyethylstarch 200/0.5 6% in NaCl 7.2%, HyperHES, Fresenius-Kabi) solutions.

Results: Hypoxic pulmonary vasoconstriction was associated with proportional increases in Ea and Ees and did not affect RV-PA coupling. Hemodilution attenuated the hypoxic response. Hemodilution with isotonic saline hydroxyethylstarch did not affect the RV-PA coupling, whereas hemodilution with hypertonic saline hydroxyethylstarch increased Ees and the Ees/Ea ratio.

Conclusion: In experimental normovolemic hemodilution, both in control and in hypoxic conditions, RV-PA coupling is unaffected by isotonic saline hydroxyethylstarch but improved by hypertonic saline hydroxyethylstarch, mainly because of an increase in RV contractility.

What We Already Know about This topic

- Hypertonic solutions have been widely used during prehospital care of trauma patients and have shown advantageous hemodynamic effects

What This Article Tells Us That Is New

- Both in control and hypoxic conditions, right ventricle-pulmonary arterial coupling is unaffected by HES 6% starch but improved by hypertonic saline, primarily because of an increase in RV contractility

HYPERTONIC solutions have been widely used during prehospital care of trauma patients and have shown advantageous hemodynamic effects.[1] Recently, there has been a growing interest in the intraoperative use of such solutions, mainly in cardiac and vascular surgery.[2–6] Reduced positive fluid balance, increased cardiac index, and decreased systemic vascular resistances were the main beneficial effects.[5] The addition of a synthetic colloid such as hydroxyethylstarch has been proposed to prolong the beneficial effects of hypertonic saline on cardiovascular function.[5] The association of hypertonic saline with hydroxyethylstarch (HS-HES) increases blood volume four times more than isotonic saline hydroxyethylstarch (NS-HES), by the osmotic effect transferring fluid from the intracellular and interstitial compartments to the intravascular compartment.[2] The re-

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sulting increase in cardiac output has been attributed to an increase in cardiac preload and/or performance, and to a decrease in systemic vascular resistance.[2,7] In the systemic circulation, local responses may differ according to the organ being studied and the composition of the infused solution.[8,9] In the pulmonary circulation, hemodilution with isotonic saline has been shown to reduce the pulmonary vascular resistance by decreasing blood viscosity.[10] Conversely, several clinical studies reported a failure of hypertonic saline or hypertonic saline dextran solutions to dilate pulmonary vessels after cardiopulmonary bypass.[11–13] The effects of HS-HES solutions on pulmonary hemodynamics and right ventricular function remain unknown.

Therefore, we studied the effect of isotonic saline and hypertonic saline solutions on the pulmonary arterial (PA) circulation and right ventricular (RV) performance in anesthetized piglets submitted to normovolemic hemodilution and to hypoxia. Piglets were chosen because they exhibit a large pulmonary vasoconstrictive response to hypoxia.[14] By analogy with the systemic circulation, we hypothesized that the hypertonic solution could have pulmonary vasodilating effects and perhaps increase the RV contractility. To clearly identify the vascular and ventricular effects of each solution, we assessed the pulmonary circulation by PA pressure-flow curves and PA impedance spectra,[15–18] and the ventricular function by pressure-volume loops, end-systolic elastance, and ventricular-arterial coupling efficiency.[19–21]

Materials and Methods

All experiments were approved by the Animal Ethics Committee of the Marseille University School of Medicine (Marseille, France), and were done in accordance with the "Guiding Principles in the Care and Use of Animals" of the American Physiologic Society.

