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Ventilator Induced Lung Injury

John A. Johnson Jr.

Ventilator Induced Lung Injury

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Candidate for B.S. Degree
in Psychology and Biology with Honors
May 2006

APPROVED

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Date:_____

Date	01/25/06		Weight	28kg		Study:	VILI
Pig #	2334		Length	38"		Group:	Control

VILI Worksheet

	Time	HR	BP	RR	Ppk	Ppl	Pm	PEEP	aPEEP	WOB	TV	EMV	Ri	Re	Comp	FiO2	CVP	PAP	PAOP	CO	REF	Temp	Fluid	UOP	Hgb	
A Baseline	9:45	152	124	14	39	21	7.9	3			279	3.9	5	10	14.6	1	5	19	8	5.71	42	36			12.8	99
V Baseline and T0 are identical in control: no need for additional reading. T0 in injury is immediately following injury.																									12.8	
A T0	10:15	113	134	14	18	16	6.6	2.4			269	3.8		23	15.5	1	5	17	7	4.8		36			12.6	
V																									12.7	
A T30	10:45	120	140	14	20	18	7.1	2.4			282	4		20	16.8	1	5	18	7	3.95	38	35.6			13.1	
V																									12.9	
A T60	11:15	117	127	14	20	18	6.7	2.9			262	3.8		11	15.9	1	5	22	7	3.83	21	35.7		200	13.8	
V																									13.9	
A T90	11:45	114	119	16	19	17	6.5	3.3			265	3.8	8	4	19.9	1	5	16	6	3.73	27	35.9			14	
V																									13.8	
A T120	12:15	121	122	14	18	16	6.2	3.4			265	3.8	6	3	19.5	1	5	22	6	4.44	20	36		400	11.1	
V																									12.1	
A T150	12:45	121	123	14	20	18	7.1	2.5			269	3.8		17	14.8	1	5	22	7	3.85	19	36.1		200	12.1	
V																									13.7	
A T180	13:15	102	121	14	19	17	6.3	4.3			264	3.7	9	3	19	1	4	24	7	2.68	20	36.6			12.8	
V																									14.1	
A T210	13:45	94	151	14	17	15	6.2	3.2			269	3.8	7	4	22.4	1	5	31	9	2.23	21	36.8		75	12.6	
V																									14.4	
A T240	14:15	93	115	14	17	16	6.5	3.1			266	3.8	9	3	21.5	1	5	26	8	2.66	24	36.6			14,5	
V																									14.7	
A T270	14:45	92	117	14	18	16	6.6	3			289	3.9	10	3	21.6	1	4	29	8	2.08	18	37		110	14.4	
V																									14.6	
A T300	15:15	90	124	14	20	18	7.2	3			300	4.2	10	7	22.7	1	6	39	9	2.11	17	37.2			14.1	
V																									14.7	
A T330	15:45	107	117	14	19	18	7.1	3			304	4.2	11	6	22	1	7	31	10	2.23	20	37.3		150	13.2	
V																									14.5	
A T360																										
V Return to 12 cc/kg PEEP 3 for 15" to check Blood Gases and Mechanics																										
A T375	16:00	136	129	14	17	16	6.6	2.9			308	4.3	9	5	25.6										14.8	
V																									14.5	

Notes:

Date	01/30/06	Weight	20kg	Study:	VILI
Pig #	2335	Length	38"	Group:	Control

VILI Worksheet

	Time	HR	BP	RR	Ppk	Ppl	Pm	PEEP	aPEEP	WOB	TV	EMV	Ri	Re	Comp	FiO2	CVP	PAP	PAOP	CO	REF	Temp	Fluid	UOP	Hgb
A Baseline	11:30	114	115	15	22	20	7.5	3	1.3	0	369	4.9	3	8	23.9	1	3	24	10	2.15	20	36.7	700		14
V	Baseline and T0 are identical in control: no need for additional reading. T0 in injury is immediately following injury.																								14.9
A T0	12:00	162	150	15	28	25	9.6	3	1.3		351	5.3	6	13	16.9	1	11	10	9	1.2	18	36.5	400		14.2
V																									14.6
A T30	12:30	142	132	15	25	23	9	3	0.5		352	5.3	7	11	18.9	1	10	29	8	1.49	19	36.5	200	1300	16.1
V																									16.3
A T60	13:00	84	119	15	25	22	8.8	3	0.7		345	5.2	7	11	19.2	1	3	36	8	1.41	15	36.4	100	200	17.1
V																									17.4
A T90	13:30	77	117	15	26	23	9.1	3	1		363	5.4	6	11	19.3	1	4	35	9	1.57	20	36.4	100	60	17.1
V																									17.3
A T120	14:00	92	122	12	26	23	8.1	3	0.9		359	4.6	7	11	19	1	3	37	8	1.11	14	36.4	50	8	18
V																									15.2
A T150	14:30	99	120	12	27	24	8.2	3	0.7		354	4.3	7	12	18.3	1	3	36	9	2.09	13	36.5	50	6	15.8
V																									14.5
A T180	15:00	105	120	12	28	25	8.4	3	0.7		355	4.3	6	12	17.8	1	4	39	9	2.43	13	36.4	50	5	15.7
V																									17
A T210	15:30	86	142	12	24	22	7.8	3	0.8		364	4.4	10	10	20.2	1	4	40	10	2.44	16	36.2	120	24	13.7
V																									14.1
A T240	16:00	94	122	12	28	25	8.7	3.1	0.5		364	4.7	9	11	20	1	3	41	8	2.68	13	36.3	100	29	14.8
V																									15.4
A T270	16:30	128	126	14	27	24	9.1	3.1	0.6		355	5	9	12	18.2	1	4	42	8	1.47	13	36.4	60	18	15.5
V																									16.3
A T300	17:00	109	120	14	29	26	9.6	3	1.1		364	5.1	8	12	16.5	1	4	39	8	1.79	13	36.5	0	26	16.7
V																									15.7
A T330	17:30	112	115	14	29	26	9.6	3	0.2		386	5.4	7	10	16.5	1	4	35	9	2.15	17	36.5	0	22	15.9
V																									17.3
A T360	18:00	106	123	14	23	20	8	3.1	0.5		348	4.8	9	10	21.5	1	3	38	8	1.99	13	36.8	0		16.4
V	Return to 12 cc/kg PEEP 3 for 15" to check Blood Gases and Mechanics																								17.1
A T375	18:15	N/A	N/A	14	25	22	9.1	3	0.2		384	5.7	8	3	17.5	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	16.6
V																									17.3

Notes:

Date	02/02/06	
Pig #	2336	
Weight	31kg	
Length	41"	
Study:	VILI	
Group:	Control	

VILI Worksheet

		Time	HR	BP	RR	Ppk	Ppl	Pm	PEEP	aPEEP	WOB	TV	EMV	Ri	Re	Comp	FiO2	CVP	PAP	PAOP	CO	REF	Temp	Fluid	UOP	Hgb	
A	Baseline	8:30	109	121	12	19	16	6.4	3			368	4.4	8	9	29.4	1	5	21	8	2.24	34	36.2	200		11.5	
V	Baseline and T0 are identical in control: no need for additional reading. T0 in injury is immediately following injury.																									12.5	
A	T0																										
V																											
A	T30	9:00	76	123	12	17	14	6.1	3	0.1		370	4.5	9	8	36	1	7	32	8	3.1	38	35.9	100		14.1	
V																										14	
A	T60	9:30	82	134	12	18	15	6.3	3	0		368	4.4	8	9	33	1	6	28	8	3.65	32	35.7	125	200	14.5	
V																										14.5	
A	T90	10:00	78	134	12	19	16	6.4	3.1	0.3		376	4.5	8	9	32	1	7	27	8	2.69	38	35.8	100		14.4	
V																										14.1	
A	T120	10:30	70	129	12	19	16	6.5	3	0		372	4.4	8	9	30.4	1	6	28	8	2.03	27	35.8	100	50	14.7	
V																										14.8	
A	T150	11:00	115	149	12	20	18	6.7	3	0.4		376	4.6	8	10	28.3	1	4	38	9	3.28	29	35.9	100		15.5	
V																										15.1	
A	T180	11:30	92	138	12	20	17	6.8	3.1	0		361	4.4	7	10	271	1	5	36	8	2.11	20	36.2	100	75	15.6	
V																										15.6	
A	T210	12:00	93	154	12	19	17	6.6	3	0.2		374	4.5	8	10	301	1	6	35	8	2.14	30	36.2	125		16.3	
V																										16.2	
A	T240	12:30	90	142	12	20	18	6.8	3			374	4.5	7	10	28.3	1	7	37	10	2.27	21	36.3	50	100	16.2	
V																										16.4	
A	T270	13:00	101	138	12	21	18	6.8	3			372	4.5	8	10	26.9	1	7	37	10	2.02	18	36.2	50		15.4	
V																										16	
A	T300	13:30	90	147	12	21	17	6.9	3	0		375	4.5	7	11	26.3	1	6	37	10	2.54	25	36.2	125	75	15.7	
V																										14.7	
A	T330	14:00	94	144	12	21	19	6.9	3	0		372	4.5	7	11	26.3	1	7	37	9	2.73	24	36.2	125		15.7	
V																										15.6	
A	T360	14:30	98	142	12	21	18	6.9	3	0		374	4.5	7	11	26.9	1	7	33	9	2.29	32	36.3	150		15.2	
V	Return to 12 cc/kg PEEP 3 for 15" to check Blood Gases and Mechanics																									15.9	
A	T375		90	138	12	20	17	6.6	3			369	4.4	8	10	28.9	1	6	35	8			36.4			15.1	
V																										15.4	

