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Title: Gene Expression Analysis of Systemic Versus Local Effects of Ventilation Induced Lung Injury in Canine Model

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Rationale: Canine model of unilateral ventilator-induced lung injury (VILI) generates 2 sets of gene expression profiles: unilateral injured and unilateral control (U_cnr) lungs. Then influence of mediators derived from the injured lung on control lung is not clear. We speculated that an addition of independent control (I_cnr) from intact dog will allow subtraction of VILI-related genes identified using U_cnr from those identified using I_cnr and distinguish direct (local) from systemically derived gene activation.

Methods: Canine lungs were lavaged and ventilated (TV=15ml/kg) for 6h. Lung tissue samples ($n_{injured} = n_{I_cnr} = n_{U_cnr} = 8$) were hybridized to human U133A GeneChip and analyzed using interspecies probe adjustment. Genes with 20% change in expression and $p < 0.05$ were considered VILI affected.

Results: Systemic effects of VILI reduced 2235 genes identified using I_cnr to 519

locally affected genes including known VILI-related genes (Table 1) where IL-8 was the only cytokine not masked by systemic effects.

Table 1 Systemic and local effects of VILI

Gene description	Symbol	Injury vs I_cnr		Injury vs U_cnr	
		FC	p value	FC	pvalue
Pre-B-cell colony-enhancing factor	PBEF	5.61	0.01241	3.65	0.02350
Thrombospondin 1	THBS1	5.20	0.00005	3.08	0.00067
Plasminogen activator inhibitor 1	PAI-1	2.55	0.01002	2.05	0.01653
Interleukin 8	IL8	1.90	0.00035	1.65	0.00140
Surfactant, pulmonary protein D	SFTPD	-2.25	0.00001	-2.10	0.00122

FC-fold change

Conclusions: We demonstrated that subtraction of gene expression profiles of a model of unilateral VILI can segregate locally and systemically affected genes and lead to refinement of therapeutic approaches in preventing VILI.

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