Preparation

After a 12-h fasting period with free access to water, 16 large, white piglets (12–15 weeks) were premedicated with ketamine intramuscular 20 mg/kg, anesthetized with midazolam 0.2 mg/kg intravenously followed by 0.2 mg/kg/h infusion, and paralyzed with pancuronium bromide 0.2 mg/kg intravenously followed by 0.2 mg/kg/h infusion. Sufentanil 0.3 μg/kg was given intravenously at induction and again before surgery, and 5–20-μg boluses were added to prevent increases in heart rate or blood pressure. The lungs were ventilated *via* a cuffed tracheostomy tube (Tracheosoft, Malindkrodt Medical, Athlone, Ireland) with a 900C ventilator (Siemens-Elema, Solna, Sweden) set to deliver a F_{IO_2} of 0.40, a positive end-expiratory pressure of 5 cm H_2O, a tidal volume of 12–15 ml/kg, and a rate to maintain the P_{ACO_2} between 35 and 40 mmHg. Inspired and expired fractions of oxygen and carbon dioxide were monitored with an ULTIMA II infrared spectrophotometer (Datex, Helsinki, Finland). Arterial blood gases were measured at least every 30 min. Temperature was maintained at 38–39°C using an electric heating pad. A pulmonary artery catheter (131H-7F, Baxter, Irvine, CA) was inserted *via* the left internal jugular vein in a branch of the pulmonary artery under pressure waveform guidance for measurements of pulmonary arterial pressures, cardiac output, and core temperature. A balloon catheter (Percor, Datascope, Paramus, NJ) was advanced into the inferior vena cava to decrease cardiac output by reducing venous return. A median sternotomy was performed and a 16- to 24-mm ultrasonic flow probe (T206, Transonic, Ithaca, NY) was positioned around the main PA. Manometer-tipped catheters (SPC 350, Millar, Houston, TX) were introduced into the RV and proximal PA. The pericardium and sternum were then closed, and thrombus formation was prevented by heparin 100 IU/kg intravenously. After surgery, the animals were allowed to rest until stabilization (stable heart rate, blood pressure, cardiac output and end-tidal carbon dioxide) for 30 min.

Data Analysis

Instantaneous pressure and flow were sampled at 200 Hz. PA resistance was assessed by pressure-flow relations obtained by rapid flow reduction.[18] PA values were interpolated at flows of 2 and 4 l/min/m^2 from individual regressions, and were averaged to obtain composite pressure-flow plots.[18] PA impedance was calculated from Fourier series expressions of pressure and flow.[17,18] From impedance spectra was derived the total resistance or impedance at 0 Hz (Zo) and the characteristic impedance (Zc) calculated as the average of moduli between 2 and 15 Hz. RV contractility and RV-PA coupling were assessed from steady-state RV pressure-volume curves using our single-beat method.[19] RV end-systolic elastance (Ees) was computed as the slope of the end-systolic pressure-volume line, PA effective elastance (Ea) as the slope of end-diastolic to end-systolic line, and ventricular-arterial coupling as the Ees to Ea ratio (Ees/Ea).[19] The method has been validated during variations of preload, afterload, and contractility, and has proved reliable in conditions of PA hypertension and RV failure.[19–23]

Protocol

Each set of measurements included flow and pressures recordings at steady state for calculations of impedance and RV-PA coupling and during a flow reduction maneuver for construction of pressure-flow relations. Each set also included blood sampling for determination of blood gases (Radiometer, Copenhagen, Denmark) and plasma osmolality (Micro-Osmometer, Advanced Instruments, Radiometer, Neuilly, France). A first set of measurements was obtained after stabilization for 30 min at F_{IO_2} 0.40, and a second set after 30 min at F_{IO_2} 0.12 to reach a P_{ACO_2} of 30–40 mmHg.[16] Each animal was then returned to the control condition and randomly allocated to the NS-HES (n = 8, weight 27 ± 2 kg) or HS-HES group (n = 8, weight 28 ± 3 kg). Normovolemic hemodilution was performed by with-

Table 1. Biologic Data, in Control (F_{IO_2} 0.40) and in Hypoxia (F_{IO_2} 0.12), before and after Normovolemic Hemodilution with NS-HES or HS-HES

	Baseline Control	Baseline Hypoxia	Hemodilution Control	Hemodilution Hypoxia
pHa				
NS-HES	7.45 ± 0.02	7.44 ± 0.05	7.39 ± 0.05	7.39 ± 0.08
HS-HES	7.43 ± 0.02	7.42 ± 0.05	7.38 ± 0.05	7.37 ± 0.08
P_{ACO_2}, mmHg				
NS-HES	39 ± 3	37 ± 6	40 ± 5	40 ± 5
HS-HES	40 ± 5	41 ± 5	42 ± 5	41 ± 5
P_{AO_2}, mmHg				
NS-HES	133 ± 46	31 ± 5*	127 ± 68	34 ± 5*
HS-HES	122 ± 36	31 ± 4*	123 ± 57	35 ± 5*
P_{VO_2}, mmHg				
NS-HES	43 ± 6	24 ± 3*	42 ± 7	25 ± 5*
HS-HES	50 ± 10	22 ± 7*	43 ± 8	26 ± 7*
Hemoglobin, g/dl				
NS-HES	11.6 ± 0.5	11.7 ± 0.6	7.1 ± 0.6**	7.6 ± 0.6**
HS-HES	11.7 ± 0.4	11.8 ± 0.4	7.1 ± 0.8**	7.6 ± 0.8**
Osmolarity, mOsm/l				
NS-HES	278 ± 27	285 ± 26	275 ± 26	293 ± 18
HS-HES	284 ± 30	298 ± 27	282 ± 42	299 ± 35

Values are mean ± SD (n = 7).