Notes:

50 BAL 5 in Para in freezer next door

	Date	03/15/06		Weight	23kg		Study:	Tween Lavage & Dye		VILI Worksheet
	Pig #	2343		Length	94cm		Group:	Tween		

		Time	HR	BP	RR	Ppk	Ppl	Pm	PEEP	aPEEP	Rcexp	Rcinsp	TV	EMV	Ri	Re	Comp	FiO2	CVP	PAP	PAOP	CO	REF	Temp	Fluid	UOP	Hgb
A	Baseline	9:44	185	88	16	19	13	13	3	0			260	4.2	12	11	29.7	0.21	9	32	11	1.54	44	35	575		12.
V	Baseline and T0 are identical in control: no need for additional reading. T0 in injury is immediately following injury.																										14.
A	T0	10:15	138	111	13	27	20	10	3				259	4.2		13	16.1	1	9	22	11	2.15	28	34.7	425		14.
V																											14.
A	T30	10:45	165	109	17	30	24	12	2.6				260	4.6	17	7	14.4	1	8	19	9	3.76	28	34.8	0		14.
V																											13.
A	T60	11:15	131	123	16	29	23	10	3				246	4	11	17	13.5	1	8	21	10	1.79	27	35.1	0	50	13.
V																											13.
A	T90	11:45	131	114	20	27	22	12	3.1				261	5.3	10	15	14.3	1	8	20	8	3.06	27	35	0		13.
V																											15.
A	T120	12:15	144	108	20	29	25	13	3				251	5.3	9	16	14	1	8	21	10	2.42	29	35	0	200	14.
V																											15.
A	T150	12:45	138	110	20	29	25	13	3				269	5.3	10	16	13.5	1	8	20	10	3.19	33	35.1	0		15.
V																											16.
A	T180	13:15:0	114	107	22	27	23	13	3				274	5.9	10	16	14.5	1	9	24	11	2.79	21	35.2	0	75	15.
V																											14.
A	T210	13:45:0	85	110	22	27	22	13	3.1				268	5.9	7	17	14.7	1	11	31	13	1.11	28	35.3	20		15.
V																											15.
A	T240	14:15	107	114	22	27	23	12	3.1				271	6	11	16	15.6	1	9	28	11	1.43	24	35.5	0	40	14.
V																											15.
A	T270	14:45	105	104	22	26	22	12	3				272	6	8	16	15.6	1	9	29	13	1.83	24	35.6	0		15.
V																											13.
A	T300	15:15	110	105	22	26	22	13	3				271	5.9	8	25	16.4	1	9	30	10	1.36	25	35.6	6	100	12.
V																											13.
A	T330	15:45	111	118	20	27	22	12	3				267	5.3	8	17	15.3	1	8	33	10	1.57	28	35.7	0		14.
V																											14.
A	T360	16:15	118	89	27	28	26	16	3				270	7.3	7	19	14.8	1	9	27	11	1.56	24	35.8	0		15.
V	Return to 12 cc/kg PEEP 3 for 15" to check Blood Gases and Mechanics																										14.
A	T375																										
V																											

Notes:

Switched tp Pcontrol PIP 35/PEEP 10 decreased RR about 40% during Tween
Why is PO2 so low without big change in lung mechanics?
Could any injury be due to hypoxia?
Is a single initial injury such as Tween the best model for VILI?
T330 PaCO2>PvCO2 - prob bad gases
1cc Succinylcholine before PV curve

Date	03/16/06	Weight	23kg	Study:	VILI
Pig #	2344	Length	94cm	Group:	Tween

VILI Worksheet

	Time	HR	BP	RR	Ppk	Ppl	Pm	PEEP	aPEEP	WOB	TV	EMV	Ri	Re	Comp	FiO2	CVP	PAP	PAOP	CO	REF	Temp	Fluid	UOP	Hgb
A Baseline	8:25	116	144	12	16	15	6	3	0.2		280	3.4	9	12	23.9	0.21	14	30	11	2.28	35	35.1	550		11
V	Baseline and T0 are identical in control: no need for additional reading. T0 in injury is immediately following injury.																								11.8
A T0	8:50	99	122	17	34	32	19	3			318	5.6	37	15	10.1	1	7	14	9	2.03	37	34.7	450		13.3
V																									14.6
A T30	9:20	85	108	18	31	30	15	3.1	3.4		332	6	26	10	11.8	1	7	21	9	4.49	31	34.4	0		13
V																									13.7
A T60	9:50	79	105	18	31	30	14	2.9			277	5	24	15	10	0.4	7	22	10	3.87	28	34	0	150	11.9
V																									13.7
A T90	10:20	98	104	18	33	31	14	3	0.4		277	5	20	17	9.9	0.9	6	20	7	4.46	39	33.8	0		13.7
V																									13.1
A T120	10:50	125	103	18	35	33	15	3			290	5.3	17	18	10.5	0.9	6	24	8	4.6	25	33.7	0	100	12.6
V																									14.2
A T150	11:20	114	104	18	36	34	16	3			268	4.8	26	20	8.6	0.9	5	27	8	4.41	18	33.7	0		14.3
V																									14.3
A T180	11:50	81	115	18	36	34	15	3	0.8		266	4.8	19	21	8.7	0.9	5	25	7	4.33	16	33.8	0	40	12.9
V																									14.5
A T210	12:20	109	106	18	37	35	16	3	1.1		262	4.8	25	20	8.3	0.8	7	30	9	4.25	15	34.1	0		12.3
V																									14.2
A T240	12:50	121	108	18	37	36	16	3.1	0.8		263	4.8	24	21	8.2	0.8	5	31		4.68	26	34.4	0	40	14.5
V																									14.6
A T270	13:20	102	109	18	43	41	17	3	0.2		257	4.6	17	24	7.4	0.8	5	31		4.68	26	34.4	0		15.8
V																									16.8
A T300	13:50	113	100	22	42	37	17	3	2.2		272	6	23	22	8.4	1	7	34		3.09	18	34.5	0	50	15.3
V																									15.2
A T330	14:20	155	97	24	38	37	19	2.9	1.7		277	6.7	21	22	8.4	1	4	30		3.87	21	34.5	0		15.1
V																									15.6
A T360	14:50	155	98	24	38	37	19	3.1	1.3		288	6.7	20	23	8.4	1	7	33		2.33	23	34.5	0	20	14.9
V	Return to 12 cc/kg PEEP 3 for 15" to check Blood Gases and Mechanics																								15.6
A T375																									
V																									

Notes:

Date 4/27/2006	Weight 21 kg	Study VILI: Control/NPV/ARDSnet/HFOV/APRV/Kinetic	Wet Wt=
Pig # 2359	Anesthesia Typ	Group: control	Dry Wt =
		5% Tween	W/D ratio=
			Dish Weight=

Appendix A (Cont'd)

Date 02/02/06	Weight 31kg	Study: VILI	VILI Worksheet
Pig # ###	Length 41"	Group: Control	

