TITLE: Depressed Pulmonary Metabolic Function After Experimental Microembolization

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Introduction. Several investigators have recently reported a close association between depressed pulmonary metabolic function and various types of experimental lung injury[1] including glass bead microembolization.[2] This latter form of injury results in a complex pathophysiological state characterized by increased pulmonary vascular resistance and microvascular permeability which are in part secondary to mechanical obstruction. In addition, circulating granulocytes are necessary for alterations in structure and function which lead to endothelial cell dysfunction.[3] Accordingly, we simultaneously measured two metabolic functions of the pulmonary endothelium angiotensin-converting enzyme (ACE) activity and 5-hydroxytryptamine (5-HT) tranport-before and after microembolization in anesthetized rabbits, and compared these data to those obtained in a granulocyte depleted group of rabbits.

Methods. Measurements were made in anesthetized, paralyzed, heparinized, mechanically ventilated rabbits in which catheters were inserted in the right atrium, aorta and pulmonary artery. To quantify pulmonary metabolic function, a mixture containing an intravascular marker, indocyanine green (ICG), ^{14}C-5-HT and ^{3}H-benzoyl-phenylalanyl-alanyl-proline (^{3}H-BPAP: synthetic substrate for ACE) was injected as a bolus into the right atrium while systemic arterial blood was simultaneously diverted into tubes in a fraction collector. Total radioactivity, ICG and ^{3}H-benzoyl-phenylalanine (^{3}H-BPhe, metabolite) were analyzed in three aliquots removed from each sample. From these indicator dilution outflow curves, we calculated cardiac output, removal of 5-HT (R[5-HT]) relative to ICG and % metabolism of BPAP (i.e. [BPhe/(BPAP + BPhe)] x 100%). Measurements were made in 10 untreated animals, before and after injection of sufficient 50u beads to double pulmonary artery pressure (Ppa). Similar measurements were made in eight additional rabbits made leukopenic by injection of mechlorethamine (1.75 mg/kg i.v.) 3 days before the study. Data are summarized as mean ± S.E. The effect of embolization was tested statistically by two-way analysis of variance and compared to the effect in leukopenic rabbits by unpaired t-test.

Results. Most physiologic and metabolic measurements were similar in the pre-embolization control period between untreated and leukopenic animals. The effect of embolism on several of these measurements is shown in Table 1 (untreated control data only shown). Embolism in both groups was associated with marked increase in mean pulmonary arterial pressure (Ppa) and a slight reduction in cardiac output. In both groups, BPAP metabolism was significantly depressed. However, granulocytes appeared necessary for 5-HT removal to be significantly altered by glass bead embolization. There were no significant changes in wet/dry weight ratios in either group compared to non-embolized control.

Conclusions. These data suggest that the pulmonary metabolic consequences of microembolization are complex and appear to reflect both mechanical disruption of microvascular hemodynamics as well as an aspect of endothelial cell dysfunction. Depressed ACE activity may reflect a large component of derecruitment and perfusion heterogenity, since it was simlarly depressed with and without granulocytes. In contrast, depressed 5-HT removal is less affected by loss of vascular surface area and is in part mediated by circulatory neutrophils suggesting cell-mediated lung injury processes contributed to altered metabolic function.

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References.

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3. Flick MR, Perel A, Staub NC: Leukocytes are required for increased lung microvascular permeability after microembolization in sheep. Circ Res 48:344, 1981.

TABLE 1

	Pre-Embolization	Post Embolization Untreated	Treated
Cardiac Output (ml/min/kg)	98 ± 5	83 ± 10	82 ± 15
Ppa (Torr)	14 ± 1	28 ± 1*	28 ± 1*
BPAP metab. (%)	76 ± 4	57 ± 5*	60 ± 5*
R(5-HT)%	82 ± 2	69 ± 2*	80 ± 3

*$p < 0.05$, significantly different from control