TITLE: FRUCTOSE 1,6 DIPHOSPHATE (ESAFOSFINA) IN ARDS.

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INTRODUCTION Fructose 1,6 Diphosphate (FDP) is a naturally occurring intermediate step of glycolysis. In pharmacological doses (125-375 mg/Kg) FDP leads to rapid production of ATP. Cardiac function is improved, cell membranes are stabilized and the damage from free radicals is reduced (1). Since those biochemical injuries have also been associated with the pathophysiology of ARDS, it has been suggested that FDP could provide protection to the lungs in acute respiratory failure (2).
METHOD After obtaining an IND approval from the FDA and informed consent, FDP was administered to mechanically ventilated patients with PaO_2/FiO_2 < 175 while breathing FiO_2 > .40. All patients had the radiographic and clinical signs of ARDS. The study represented a Phase 1 trial of the drug, and the search for an effective dosage was the primary goal of the investigation. Thus, 250 mg/Kg of FDP was administered 11 times and 375 mg/Kg 9 times. The drug was given as a continuous infusion over a period of 2 hours. Measurements of hemodynamic variables and blood gases were obtained before the infusion started, after 50% of the drug had been given, and 15 and 60 minutes after completion of the infusion.
RESULT There were no changes in PaO_2/FiO_2 ratio (Tab. 1), Mean Arterial Pressure, Pulmonary Capillary Wedge Pressure or Cardiac Output at any time interval, with any dose of FDP administered.
CONCLUSION The therapy of ARDS is complicated by the scarcity of substances that directly treat the biochemical causes of lung injury. Mechanical ventilation only controls the symptoms of the disease but has little effect on its pathophysiology, if it does not actually worsen the conditions of the lungs. Animal studies had suggested that pharmacologic doses of FDP could have beneficial effects on gas exchange function, improving PaO_2/FiO_2 ratio and lowering shunt fraction. There have been reports of improved hemodynamic function after administration of FDP. Our investigation could not duplicate these results in critically ill patients with severe respiratory failure. The slightly better response noted with the 375 mg/Kg dose may suggest that even higher amounts of FDP or more prolonged infusion periods could ameliorate respiratory failure in ARDS. At this time, however, there is no firm indication for the use of FDP in that morbid condition.

Table 1

Time	PaO_2/FiO_2 250 mg/Kg	PaO_2/FiO_2 375 mg/Kg
Baseline	143 ± 24	157 ± 36
50%	141 ± 29	170 ± 31
15 min	156 ± 39	175 ± 31
60 min	146 ± 28	177 ± 28

All Values are mean ± SD

References

1. Surgery 90:482-488, 1981.
2. Am J Cardiol 56:266-269, 1985.

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Title : BODY POSITION AND DISPLACEMENT OF CANINE DIAPHRAGM

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Dominant dependent regional diaphragm displacement (rDD) during spontaneous ventilation (SV) in supine (S) body position was attributed to advantageous shape and favorable length-tension (L/T) relationship induced by abdominal load and hydrostatic gradient.[1] Favored nondependent displacement during mechanical ventilation (MV) was assigned to the coupling with the vertical abdominal hydrostatic gradient that less opposes inflation of nondependent lung.[1] If this interpretations for observed phenomenology were correct then the pattern of diaphragm displacement along the gravitational axis should be independent of body position. We tested this hypothesis after the approval for the study was obtained from the Investigational Animal Research Committee. Four hydrostatic diaphragm regions were studied after the radiopaque markers were surgically sutured, in a row fashion, into the costal ventral (CoV), middle (CoM), dorsal (CoD) and crural (Cr) diaphragm in 5 dogs, as described elsewhere.[2] The rDD of diaphragm marker closest to the central tendon were studied with biplane videofluorography in S and prone (P) body positions during SV and MV [same tidal volumes]. Calculation of absolute displacement (cm) was performed by the operator interactive computer software from the change of marker positions in three-dimensional coordinate system from the reference point at functional residual capacity (FRC).
Fig.1 shows that active S diaphragm contraction displaces mostly dependent regions (CoM,CoD,Cr) while passive lung inflation nondependent (CoV). Mechanically inflated lung displaced diaphragm 40-60% less then SV (P<0.05-0.01), except in nondependent, CoV region, that was displaced nonsignificantly more with MV. In P dogs (Fig.2) active diaphragm contraction predominantly displaced dorsal regions (Cr and CoD) while CoM remained unchanged comparing to S. Passive P rDD was preferentially distributed to nondependent diaphragm (CoM,CoD,Cr) and maximally decreased in dependent, CoV region (P< 0.01). Average rDD was higher in P then in S dogs although the regional diaphragm length at FRC (L_{FRC}) was generally longer in S: mean combined L_{FRC} ratio S/P for Cr, CoM and CoD was 1.09 (P<0.001), and for CoV was 1.0 (P=NS).
The rDD during active contraction preferentially displaced dorsal regions, regardless the body position. In both body positions passive rDD generally follows, in inverse fashion, vertical abdominal hydrostatic gradient. In both body positions diaphragm displaced less during MV than during SV for the same tidal volume. Finding that S diaphragm with more stretched resting length at FRC is displaced less than P indicates that the S diaphragm is stretched beyond the optimal point for contraction on the L/T curve. CoM region, positioned approximately at mid-heights between dependent and nondependent, displaced equally in P and S in spite of shorter resting length in P while CoV diaphragm has the same length in both body positions, but in P dogs is displaced more. Both suggest that no single mechanism can be attributed to rDD. The facts that actively contracted dorsal diaphragm and shorter muscle in P dogs are always preferentially displaced, suggest that intrinsic muscle characteristics or anatomic differences (shape) determine rDD. While abdominal hydrostatic pressure gradient plays significant role in passive rDD it may have only minor effect on active rDD by influencing position of the region on the L/T curve as well the shape of the diaphragm.
References: 1. Anesthesiology 41: 242, 1974; 2. J Appl Physiol 67: 655, 1989.
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