		Time	RR	Ppk	Ppl	Pm	TV	PEEP	aPEEP	EMV	COMP	Rcinsp	Rcexp	Re	Ri	MAP	HR	CVP	PAP	PAOP	CO	Temp	Fluid	UOP	FiO2	Hgb	Sat	BE	pH	pO2	pCO2	Samples
A	Baseline	8:50	12	24	21	8.2	218	3		3.1	17	0.12	0.26	9	7	109		9	34	10	6.3	35.6	1000		21	13	94.3	0	7.45	85	34	Cy+P/V
V	Baseline and T0 are identical in control: no need for additional reading. T0 in injury is immediately following injury.																									13.4	62.6	2	7.42	41	42	
A	T0	9:30	23	31	29	13	232	3		5.1	8.6	0.18	0.23	14	21	116	160	8	30	9	6.79	35.2			100	12.7	87.7	1	7.43	64	38	Cy +P/V
V																										14.3	54.4	2	7.4	39	45	
A	T30	10:00	23	31	29	13	229	3	2	5.1	8.6	0.14	0.2	13	15	111	160	6	25	9	4.85	34.6		40	100	14.5	75.8	3	7.44	77	40	
V																										14.4	41.5	3	7.4	32	46	
A	T60	10:30	23	32	31	13	232	3	1.5	5.1	7.6	0.08	0.19	15	10	108	143	6	24	9	3.86	34		70	100	14.5	71.1	2	7.43	46	40	Cy
V																										14.6	39.1	3	7.4	30	45	
A	T90	11:00	23	34	32	14	236	3.1	1.9	5.1	7.4	0.07	0.19	16	11	109	139	6	23	8	3.31	33.9		40	100	15.1	79.6	3	7.45	52	39	
V																										15	46.5	3	7.4	35	46	
A	T120	11:30	23	34	32	14	229	3	1.8	5	7.3	0.09	0.2	17	11	114	145	6	29	8	2.9	33.8	100	16	100	15	81.5	2	7.45	54	37	Cy
V																										14.9	39.2	3	7.42	31	44	
A	T150	12:00	23	34	32	18	224	3	2.1	4.9	6.9	0.1	0.2	17	13	107	158	8	39	12	2.87	33.8	100	6	100	14.8	77.2	1	7.44	49	36	
V																										15.1	33.5	3	7.4	28	46	
A	T180	12:30	23	35	32	15	222	3.1	2.4	4.9	6.7	0.11	0.2	22	18	106	175	8	35	10	2.18	33.8	300	**50??**	100	15.4	68.9	1	7.42	46	39	Cy+P/V
V																										15.5	25.1	2	7.38	26	47	
A	T210	13:00	23	35	33	12	218	3	1.1	4.8	6.3	0.11	0.19	19	18	103	177	8	17	9	2.94	33.8		4	100	15.4	68.9	1	7.38	47	41	
V																										14.9	28.6	0	7.34	27	49	
A	T240	13:30	23	34	32	12	213	3	0.9	4.6	6.1	0.11	0.18	18	17	100	196	7	29	10	2.08	34		3	100	13.8	69.6	-3	7.36	49	40	Cy
V																										14.8	30.9	-1	7.32	26	50	
A	T270	14:00	23	34	32	12	195	3		4.2	5.5	0.11	0.18	17	19	96	200	8	20	10	1.13	34	200	5	100	15.8	70.8	-2	7.35	48	43	
V																										14.7	21.8	-2	7.31	27	51	
A	T300	14:30	23	35	33	11	188	3		4.4	5.4	0.1	0.17	17	20	95	203	8	30	8	1.69	34.1	100	2	100	15.3	61.3	-2	7.33	49	46	Cy
V																										14.9	25.4	1	7.33	29	48	
A	T330	15:00	23	34	32	12	190	3		4.5	4.9	0.13	0.16	11	23	99	207	8	34	11	1.66	34.1	100	3	**1??**	14.6	65.9	-3	7.34	48	44	
V																										14.4	24.2	-1	7.3	26	38	
A	T360	15:30	23	34	32	12	184	3.2		4.5	4.7	0.1	0.15	14	34	94	216	8	26	8	1.61	34.2	25		**1??**	14.5	66.2	-2	7.33	47	45	Cy+P/V
V																										14.1	67.6	-2	7.29	25	38	
V	**Return to 12 cc/kg PEEP 3 for 15" to check Blood Gases and Mechanics**																															
A	T375																													Lung, Liver, Kidney		Fix and F
V																														Bal spin and freeze		

Notes:

Catheter leak Tween -> lost ~60mL so added an additional 10mL to original 30mL close to RT Lung

Liquid edema filled the trachea tube at necropsy. It appeared to contain a great deal of plasma since it was "yellowish" and clotted.

BAL missed

Lung injury was excellent - very heterogenous injury - small atelactatic areas throughout lung

No bleeds lung inflation during necropsy similar to previous studies. In past studies belbs occurred not during the study but only when the lung was inflated out of the chest. Over expansion

due to loss of the chest wall is an obvious answer, however, these lungs blebbed before the atelactasis was (??). Blebs popped up in both normal and atelactactic areas. In this

study, we inflated the lung (??) Pcontrol 5 and slow rises in PEEP. This slow type of inflation opened all of the atelactasis without causing blebs.

Table 1. **Blood Chemistry Parameters**

Variable	Group	T0	T30	T60
pH	Control	ND	7.47 ± 0.01	7.47 ± 0.03
	5% Tween	7.38 ± 0.05	7.58 ± 0.31	7.40 ± 0.08
PCO_2	Control	ND	39 ± 0.5	39 ± 2.5
	5% Tween	44 ± 6.0	42 ± 2.0	43 ± 7.0
BE	Control	ND	5	3.33
	5% Tween	44 ± 6.0	42 ± 2.0	43 ± 7.0

Table 2. **Hemodynamic Parameters**

Variable	Group	T0	T30	T60
PAP	Control	13.5	26.3 ± 7.4	28.7 ± 7.0
	5% Tween	12 ± 5.7	13.3 ± 1.4	14.3 ± 0.7
Ppw	Control	8	7.7 ± 0.6	7.7 ± 0.6
	5% Tween	16.7 ± 12	14.3 ± 9.2	14.7 ± 8.1
CO	Control	3	2.8 ± 1.2	3.0 ± 1.3
	5% Tween	3.7 ± 2.7	4.4 ± 0.6	3.2 ± 1.2

Table 3. **Pulmonary Parameters**

Variable	Group	T0	T30	T60
Ppeak	Control	23	21 ± 4.0	21 ± 3.6
	5% Tween	31 ± 3.5	31 ± 0.6	31 ± 1.5
Pplat	Control	20.5	18 ± 4.5	18 ± 3.5
	5% Tween	27 ± 6.2	28 ± 3.2	28 ± 4.4
Compliance	Control	16.2	23.9 ± 10.5	22.7 ± 9
	5% Tween	11.6 ± 4	11.6 ± 2.9	10.4 ± 3

Table 1. **Blood Chemistry Parameters** (Cont'd)

T90	T120	T150	T180	T210
7.46 ± 0.03	7.45 ± 0.03	7.44 ± 0.02	7.43 ± 0.02	7.41 ± 0.05
7.40 ± 0.08	7.42 ± 0.05	7.42 ± 0.05	7.42 ± 0.04	7.41 ± 0.04
40 ± 5.1	41 ± 2.1	43 ± 0.6	44 ± 4.2	42 ± 3.1
40 ± 2.6	39 ± 3.2	40 ± 4.0	39 ± 1.5	39 ± 2.1
2.67	2.67	2.67	2	2
40 ± 2.6	39 ± 3.2	40 ± 4.0	39 ± 1.5	39 ± 2.1

Table 2. **Hemodynamic Parameters** (Cont'd)

T90	T120	T150	T180	T210
26 ± 9.5	29 ± 7.5	32 ± 8.7	33 ± 7.9	35.3 ± 4.5
13.3 ± 0	15 ± 2.1	15.7 ± 4.9	16.3 ± 0.7	20.3 ± 0.7
7.7 ± 1.5	7.3 ± 1.2	8.3 ± 1.2	8 ± 1	9 ± 1
12.7 ± 9	15.7 ± 11.6	19 ± 17.3	17.7 ± 15.1	13 ± 4
2.7 ± 1.1	2.5 ± 1.7	3.1 ± 0.9	2.4 ± 0.3	2.3 ± 0.2
3.6 ± 0.7	3.3 ± 1.1	3.5 ± 0.8	3.1 ± 1.1	2.8 ± 1.6

Table 3. **Pulmonary Parameters** (Cont'd)

T90	T120	T150	T180	T210
21 ± 4.0	21 ± 4.4	22 ± 4.0	22 ± 4.9	20 ± 3.6
31 ± 3.8	33 ± 3.6	33 ± 3.2	33 ± 5.3	33 ± 4.9
19 ± 3.8	18 ± 4.0	20 ± 3.5	20 ± 4.6	18 ± 3.6
28 ± 5.5	30 ± 4.4	30 ± 4.7	30 ± 5.9	30 ± 7
23.7 ± 7.2	23 ± 6.4	20.5 ± 7	21.3 ± 5.1	24.2 ± 5.2
10.5 ± 3.5	10.6 ± 3.4	9.7 ± 3.4	10 ± 4.1	9.8 ± 4.4

Table 1. **Blood Chemistry Parameters** (Cont'd)

T240	T270	T300	T330	T360
7.43 ± 0.05	7.43 ± 0.04	7.43 ± 0.03	7.43 ± 0.04	ND
7.41 ± 0.04	7.34 ± 0.10	7.37 ± 0.05	7.31 ± 0.12	7.41 ± 0.08
43 ± 4.4	41 ± 5.0	42 ± 3.2	41 ± 3.5	ND
39 ± 1.5	53 ± 24	42 ± 8.7	47 ± 8.8	38 ± 7.0
2	1.67	2	2.33	2
39 ± 1.5	53 ± 24	42 ± 8.7	47 ± 8.8	38 ± 7.0