* $P < 0.05$ hypoxia *vs.* control; ** $P < 0.05$ hemodilution *vs.* baseline.

HS-HES = hypertonic saline hydroxyethylstarch; NS-HES = isotonic saline hydroxyethylstarch; pHa = arterial pH; P_{ACO_2} = arterial carbon dioxide partial pressure; P_{AO_2} = arterial oxygen partial pressure; P_{VO_2} = mixed venous oxygen partial pressure.

drawal of 20 ml/kg whole blood and administration of either 20 ml/kg NS-HES (NaCl 0.9%, hydroxyethylstarch 130/0.4 6%, Voluven) or 5 ml/kg of a HS-HES solution (NaCl 7.2%, hydroxyethylstarch 200/0.5 6%, HyperHES). The volumes of solution were adjusted to the threefold to fourfold higher volume effect of HS-HES compared with NS-HES.[2,3] Two animals (one in each group) did not complete the hemodilution phase and were excluded from the analysis. A third set of measurements was obtained after stabilization for 30 min at F_{IO_2} 0.40, and a fourth set after 30 min at F_{IO_2} 0.12. The F_{IO_2} values of 0.40 and 0.12 were selected as those suppressing and maximizing hypoxic pulmonary vasoconstriction in pigs.[16]

Statistics

Data were expressed as mean ± SD. Results were analyzed with a carefully validated homemade software by analysis of variance followed by Student *t* tests. Intergroup comparisons were done to test the effect of HS-HES *versus* NS-HES, and intragroup repeated-measures comparisons to test the effects of hypoxia *versus* control and hemodilution *versus* baseline. Two-tailed testing *P* values less than 0.05 were considered statistically significant. Initially, eight animals were included in each group because in our experience this number is sufficient to reach statistical significance when effects are observed. Because the results were clear-cut and consistent, seven remaining animals in each group was estimated to be sufficient.

Results

Baseline

Baseline blood gases and hemodynamic measurements were similar in both groups (tables 1 and 2, figs. 1, 2A and B). Acute hypoxia decreased the P_{ACO_2} to 30–35 mmHg and increased heart rate, cardiac output, and pulmonary arterial pressure. It shifted the PA pressure-flow relations upward (fig. 1), and increased Zo without affecting Zc (table 3). Hypoxia increased Ea and Ees proportionally, so that the Ees/Ea ratio remained unchanged (table 3).

Hemodilution with NS-HES

Hemodilution decreased the hemoglobin concentration to approximately 7 g/dl, and did not affect heart rate, cardiac output or arterial pressure (tables 1 and 2). The pressure-flow relations and pulmonary vascular impedance spectra remained unchanged (fig. 1). Ees and Ees/Ea decreased nonsignificantly (table 3, fig. 2, A and C). After hemodilution, hypoxia was associated with less upward shift of the flow-pressure relations than before hemodilution (fig. 1). Hypoxia caused increases in Zo and Ea, whereas Ees remained unaffected (table 3).

Hemodilution with HS-HES

Hemodilution decreased the hemoglobin concentration to approximately 7 g/dl and did not affect heart rate or arterial pressure, but increased cardiac output (tables 1 and 2). The pressure-flow relations and pulmonary vascular impedance spectra remained unchanged (fig. 1). Ees and Ees/Ea in-

Table 2. Hemodynamic Data, in Control (F_{IO_2} 0.40) and in Hypoxia (F_{IO_2} 0.12), before and after Normovolemic Hemodilution with NS-HES or HS-HES