Table 2. **Hemodynamic Parameters** (Cont'd)

T240	T270	T300	T330	T360
34.7 ± 7.8	36 ± 6.6	38.3 ± 1.2	34.3 ± 3.1	35.5
19.7 ± 2.1	20 ± 1.4	21.3 ± 2.8	21 ± 2.1	20 ± 4.2
8.7 ± 1.2	8.7 ± 1.2	9 ± 1	9.3 ± 0.6	8.5
20 ± 12.7	16.5 ± 4.9	20 ± 14.1	22 ± 17	18.5 ± 10.6
2.5 ± 0.2	1.9 ± 0.3	2.1 ± 0.4	2.4 ± 0.3	2.1
2.7 ± 1.7	2.5 ± 1.9	2.0 ± 0.9	2.4 ± 1.3	1.8 ± 0.4

Table 3. **Pulmonary Parameters** (Cont'd)

T240	T270	T300	T330	T360
22 ± 5.6	22 ± 4.6	23 ± 4.9	23 ± 5.3	22
33 ± 5.1	34 ± 8.5	34 ± 8.0	33 ± 5.6	33 ± 5.0
20 ± 4.7	19 ± 4.2	20 ± 4.9	21 ± 4.4	19
30 ± 6.7	32 ± 9.5	31 ± 7.8	30 ± 7.6	32 ± 5.5
23.3 ± 4.4	22.2 ± 4.4	21.8 ± 5	21.6 ± 4.9	24.2
10 ± 5	9.5 ± 5.4	10 ± 5.7	9.5 ± 5.3	9.3 ± 5.1

ABSTRACT:

Severe physical-trauma can lead to the development of acute respiratory distress syndrome (ARDS). Currently, the only known treatment for ARDS is mechanical ventilation. However, if mechanical ventilation is applied inappropriately further injury and malfunction of the lungs may occur, and thus, causing a ventilator induced lung injury (VILI).

VILI has several manifestations including volutrauma, atelectrauma, and biotrauma. These mechanisms often exacerbate one another adding further insult to the injury. The goal of this current study is to establish a stable control pig model of ARDS as a comparison for ventilatory strategies that will act in a more protective manner than an injurious manner.

ACKNOWLEDGEMENTS

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BACKGROUND: VENTILATOR-INDUCED LUNG INJURY

Mechanical ventilation has been used to support acutely ill patients for several decades. However, it has become apparent, especially to researchers and clinicians within the specialty, that even though there are many life saving benefits of mechanical ventilation, it also has several serious drawbacks. Recently a serious complication of mechanical ventilation known as ventilation induced lung injury (VILI) has been identified. Initially, the mechanisms of VILI was believed to be barotrauma, which are gross tears that cause leakage of air into the thorax due to disruption of the epitheal cells that form the wall of the alveoli. This extra-alveolar accumulation of air can bring about several complications (1) the most threatening of which is a tension pneumothorax, or the accumulation of air in the pleural cavity. The adverse results of these macroscopic occurrences are usually immediately obvious, and macroscopic form of barotrauma has been the subject of clinical studies and the experimental studies of Macklin and Macklin (2).

It was not until recently that microscopic pathologic damage was found to occur during improper mechanical ventilation of patients with acute respiratory distress syndrome (ARDS). This newly recognized form of injury is currently of major interest to researchers and clinicians caring for ARDS patients requiring the application of ventilatory support. Although several fundamental experimental studies were published prior to 1975, it wasn't until 10 years later that renewed interest in VILI stimulated a major research effort (3). Unlike the belief that gross barotrauma (i.e., gross tearing of the lung) was the primary mechanism of VILI,

the contemporary belief is that microscopic damage to the pulmonary parenchyma is the major mechanism of VILI (4). These microscopic injuries cause increases in endothelial and epithelial permeability leading to alterations in lung fluid balance. The microscopic injury observed for VILI (5) does not have specificity. In other words, the injury due to VILI has a similar pathology compared to other pulmonary injuries. Thus, the non-specific pathological outcome of VILI makes it difficult to discern a pulmonary injury solely as a result of VILI or another mechanism. It similarly approximates the injury that can be observed in additional models of acute lung injury (6). The pathophysiology of VILI does not differ significantly from the disperse injury of alveoli observed during ARDS (7). Therefore, VILI is indistinguishable from the initial respiratory failure, which the ventilator is attempting to treat. The concept that mechanical ventilation can truly bring about further aggravation of pre-existing acute lung disease is now widely acknowledged (8). Any demonstration of VILI superimposed over the pulmonary disease (i.e. ARDS) would be illusive. Thus, this concept derived from animal studies has resulted in complete reassessment of the use of mechanical ventilation for patients with acute lung diseases and underlies current trends; such as ARDSnet and HFO ventilatory strategies, in the clinical practice of mechanical ventilation (9). Indeed, the current orientation is to emphasize the potential importance of easing the stress on acutely injured lungs by using modes of ventilation that limit the pressure and volume of gas delivered to the lungs (10-11).

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute Respiratory Distress Syndrome (ARDS) is an acute, severe injury to most or all of both lungs. Patients with ARDS experience severe shortness of breath and often require mechanical ventilation, because of respiratory failure. ARDS is not a specific disease, instead, it is a type of severe, acute lung dysfunction and it is associated with a variety of diseases, such as pneumonia, shock due to sepsis; which is a severe infection in the body, and trauma. ARDS can be confused with congestive heart failure, which is another common condition that can also cause acute respiratory distress.

At the onset of ARDS, lung injury may first appear in one lung, but then quickly spreads to affect most of both lungs. When alveoli are damaged, some collapse and lose their ability to receive oxygen. With some alveoli collapsed and others filled by fluid, it becomes difficult for the lungs to absorb oxygen and get rid of carbon dioxide. Within one or two days, progressive interference with gas exchange can bring about respiratory failure requiring mechanical ventilation. As the injury continues over the next several days, the lungs fill with inflammatory cells derived from circulating blood and with regenerating lung tissue. Fibrosis, or the formation of scar tissue, begins after about 10 days and can become quite extensive by the third week after onset of injury. Excessive fibrosis further interferes with the exchange of oxygen and carbon dioxide.

Knowledge of the cause of ARDS is not well defined. Current information supports several theories about its development, but the precise reason ARDS occurs remains unknown. What is known, however, is that the onset of ARDS can come about by one of two basic mechanisms. The *first* is a direct physical or toxic

injury to the lungs. Examples include inhalation of vomited stomach contents, smoke or other toxic fumes, and a severe "bruising" of the lungs that usually occurs after a severe blow to the chest. The *second* mechanism is more common, but less understood. This is an indirect, blood initiated injury to the lungs. When a person is extremely sick or the body is severely injured, cytokines and other signals are released into the bloodstream. These signals reach the lung, and the lung becomes overwhelmed by an inflammatory response, thus causing lung dysfunction. Examples of this type of indirect lung injury include the presence of sepsis and severe injury - the two most common factors in ARDS cases (12).

THE ALVEOLI

An alveolus sac is the point where gas exchange occurs within the lung; typically carbon dioxide is exchanged for oxygen. About 300 million alveoli are located within a normal, human lung. In addition, each alveolus has a diameter of about 250μm and is enveloped by as many as 1000 capillaries. A rough estimation for the area of contact between the alveoli and the capillaries has been in the range of 50 to 100 meter^2. This large area allows for the exchange of oxygen and carbon dioxide through the process of diffusion from higher areas of concentration to areas of lower concentrations. This provides for an excellent example of the natural phenomena of a large surface area being placed within a relatively small volume of space.

The surface of an alveolus sac is composed of a single layer of epithelial cells, which compose about 93% of the alveoli surface area; type I alveolar cells. Found amongst the type I cells, the larger cells that produce the fluid layer lining

the alveoli are known as type II alveolar cells. Additionally, a phagocyte can be found within the extracellular fluid lining of the alveolar surface providing for primary immune defense.

THE PHYSIOLOGICAL BASICS OF THE LUNG

The exchange of gases between the air located outside the alveoli and air within the alveoli is known as ventilation. Commonly known, air moves from a region of higher pressure to a region of lower pressure.

$$F = \Delta P / R$$

This is known as the flow of air (F) is equivalent to the difference in pressure (ΔP) among two different regions, and the resistance(R) experienced by the air decreases the flow of air. Concerning the issue of the flow of air into and out of the lungs, the pressure inside the alveoli sacs themselves is known as the alveolar pressure (P_{alv}), and the atmospheric pressure (P_{atm}) are of significance.

$$F = (P_{atm} - P_{alv}) / R$$

Over the course of ventilation, air moves into and out of the lungs because the alveolar pressure is alternating between pressures less than and greater than that of the atmospheric pressure. The change in alveolar pressure is caused by changes in the volume of the chest wall and lungs.

To understand this concept, it is essential to know Boyle's law

$$P_1 V_1 = P_2 V_2$$

During inspiration, for example, the diaphragm lowers and the chest extends creating a larger volume for the lungs to occupy, and thus decreasing the pressure within the lung. This change from a higher to lower pressure causes air to flow

into the lungs, and vice versa during expiration.

The surface of the alveoli cells is moist, and so the alveoli can be thought of as air filled sacs externally lined with water. At an air-water interface, the attractive forces between water molecules, known as surface tension, cause the water molecules composing the water lining to form a pulling force amongst each other. An excellent demonstration of this would be adding water drop by drop onto the surface of a penny. If carefully done a bubble of water will form and maintain its form as long as it is not greatly disturbed. Essentially, to expand the lung, energy is required not only to stretch the connective tissue of the lung, but also to overcome the surface tension of the fluid layer lining the alveoli.

The role of type II alveolar cells is to prevent the fluid layer lining the alveoli from becoming a great force to be overcome during lung expansion, which could potentially lead to the collapsing of alveoli sacs. Type II alveolar cells secrete a substance similar in nature to detergent molecules, known as pulmonary surfactant, and these molecules greatly reduce the cohesive forces between water molecules on the alveolar surface by disrupting their molecular interactions, such as hydrogen bonding and van der Waals forces. Therefore, surfactant is able to decrease the surface tension that would otherwise be a greater force to overcome. The presence of surfactant is essential to lung compliance and allows the lungs to expand with greater ease.

Pulmonary surfactant is a complex of both lipids and proteins, however it's mostly composed of phospholipids consisting of both a hydrophilic tail and a hydrophobic head and these act by forming a monolayer between the air and

water at the alveolar surface. During times of non-strenuous, consistent breaths, the concentration of surfactant has a tendency to decrease, since there is a smaller tidal volume, and with it a less dynamic change, in the lung tissue itself. However, a deep breath causes the type II alveolar cells to be stretched and in turn stimulates the secretion of surfactant by these cells as well. The Law of Laplace:

$$P = 2T / r$$

shows the relationship between pressure (P), surface tension (T), and the radius (r) of an alveolus. As the inner radius of the alveolus decreases, the pressure increases. For two alveoli next to each other sharing alveolar duct, the inner radius of the alveoli is larger than the other. If the surface tension (T) is equal for both alveoli, the alveolus with the smaller radius would have a higher pressure according to the Law of Laplace. And if pressure of alveolus with the smaller radius is higher than pressure of alveolus with a larger radius then air will flow from the alveolus with a smaller radius to the alveolus with a larger radius. This will lead the alveolus with a smaller radius to collapse (13). Thus, alveoli with smaller radii are more unstable and are more likely to collapse into larger alveoli.

Taking the radii of alveoli into consideration, it is appropriate to attend to an additional property of surfactant which is its ability to stabilize alveoli of different sizes by altering surface tension, depending on the surface area of the alveolus. When an alveolus becomes smaller, the molecules of surfactant on its surface are more concentrated since more molecules of surfactant are spread across a smaller area, thus reducing the surface tension. This reduction in surface tension aids a smaller alveolus to maintain a pressure equal to that of a larger

alveolus (13). Thus, surfactant acts to stabilize alveoli of different size.

TYPES OF VENTILATOR-INDUCED LUNG INJURY

Definitive evidence that mechanical ventilation can cause damage to the lungs in humans is difficult to obtain, since it is clearly not possible to perform experiments in which humans are exposed to strategies of ventilation that are thought to be injurious, solely for the purpose of examining the lung injury that it can cause. Thus, the injuries known as ventilator-induced lung injury (VILI) can be thought of as correlating with ventilator maneuvers, since no definitive cause and effect relationship can truly be distinguished as of now. However, the evidence obtained from experimental animal studies and correlative human studies, and other studies focusing on the side effects of different ventilatory parameter manipulations have become swayed and are joining the band wagon that this matter of concern is a priority for critical care clinics.

Barotrauma

The concept that high airway pressures during positive pressure ventilation can cause a massive injury in the form of air leaks, known as pneumothorax, has been well known and investigated for many years. However, the issue that has not been clear as night and day is which pressure parameters; such as peak, mean, PEEP, etc., are of utmost significance and the exact values at which these pressure parameters induce VILI. However, it has become clear that the absolute airway pressure alone does not directly bring about the injury. Even though it is a modality for airway pressures to be monitored clinically, transpulmonary (alveolar pressure minus pleural pressure) pressures are of greater

significance. This can be better understood by the observation that very high airway pressures can often be achieved, however, the presence of barotrauma is rather uncommon (14). The attribute of utmost significance in the development of pneumothorax appears to be the degree with which different regions of the lung are distended.

Volutrauma

In addition to the obvious manifestations of overdistention previously discussed, an even more inconspicuous injury can be induced by mechanical ventilation. Webb and Tierney (15) produced strong evidence that overdistention associated with high peak airway pressures could lead to the development of pulmonary edema and the death of rats within 1 hour. Since this study, a large number of investigators have observed that high end inspiratory lung stretch could inflict diffuse alveolar damage, the formation of pulmonary edema, an increased fluid filtration, an increased epithelial permeability, and an increased pulmonary capillary permeability. It has been demonstrated by Egan et al. (16) that static inflation of sheep lungs up to pressures of 40 cm H_2O leads to an increase in pore radius of a magnitude that potentially allows fluid to leak into the alveoli. In addition, Parker et al. (17) performed ventilation on isolated dog lungs for 20 minutes and noted that peak pressures of more than 20 cm H_2O lead to an increase in capillary filtration correlating with the increase of peak pressure.

Hence, Dreyfuss et al. (18) came up with the term volutrauma. This is pertinent as to indicate that the cause of injury was not exclusively due to airway pressure, but rather to the volume. In this study rats were grouped to undergo one

of three ventilatory strategies: high pressure and high tidal volume which was found to lead to an increase in lung water; an application of low pressure and high volume for which the rats underwent negative pressure ventilation of high tidal volumes also leading to an increase in lung water; and lastly, a strategy of high pressure and low volume calling for the chest walls of the rats to be strapped down over the course of ventilating them with high pressures and low tidal volumes even though there was a decrease in compliance, the lung water was within the expected range for rats (18). Thus, further supporting the theory that lung volume was the significant factor in inducing increased lung water in opposition to pressure. In further studies of rats, Dreyfuss et al. (19)showed that the time course of such injury was very rapid, with more than a 50% increase in lung water within 20 minutes. The rapid progression with which this degree of the lung injury was achieved was further exacerbated if the high tidal volumes were decreased reasonably quickly. Expanding upon this study, Dreyfuss and colleagues (20) were able to show that an interaction between pre-existing acute lung injury (ALI) and mechanical ventilation did exist. This was accomplished through a study in which an injury model called for the lungs to be damaged with alpha-naphthyl-thiourea (ANTU). A combination of both injurious factors of high volume and ANTU had a synergistic effect by increasing extravascular lung water(20).

An endless array of mechanisms have been proposed to account for this increase in alveoli and pulmonary capillary permeability that is observed with the application of high tidal volume ventilation. For instance West et al. (21) have

conducted elaborate studies with the proposal of wall stress failure as a mechanism. The build up of excessive wall stress is a dependency of stress failure; it is the ratio of alveolar wall tension to the thickness of the alveolar wall. To demonstrate, Fu et al. (22) showed that at a constant transmural pressure, an increase in transpulmonary pressure from 5 to 20 cm H_2O produced a significant increase in the number of breaches within the epithelial and endothelial cell layers. Moreover, it was found that a further increase in the occurrence of cell layer breaks while transpulmonary pressure was held constant and when the pressure across the capillary wall was further increased.

Although these mechanical factors causing the cellular damage are important, a recent study by Parker et al. (23) suggests that increased permeability due to VILI may be caused by a much more subtle mechanism. These investigators examined the hypothesis that microvascular permeability might be actively altered by a cellular response to mechanical injury, and that this response might be initiated by stretch-activated cation channels through increases in intracellular calcium concentration. The results show that the coefficient for capillary filtration increased 3.7 fold that at baseline in lungs ventilated with a peak airway pressure of 35 cm H_2O, which was unchanged from the baseline when the lungs were ventilated under the same ventilatory parameters.

Atelectrauma

In addition to the injury caused by ventilation at high lung volumes, there is a collective amount of evidence indicating that ventilation at low lung volumes may contribute to injury as well. This injury is believed to be related to the

continuous opening and closing of the alveoli sacs. This concept of injury caused by the repetitive opening and collapse of distal airways was first proposed by Robertson et al. (24) to explain the lung injury observed in infants with respiratory distress syndrome (IRDS). The results of the study suggested that in a lung undergoing atelectasis, the air-liquid interface may be located relatively close to the ending tips of the airways, rather than at the alveoli themselves. To open the airway with such an air-liquid interface would require a relatively high pressure. And in the process of opening the air way, the shear stress experienced by the airway duct may lead to the disruption of epithelial cells lining the airway duct. The evidence that lung injury can be caused by ventilation at low lung volumes has been collected across studies using different species (such as rats, rabbits, and dogs), different lung injury models (saline lavages and ventilator-induced lung injuries), and examined by the use of different ventilatory strategies (such as differing PEEP settings and different mechanical ventilators like high-frequency oscillation (HFO)) (25-26).