	Baseline Control	Baseline Hypoxia	Hemodilution Control	Hemodilution Hypoxia
Heart rate, beats/min				
NS-HES	73 ± 12	84 ± 18*	85 ± 18	92 ± 26
HS-HES	75 ± 10	85 ± 12*	85 ± 12	93 ± 12
CO, l · min · m^2				
NS-HES	3.1 ± 0.9	4.1 ± 1.1*	3.4 ± 1.0	4.0 ± 0.9*
HS-HES	2.9 ± 0.8	4.0 ± 1.0*	4.1 ± 0.8** ***	4.7 ± 0.8** ***
Psa, mmHg				
NS-HES	89 ± 13	89 ± 10	90 ± 8	89 ± 13
HS-HES	93 ± 8	99 ± 12	84 ± 8	90 ± 15
Ppa, mmHg				
NS-HES	20 ± 4	33 ± 3*	24 ± 3	35 ± 7*
HS-HES	20 ± 3	34 ± 3*	24 ± 2	35 ± 8*
Ppao, mmHg				
NS-HES	11 ± 3	11 ± 2	11 ± 3	11 ± 2
HS-HES	11 ± 2	11 ± 3	11 ± 3	11 ± 2
Pra, mmHg				
NS-HES	9 ± 4	10 ± 3	10 ± 2	10 ± 2
HS-HES	9 ± 3	9 ± 3	9 ± 3	10 ± 3

Values are mean ± SD (n = 7).

* $P < 0.05$ hypoxia *vs.* control; ** $P < 0.05$ hemodilution *vs.* baseline; *** $P < 0.05$ HS-HES *vs.* NS-HES.

CO = cardiac output; HS-HES = hypertonic saline hydroxyethylstarch; NS-HES = isotonic saline hydroxyethylstarch; Ppa = mean pulmonary arterial pressure; Ppao = occluded Ppa; Pra = right atrial pressure; Psa = mean systemic arterial pressure.

creased nonsignificantly (table 3, fig. 2, B and D). After hemodilution, hypoxia was associated with less upward shift of the flow-pressure relations than before hemodilution (fig. 1). Hypoxia caused increases in Zo and Ea, whereas Ees remained unaffected (table 3). Compared with hemodilution with NS-HES, hemodilution with HS-HES was associated with markedly higher cardiac output, Ees and Ees/Ea, both in control and hypoxic conditions (table 3, fig. 2, C and D).

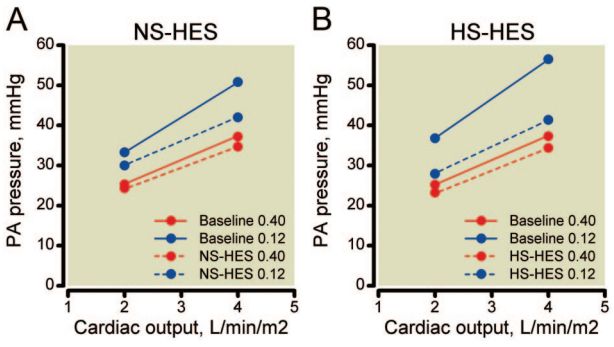

Fig. 1. Pressure-flow relations in control (F_{IO_2} 0.40) and hypoxic (F_{IO_2} 0.12) conditions before (baseline) and after normovolemic hemodilution with isotonic saline hydroxyethylstarch (NS-HES, *A*) or hypertonic saline hydroxyethylstarch (HS-HES, *B*). Standard deviations not shown for sake of clarity. PA = pulmonary artery. Hypoxia shifted the pressure-flow relation upward ($P < 0.05$). NS-HES and HS-HES did not affect the relation in control conditions and attenuated the response to hypoxia ($P < 0.05$).

Discussion

The current results show that acute normovolemic hemodilution with HS-HES has advantages over NS-HES in that it

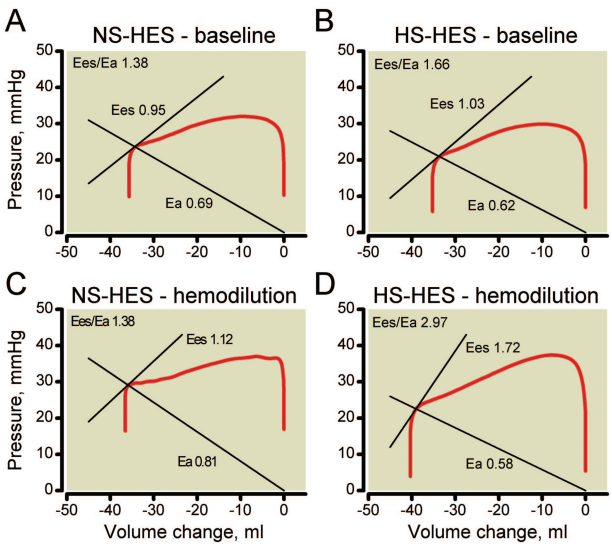

Fig. 2. Illustrative examples of right ventricular-arterial coupling at baseline (*A* and *B*) and after normovolemic hemodilution (*C* and *D*) with isotonic saline hydroxyethylstarch (NS-HES, *A* and *C*) or hypertonic saline hydroxyethylstarch (HS-HES, *B* and *D*). Ees = right ventricular end-systolic elastance, Ea = pulmonary arterial effective elastance. NS-HES did not affect the ventricular-arterial coupling. HS-HES increased the ventricular contractility (Ees) and coupling efficiency (Ees/Ea).