The comparison of conventional mechanical ventilation with HFO has been done across numerous studies (27). For these studies, rabbits that were ventilated with HFO had a greater concentration of oxygen over the course of the study and a decrease in lung injury was accounted for through pathological analysis showing hyaline membrane formation, which is representative of insufficient surfactant concentrations. Further, McCulloch et al. (28) found that the beneficial effect was not solely due to HFO itself, but in addition, interdependent interactive effects exist concurrently with the mean airway

pressure and the mean lung volume. Rabbits that were ventilated at low mean airway pressures manifested a significantly greater degree of lung injury than the rabbits ventilated at a higher mean airway pressure, even though both of the groups were ventilated with HFO.

Additional studies using conventional mechanical ventilation reported similar findings that high mean lung volume ventilation appeared to be protective with different levels of PEEP (29). Most of these studies were *in vivo* models, which prove to be advantageous through the utilization of intact animals, and thus provide for a model with a higher degree of external validity for clinical application. However, a problem that arises with the use of such a model is the difficulty of maintaining the same, if not similar values for partial pressure of oxygen (PaO_2), fraction of inspired oxygen (FiO_2), and arterial blood pressures amongst the individual animals within each treatment group. Unfortunately, this can make interpretation and application of the data from these studies more challenging, especially when trying to distinguish amongst the direct mechanical effects of ventilation on the lung and the other indirect factors. To circumvent this obstacle, Muscedere et al. (26) utilized an *ex vivo,* non-perfused rat lung system. In this study, it was observed that the application of PEEP above the inflection point of alveolar recruitment and derecruitment, will significantly reduce the rate at which the lung compliance will decrease. A decrease in lung compliance is typically observed with lower PEEP level applications. Further, it was also found that less pathologic typical attributes of lung injury were observed when assessing by airway injury and the formation of the hyaline membrane. Results from this

particular model need to attend to the fact that the degree of recruitment and derecruitment is interacting synergistically, because there is no chest wall and thus at a PEEP of 0, the transpulmonary pressure is going to be 0. However, this is not the case *in vivo*.

In addition to the recruitment and derecruitment discussed, a number of other possible mechanisms exist that can lead to the development of lung injury with low lung volume ventilation. The extent to which the alveoli collapse or become filled with fluid, will correspond with a decrease in alveolar PaO_2 that can permanently damage cells. Ventilation at low lung volumes can also lead to the inhibition of surfactant production and lead to surfactant being squeezed out of the alveoli. In addition, the re-recruitment of atelectatic regions of complete alveolar collapse to the fully recruited regions has been found to be associated with the further insult to the areas under regional stress. Mead et al. (30) proposed that an unexpanded lung region completely dispersed amongst regions of expanded lung would experience a pressure much greater than the transpulmonary pressure. This has the potential to cause significant, local amplification at pressures that lead to the overdistension of the alveoli.

Biotrauma

The previously discussed types of injury are largely thought to be mechanical injuries brought about by mechanical factors. However, in more recent years, there has been increasing evidence that mechanical factors can lead to injury that is cell and inflammatory mediator based, with a greater emphasis on the biological mechanisms of injury, which is the mechanism of injury known as

biotrauma (31).

Numerous studies have found that the mechanical ventilation of injured lungs could lead to a further injury that is an inflammatory response. Kawano et al. (32) studied rabbit lungs that were injured by the administration of a lavage and were conventionally ventilated. The study showed that the animals developed severely depleted levels of oxygen, and the histological analysis revealed that a large number of neutrophils were found within the lung, whereas animals that were neutrophil depleted by treatment with nitrogen mustard which is a toxic compound, prior to the lung lavage had significantly better oxygenation. The investigators suggested that cytokines released from neutrophils played a crucial role in VILI. Further, Imai et al. (33) compared conventional mechanical ventilation with HFO in a lung lavage model and observed that HFO was associated with a large decrease in the amount of neutrophils, cytokines, and other cellular immune signals in the lung lavage, including platelet-activating factor.

Most of these studies have been performed in animal models which have limitations when attempting to apply the findings to human, clinical treatments. A clinical study conducted by Amato et al. (34) examined if a ventilatory strategy that was aimed at minimizing lung injury would decrease the mortality of patients with ARDS. They studied 53 patients who were assigned at random to receive a protective ventilatory strategy consisting of recruitment, high levels of PEEP, and pressure limitation at end-inspiration compared with a control group that received conventional mechanical ventilation. The findings showed that the patients who underwent the protective ventilatory strategy had a mortality rate of 38% in

comparison to the 71% mortality rate of the control group. Further, a National Institutes of Health - National Heart, Lung, and Blood Institute trial study showed that the utilization of a tidal volume of 6 mL/kg lead to about a 25% decrease in mortality compared to 12 mL/kg tidal volume in patients with ARDS (35). One proposed mechanism to account for the significant decrease in mortality was proposed through a study by Ranieri et al. (36) for which two similar ventilatory strategies were used and it was found that the group treated with a minimal tissue stress strategy had a decrease in the concentration of cytokines compared to the control group.

Further, other studies have led to the speculation that injurious strategies of mechanical ventilation could lead to the development of multisystem organ failure (MSOF) (37). If this is the case, it could help better account for the high mortality rate of patients with ARDS and more importantly could lead to additional modifications for ventilatory strategies and interventions in critically ill patients which may in turn lead to a decrease in mortality.

PULMONARY EDEMA

Pulmonary edema is the accumulation of fluid in the lung. This pathology may be induced by a number of physiologic abnormalities, which ultimately result in impaired gas exchange. The edema first accumulates in the interstitial and then the alveoli, as edema accumulation progresses it causes a decrease in gas exchange, especially oxygen. This due to the fact that the capillary epithelium has a greater permeability of water than the alveolar epithelium.

Lymph Drainage from the Lung.

Fluid that reaches the pulmonary interstitial can only be removed by the lymphatic connection of the lung. It is now believed that the volume of lymph flowing from the lung is as great as that of any other organ in the human body. The lymph drainage also is believed to achieve a rate 10 fold the normal drainage volume during pathologic conditions. When the lymphatic drain is overwhelmed, however, the accumulation of pulmonary edema can compromise the well being of an individual.

There are a number of conditions that can lead to the development of pulmonary edema. Factors that bring about the destruction of the capillary endothelium such as infection or toxin, can cause localized pulmonary edema (13).

LUNG COMPLIANCE

The lungs are organs that are characterized by elasticity and have the ability to retain their initial shape after being stretched. Lung compliance (C_L) is defined as the amount of change in lung volume (ΔV_L) induced by a given change in the transpulmonary pressure.

$$C_L = \Delta V_L / \Delta (P_{alv} - P_{ip})$$

Thus, the greater the lung compliance, the easier it is to expand the lungs at any given change in transpulmonary pressure. Compliance is basically the inverse of stiffness. Thus, a low value of lung compliance will require a greater than normal transpulmonary pressure to be established across the lung in order to cause given amount of lung expansion.

Two determinants of lung compliance are stretch ability and surface

tension at the air-water interface among alveoli. Stretch-ability of the lung tissue itself, particularly the elastic connective tissues, can have an affect on lung compliance. Thus, a thickening of lung tissue decreases the lung compliance. The accumulation of edema and neutrophils may act to decrease the compliance of the lung through a tissue thickening mechanism. The compliance of the lung is also dependent in part upon the concentration of surfactant and the accumulation of extracellular fluid acts to decrease the concentration of the surfactant molecules on the alveoli.

RESEARCH PERFORMED IN THE DEPARTMENT OF SURGERY OF THE *STATE UNIVERSITY OF NEW YORK – UPSTATE MEDICAL UNIVERSITY*

INTRODUCTION:

As mentioned previously, severe physical-trauma can lead to the development of acute respiratory distress syndrome (ARDS). Currently, the only known treatment for ARDS is mechanical ventilation. If a patient is connected to a mechanical ventilator at inappropriate settings, however, further injury and malfunction of the lungs may occur, and thus, causing ventilator induced lung injury (VILI). The global goal of this research is focused on reducing or even eliminating VILI for patients on mechanical ventilation. The lab believes this goal can be achieved through defining the ideal mechanical ventilatory parameters specific to ARDS-like states as well as other factors, such as kinetic application, non-native surfactant administration and the prevention of degradation of intercellular lung, protein adherins, which may offer additional protective

advantages; either act independently or have a synergistic effect.

In order to develop these ideal ventilatory strategies a relatively stable, *in vivo* model that can be translated to human applicability must be established. Thus, the focus of the current research is to establish a reliable model of ARDS in pigs, since pigs have a similar respiratory and circulatory system to humans. Two current, protective modes of ventilation high frequency oscillatory ventilation (HFOV) and adaptive pressure release ventilation (APRV) in congruence with the current clinically-utilized standard of care method of ventilation established by the ARDS Network (ARDSnet) will be compared with the progress of this particular study.

In an ARDS model caused by tween, which is a detergent that deactivates pulmonary surfactant, application of non-protective ventilation group will exhibit many symptoms of ARDS compared to the control pigs that are ventilated without the establishment of any injury to the lungs. Thus, it is predicted that the pigs in the non-protective ventilation treatment will exhibit larger amounts of pulmonary edema, a higher concentration of collapsed alveoli, more evidence of an inflammatory response, and will exhibit lower concentrations of PaO_2 as a result of a decreased surface area for gas exchange.

MATERIALS AND METHODS:

Animal Preparation

Six female Yorkshire pigs were anaesthetized by an animal care specialist at SUNY Upstate Medical University approximately 15 minutes before intubation. Continued anesthesia was administered on a need-basis using two mg

per kilogram of xylazine. Once secure intubation was established the pigs were continually ventilated at a pre-calculated volume. The surgical technician and the physician cannulated the pig's right internal jugular vein and the right carotid artery under sterile conditions. Baseline measurement and the fractional inspired oxygen (FiO_2) was room air (21% O_2).

After the catheters were secured in place, the following baseline measures were recorded for the heart rate (HR), respiratory rate (RR), temperature (°C), arterial pressure, arterial blood gases (ABGs), and venous blood gases (VBGs). In addition, a Foley catheter was inserted into the bladder to measure urine output. Blood samples were collected hourly to measure the concentrations of plasma cytokines and proteases at baseline that were compared with plasma samples following injury to elucidate the inflammatory response.

Non-injurious Protocol

After the surgical preparation mentioned above, the pigs (n=3) will be ventilated at a tidal volume (Vt) of 12 mL/kg and a positive-end expiratory pressure (PEEP) of 3 cm H_2O over the course of each 6 hour study. Parameters such as hemodynamic, lung function, ABGs, and VBGs measures will be recorded every 30 minutes. Arterial blood samples (30 mL) will be drawn hourly for plasma cytokine and matrix metalloproteinase measurements. Blood samples will be injected into six vacuum sealed test tubes and spun in a centrifuge for 10 minutes at 3500 RPM at 15°C. The upper plasma layer of the freshly spun, blood samples were carefully aliquotted into eight, 2 mL cryo-vials and submersed within liquid nitrogen to immediately freeze the samples for storage.

At necropsy, the lung was fixed for histologic analysis, edema will be assessed by wet/dry weight ratio (W/D), and bronchoalveolar lavage fluid (BALF) will be sampled for protein concentration, cytokine and protease analysis, 7S Fragment concentration and surfactant function.

Injury with Non-protective Ventilation Protocol

Similar to the protocol for non-injurious, control group, after the surgical preparation, the pigs (n=3) will be ventilated at a tidal volume (Vt) of 12 mL/kg and a PEEP of 3 cm H_2O initially. Parameters such as hemodynamic, lung function, ABGs, and VBGs measures will be recorded every 30 minutes. Arterial blood samples (30 mL) will be drawn hourly for plasma cytokine and matrix metalloproteinase (MMP) measurements.

Lung injury (ARDS) was caused by the instillation of the 5% Tween/Saline by lavage. PEEP was increased to 10 cm H_2O and peak inspiratory pressure (PIP) was adjusted to 35 cm H_2O during and for 10 minutes post tween instillation. The pig was tilted on its right side for the instillation of half of the Tween dose into the lung with a suction catheter. The suction catheter was moved in and out approximately 6 cm over the course of the instillation to try to assure that the Tween was not instilled into only a single lobe. Post-instillation, the pig was kept on its right side for 10 minutes under the ventilatory parameters of Vt of 12 mL/kg and PEEP of 10 cm H_2O, PIP of 35 cm H_2O. After the 10 minute period, the pig was laid on its left side and the procedure just discussed was repeated for the second half of the Tween instillation. Following tween instillation the pig was returned to the supine position and the PEEP returned to 3 cm H_2O.

Mechanical ventilation was resumed with a Vt of 12 mL/kg and PEEP of 3 cm H_2O and this was determined as time zero (T0).

Pulmonary Edema

To determine if pulmonary edema was present within the lung, sections from each lobe of the lung was incised. Each sectioned piece of lung was placed within a pre-weighed dish and weighed; this provides what is known as the wet weight of the lung, which will be increased if the lung is edematous. The pre-weighed dish containing the lung was then placed in an oven at 65°C for a period of 24 hours, and was weighed again. This process was repeated until no weight change was observed over the course of the 24 hour period, so the lung samples were determined to be dry. The fluid (edema) within the lung was determined to be equivalent to the wet-to-dry weight ratio (W/D).

Histology

Histology was carried out to assess the lungs for pathologic injury. First, the lungs were instilled and immersed with formalin for a minimum of 48 hours. Two tissue samples were sectioned from the left lung; one dependent and one non-dependent position. The right lung will be used for histological analysis and the left lung will be used for cytokine and cellular analysis. To accomplish this, the trachea was cannulated while the left bronchiole was clamped-off, so that the right lung was able to be instilled with formalin to a fixed pressure of 20 cm H_2O for 60 hours. The lung was then incised horizontally from posterior to anterior positions at a thickness of one centimeter. And from each section, two cubes of 1 cm^3 size are selected at random; one from the upper and from the lower portion.

Further, three slices of 5 μm thickness from each of the cubes was embedded in paraffin wax and hematoxylin-and-eosin staining was done for cell detection and measurement.

RESULTS:

Appendix A contains all of the individual data sheets for each of the pigs used in the study.

Appendix B contains the compiled blood chemistry, hemodynamic, and pulmonary parameter data in tables 1, 2, and 3, respectively. *Table 1* consists of arterial blood pH, partial pressure of carbon dioxide (PCO_2), and base excess (BE), which is the amount of acid (in mmol/L) required to return the blood pH of an individual to the normal value. *Table 2* consists of the mean pulmonary arterial blood pressure (PAP), pulmonary wedge pressure (Ppw) which is used to measure the back pressure from the pulmonary veins, and cardiac output (CO) is the volume of blood being pumped by the heart per minute (in L/min). *Table 3* consists of the peak airway pressure (Ppeak), plateau pressure (Pplat), and lung compliance (compliance). All the data values are expressed as the mean plus/minus standard deviation (mean ± SD).

Appendix C contains the graphs of all the parameters measured over the course of the study. *Figure 1* shows that the pigs in the non-protective ventilatory group had a pH that fluctuated near the beginning and the end of the studies compared to the control. *Figure 2* the partial pressure of CO_2 remained relatively stable and similar for both groups. *Figure 3* the BE of the non-protective ventilatory group was lower compared to the BE of the control group. *Figure 4* the mean pulmonary

pressure increased at a higher rate over the course of the study for the non-protective ventilatory study compared to the control group. *Figure 5* the mean Ppw was greater and fluctuated more in the non-protective ventilatory group compared to the control group. *Figure 6* the mean CO for both groups decreased at a similar rate; however, the mean CO remained slightly greater in the non-protective group compared to the control group. *Figure 7* the MAP was parallel among the two groups; however, the MAP of the control group was greater compared to the non-protective ventilatory group. *Figure 8* the mean Ppeak was greater in the non-protective ventilatory group compared to the control group. *Figure 9* the mean Pplat was higher for the non-protective ventilatory group and increased over the course of the study, while the end Pplat control group remained relatively stable and equal to its initial Pplat. *Figure 10* the lung compliance dramatically increased within the first 30 minutes post tween administration and remained relatively stable for the remainder of the study. However, the lung compliance of the non-protective ventilatory group decreased a small amount over the course of the study.

Appendix D consists of photographs of gross and microscopic pathogical outcomes of both the control and non-protective ventilatory groups. *Figure 11* is the photograph of a gross, excised lung from a pig in the control group. The lung exhibits homogeneity and is healthy in appearance. However, *Figure 12* is the photograph of a gross, excised lung from a pig in the non-protective ventilatory group and exhibits great morphology compared to the control group pig's lung. *Figure 13* is a histological photograph of a pigs lung tissue from the control group

and the histopathology of this tissue shows the healthy thin walls of the alveoli. In comparison, *Figure 14* is a histological photograph of a pig's lung tissue from the non-protective ventilatory group. A clear distinction exist between the two histological slides. The histopathology of the pig from the non-protective ventilatory group shows that a thickening of the alveolar walls has occurred, as well as an accumulation of extracellular fluid (edema) and immune cells.