Table 3. Pulmonary Vascular Impedance and Right Ventricular-Arterial Coupling Data, in Control (F_{IO_2} 0.40) and in Hypoxia (F_{IO_2} 0.12), before and after Normovolemic Hemodilution with NS-HES or HS-HES

	Baseline Control	Baseline Hypoxia	Hemodilution Control	Hemodilution Hypoxia
Zo, dyn · s · cm^{-5} · m^2				
NS-HES	622 ± 200	980 ± 405*	650 ± 306	950 ± 406*
HS-HES	625 ± 163	1,031 ± 208*	568 ± 143	905 ± 348*
Zc, dyn · s · cm^{-5} · m^2				
NS-HES	85 ± 28	88 ± 21	84 ± 16	89 ± 41
HS-HES	93 ± 39	108 ± 28	98 ± 38	111 ± 34
dP/dt max, mmHg/s				
NS-HES	358 ± 114	566 ± 143*	377 ± 83	577 ± 190*
HS-HES	385 ± 83	575 ± 145*	527 ± 168	617 ± 112
Ea, mmHg/ml				
NS-HES	0.64 ± 0.20	1.14 ± 0.23*	0.69 ± 0.18	1.17 ± 0.50*
HS-HES	0.59 ± 0.18	1.18 ± 0.26*	0.68 ± 0.25	1.04 ± 0.30*
Ees, mmHg/ml				
NS-HES	1.10 ± 0.30	1.52 ± 0.29*	0.92 ± 0.26	1.18 ± 0.46
HS-HES	1.16 ± 0.16	1.57 ± 0.42*	1.48 ± 0.50***	1.63 ± 0.36***
Ees/Ea				
NS-HES	1.87 ± 0.78	1.39 ± 0.42	1.40 ± 0.44	1.16 ± 0.52
HS-HES	1.88 ± 0.48	1.45 ± 0.52	2.18 ± 0.59***	1.65 ± 0.57***

Values are mean ± SD (n = 7).

* $P < 0.05$ hypoxia *vs.* control; ** $P < 0.05$ hemodilution *vs.* baseline; *** $P < 0.05$ HS-HES *vs.* NS-HES.

Ea = pulmonary artery effective elastance; Ees = right ventricular end-systolic elastance; HS-HES = hypertonic saline hydroxyethylstarch; NS-HES = isotonic saline hydroxyethylstarch; Zc = characteristic impedance; Zo = 0-Hz impedance.

restores RV-PA coupling and cardiac output by increasing RV contractility without affecting RV afterload.

Hypoxic Pulmonary Vasoconstriction

Hypoxic pulmonary vasoconstriction (HPV) is an intrapulmonary mechanism that diverts blood flow from poorly ventilated to well-ventilated and -oxygenated lung regions. Variations in local pulmonary vascular tone are attributed to changes in the balance between endothelium-derived vasodilators (nitric oxide, prostacyclin) and vasoconstrictors (thromboxane). Enhancing the HPV can improve pulmonary gas exchange but also increase RV afterload and prompt RV failure. Attenuating the HPV can facilitate the RV ejection and increase cardiac output, but also result in hypoxemia. The extent of oxygenation and cardiovascular changes will depend on the presence of hypoxic lung regions and of RV dysfunction.