CONCLUSIONS:

The high level of constancy among animals within each of the treatment groups shows that this model of ARDS can reliably be reproduced in different subjects. The differences observed of the blood chemistry, homodynamic, and pulmonary parameters can be easily observed on the graphs of *Appendix C*. The tell-tale signs of ARDS, such as a lower BE, increased pulmonary pressure, and a decrease in lung compliance, are clearly demonstrated by the experimental group in comparison to the control group.

By establishing this stable model of ARDS, further research into VILI as well as other respiratory illnesses can be accomplished with great validity. Future studies will be able to rely upon the stability of this ARDS model, so the differences observed among groups undergoing different treatment conditions will be truly the result of the treatment differences. Once an effective treatment has been established through bench work then this research can be further be introducing the methods through clinical studies. Eventually, research concerning ARDS and VILI may be defined enough to help dramatically decrease the high rates of morbidity and the mortality of today. And there is even the possibility of

eradicating VILI altogether.

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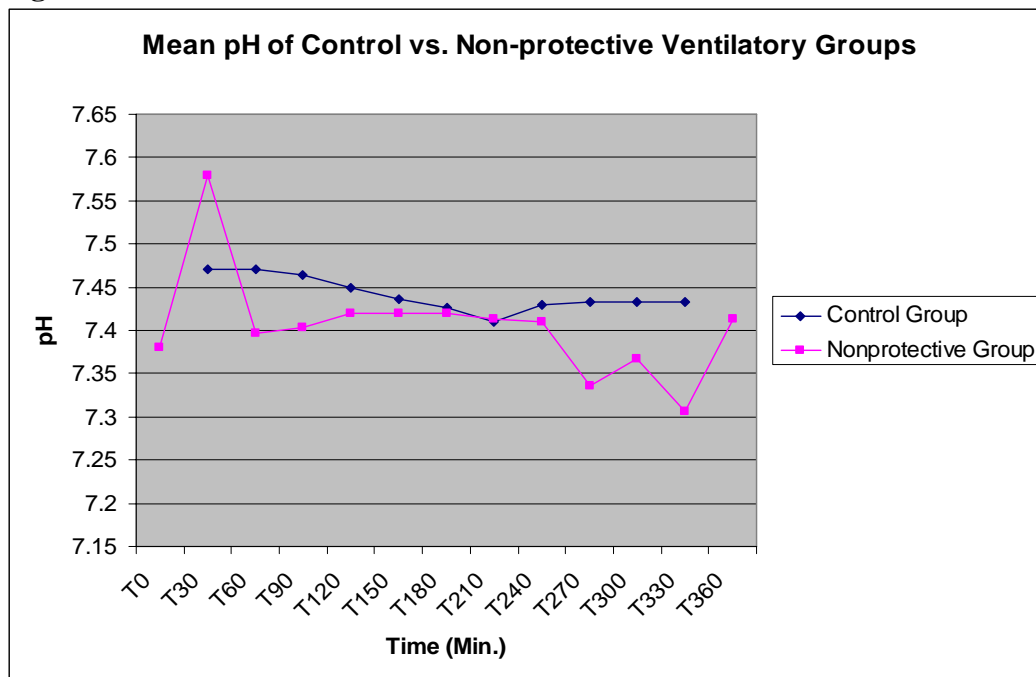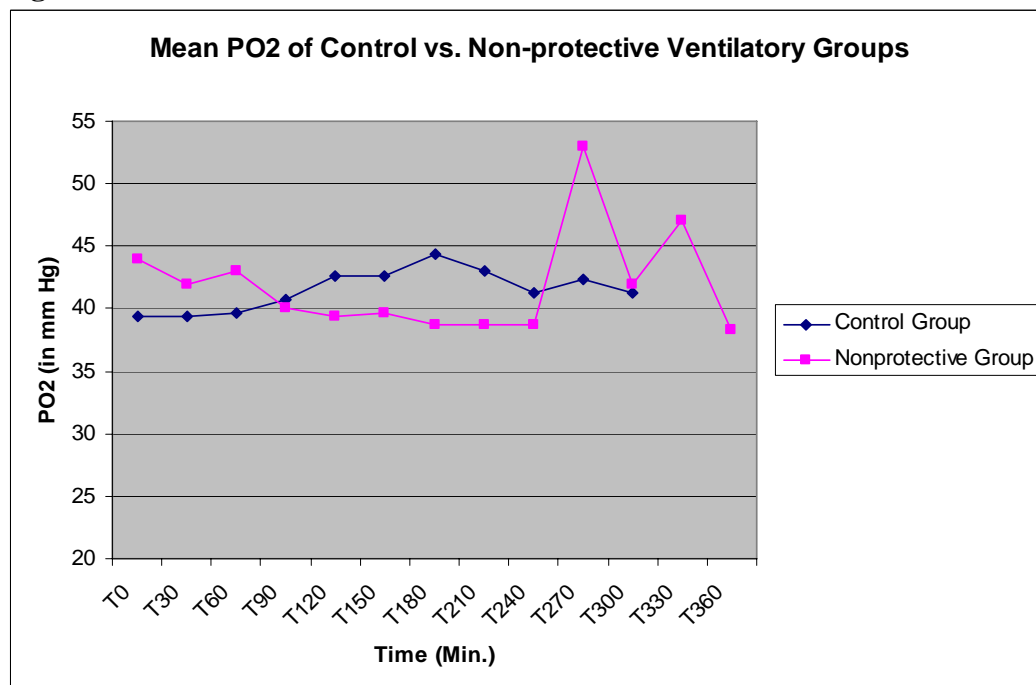
Appendix C

Figure 1.

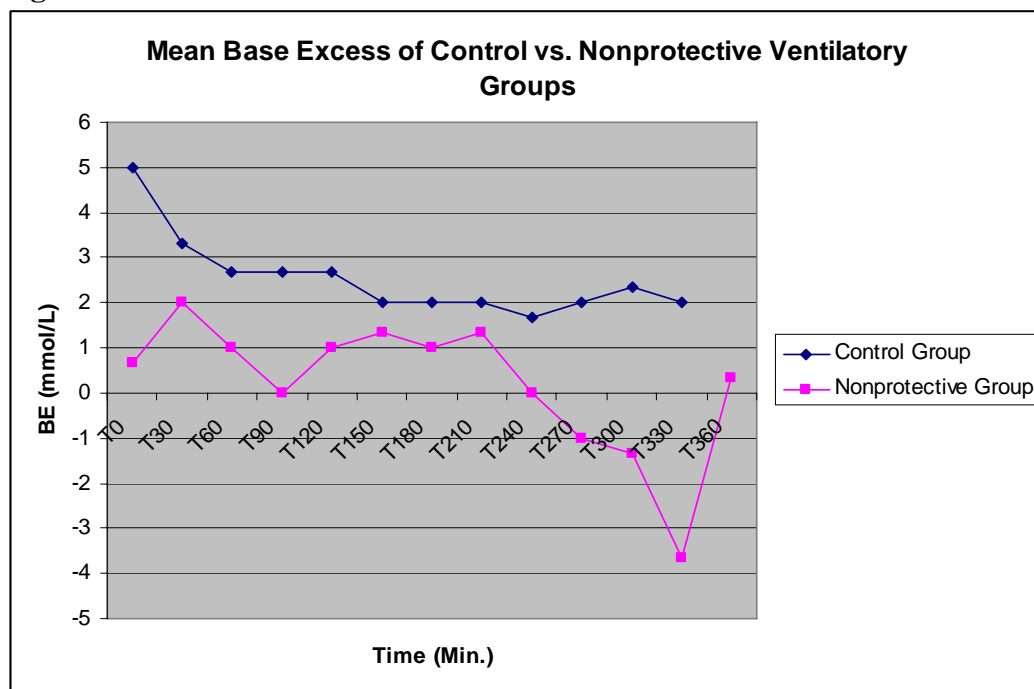Mean pH of Control vs. Non-protective Ventilatory Groups

Figure 2.

Mean PO2 of Control vs. Non-protective Ventilatory Groups

Figure 3.

Mean Base Excess of Control vs. Nonprotective Ventilatory Groups

Figure 4.

Mean Pulmonary Arterial Pressure of Control vs. Nonprotective Ventilatory Groups

Figure 5.

Mean Pulmonary Wedge Pressure of Control vs. Non-protective Ventilatory Groups

Figure 6.

Mean Cardiac Output of Control vs. Nonprotective Ventilatory Groups

Figure 7.

Mean Arterial Pressure of Control vs. Non-protective Ventilatory Groups

Figure 8.

Mean Peak Pressure of Control vs. Non-protective Ventilatory Groups

Figure 9.

Mean Plateau Pressure of Control vs. Non-protective Ventilatory Groups

Figure 10.

Mean Lung Compliance of Control vs. Non-protective Ventilatory Groups