Pulmonary Hemodynamics

Pulmonary vascular mechanics are commonly described by PA pressure and calculated resistance, but these variables are flow-dependent and fail to take into account the pulsatile nature of circulation. Flow-pressure relations better discriminate between passive (flow-induced) changes and active (tone-induced) changes in PA pressure, and allow detection of more subtle changes in vascular tone.[24] Flow-pressure curves here were generated with transient flow reductions (less than 10 s) to prevent cardiovascular responses because of sympathetic activation.[18] Pulmonary vascular impedance allows for the quantification of the three components that oppose blood ejection from the ventricle into the artery, *i.e.*, resistance because of small distal vessels, elastance because of large proximal vessels, and reflected waves that increase pressure and decrease forward flow.[25] In this experimental study, in addition to conventional measurements of PA pressure and resistance, we used pressure-flow curves to better detect resistance changes caused by distal small muscular arteries and pulmonary vascular impedance to assess elastic changes caused by large proximal arteries.[18,25]

Hypoxia

Hypoxia caused an increase in cardiac output, likely because of sympathetic stimulation, and in PA pressure. Pressure-flow relations were shifted to higher pressures, indicating that the increase in pressure resulted not only from the flow change but also from an increased resistance of small distal vessels. Zc did not change, indicating a balance between an increase because of the higher pressure, a decrease because of the larger diameter (passive dilation of proximal arteries in presence of distal vasoconstriction), and possible effects of changes in proximal elastance.[17,18] The combination of higher resistance and unchanged elastance caused an increase of Ea. Ees increased in a roughly proportional way, because of the sympathetic stimulation and/or to the homeometric autoregulation or Anrep effect.[19,26] As a result, RV-PA coupling efficiency was maintained. These results are similar to those reported previously.[19]

Hemodilution with NS-HES

Under control conditions, normovolemic hemodilution with NS-HES did not affect pulmonary vascular resistance or

impedance, ventricular afterload, or ventricular contractility. In hypoxia, hemodilution attenuated the hypoxic response as clearly shown by the downward shift of the pressure-flow relations. This finding is consistent with previous studies reporting acute isovolemic anemia to alter pulmonary gas exchange, possibly by reducing hypoxic pulmonary vasoconstriction.[27] Hypothetical mechanisms included a decreased blood viscosity improving microcirculatory flow (rheologic effect) or an accumulation of vasodilating mediators such as nitric oxide.[28,29] This finding is also consistent with our previous study, in which we showed the role of changes in viscosity and the possible role of reactive oxygen species scavenging in the hemodilution-induced HPV attenuation.[10] Despite the HPV attenuation, hemodilution with NS-HES did not cause a deterioration of arterial oxygenation. This can be explained by the absence of hypoxic lungs regions where HPV would be protective.

Hemodilution with HS-HES

Many studies have reported hypertonic solutions to increase cardiac output and decrease systemic vascular resistance.[2–6,11,12] Left ventricular contractility was found to be decreased,[30] unchanged,[31] or increased.[12] In the current study, we also observed an increase in cardiac output and a decrease in systemic vascular resistance. Left ventricular contractility was not specifically investigated, but the increase of cardiac output at unchanged preload suggests a positive inotropic effect of HS-HES. To our knowledge, no previous study was devoted to the effect of hypertonic solutions on the RV function. In the current study, HS-HES markedly increased RV contractility compared with NS-HES, both in control and hypoxic conditions. RV afterload was unaffected, and HS-HES therefore improved the RV-PA coupling and increased cardiac output.

Effects of hypertonic saline solutions on respiratory function and oxygenation have been reported variably. In patients undergoing cardiopulmonary bypass, hypertonic solutions reduced the time to extubation or maintained a better oxygenation.[13,32] In pigs submitted to hemorrhagic shock, isotonic and hypertonic hyperoncotic solutions resulted in similar acute lung injury.[33] In a more recent study by the same group, hypertonic saline worsened ischemia and reperfusion lung injury.[34] According to the clinical condition or experimental model, hypertonic saline solutions can thus improve and not affect or worsen pulmonary gas exchange. Such discrepancies are easily explained by the absence or presence of lung injury. In the absence of lung injury, HPV is not activated (normoxia) or activated everywhere (global hypoxia). HPV is absent or ineffective, and hemodilution-induced HPV attenuation will not affect oxygenation. In the presence of lung injury, HPV is activated electively in hypoxic lung regions, diverts blood flow to normoxic regions, and improves gas exchange. HPV is useful, and hemodilution-induced HPV attenuation will cause deterioration of oxygenation. In the presence of lung disease, hemodilution with hypertonic solutions also can improve arterial oxygenation by increasing cardiac output and mixed venous oxygenation. This factor probably explains their beneficial effect on oxygenation in patients undergoing cardiac surgery, who commonly develop atelectasis and local hypoxia during and after surgery.[13,32] Finally, hypertonic solutions also have been reported to worsen lung injury not by affecting HPV or cardiac output but probably by a direct deleterious effect of hyperosmolarity on endothelial permeability.[34] In the current study, as could be expected in pigs with uninjured lungs, hemodilution with HS-HES did not deteriorate arterial oxygenation despite the HPV attenuation.

Hypertonic saline solutions cause a transient hyperchloremic metabolic acidosis[35] that could affect pulmonary vascular tone or ventricular function. Previous studies reported the acidosis to be maximal at 1 min, and almost gone 10 min after administration. Consistently, no significant metabolic acidosis was observed in the current study 30 min after the hemodilution procedure. The absence of plasma acidosis may be attributed to the rapid shift of fluid from the interstitial and intracellular compartments to the plasma and to the diffusion of sodium and chloride in the opposite direction. Immunomodulatory effects of hypertonic solutions have been reported in animal studies but have not been confirmed in humans.[5]

Limitations

The study was done in normal piglets, and its results should be transposed only with caution to other species or to conditions of disease. It was done in anesthetized animals to mimic human intraoperative conditions, with the possible drawback of interference between anesthetic agents and the processes being investigated. We used a single-beat method that does not require measurement of instantaneous RV volume or modification of the preload or afterload to assess RV contractility and RV-PA coupling, and different results might be obtained with other approaches (*e.g.*, measuring PA flow and/or RV volume by echocardiography or magnetic resonance imaging, assessing myocardial contractility by changing preload or afterload, or defining contractility by preload recruitable stroke work).

Clinical Relevance

Three aspects of the current results have relevance to clinical care, assuming that the data obtained in experimental animals may be translated to patients: the attenuation of HPV by hemodilution, the enhancement of RV contractility by the hypertonic solution, and the selection of the anesthetic drugs. HPV attenuation was observed with both NS-HES and HS-HES, and thus should not influence the choice of isotonic *versus* hypertonic solutions in patients. As mentioned previously, HPV is a protective mechanism in the presence of lung disease, and HPV attenuation should thus be a concern in patients with lung disease and hypoxemia. Conversely, increased PA pressure is a burden on the right ventricle, and HPV attenuation may thus be beneficial to patients with pulmonary hypertension and RV dysfunction. Because lung disease and pulmonary hypertension are often present in the same patients, HPV attenuation may be beneficial or deleterious according to the respective severity of

hypoxemia and RV dysfunction. Compared with NS-HES, HS-HES was found to increase RV contractility, improve RV-PA coupling, and increase cardiac output. Hypertonic solutions may therefore be preferred in patients with pulmonary hypertension or RV failure. As usual, the benefit of increased contractility must be balanced against the risk of myocardial ischemia in patients with ischemic heart disease. Excessive doses of hypertonic solutions may also result in hypervolemia and systemic or pulmonary edema in patients with compromised cardiac function. Finally, the inotropic benefits of hypertonic solutions might be more effective in patients who receive anesthetic drugs decreasing cardiac output and arterial pressure (volatile agents, propofol) than in pigs receiving agents selected for their minimal cardiovascular toxicity (ketamine, midazolam).

Conclusion

In summary, we investigated in control and hypoxic conditions the effects of normovolemic hemodilution with two hydroxyethylstarch solutions on the pulmonary circulation, RV function, and right ventricular-arterial coupling in anesthetized piglets. Both NS-HES and HS-HES attenuated hypoxic pulmonary vasoconstriction. NS-HES had no effect on ventricular afterload or contractility, whereas HS-HES increased ventricular contractility and RV-PA coupling efficiency.

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ANESTHESIOLOGY REFLECTIONS

Alvatunder Bottle by the Hisey Dental Manufacturing Company

By the late 1890s, the Hisey Family of Toledo, Ohio, had popularized the use of Alvatunder, their proprietary local anesthetic mixture. According to the manual titled *The Newer Remedies*, Alvatunder was compounded from "1 gm. of cocaine hydrochlorid[e], 3 drops of liquefied phenol, 3 drops decolorized t[inctu]r[e]. of iodin[e], 10 grammes glycerin and water sufficient to make 100 gms." Eventually mass-producing their bottles of Alvatunder from St. Louis (*above*), the Hiseys advertised in a manner that convinced New York dentist S. J. Bartlett to exaggerate that Alvatunder had "no poisonous effects of cocaine, no sloughing of gums, no swelling of jaw, no danger from injection . . . any amount can be used." (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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