Pros and cons of man’s closest non-primate relative: The pig

P. Asfar\textsuperscript{1}, P. Radermacher\textsuperscript{2}

\textsuperscript{1}Département de Réanimation Médicale, CHU, Angers, \textsuperscript{2}Institut APV, Universitätsklinikum, Ulm
Do we need the „Animal ICU“?

Age, pre-existing co-morbidity?

How long should animal models last?

Pros of pigs?

Cons of pigs?
“…Would you as a critical care physician accept data on a septic patient who was not resuscitated? Would you accept data from a drug study on an intensive care patient who was not only not resuscitated with fluid but who did not even have blood pressures and heart rates monitored?... If the animals are resuscitated, is the resuscitation to a specific physiologic variable?... The pathophysiology and outcome of an unresuscitated, unmonitored, septic patient is certainly different….”
Severe Sepsis and Septic Shock
Derek C. Angus, M.D., M.P.H., and Tom van der Poll, M.D., Ph.D.


"... Longer experiments with more advanced supportive care would allow better mimicry of the later stages of sepsis and multiorgan failure, permitting the testing of drugs in a more realistic setting ...."
The „Pig Intensive Care Unit“-Concept
LV-Pressure-Volume-Loops
Hemorrhage: Experimental design

- **Protocol**
  - Instrumentation (4h), recovery period (4h)
  - **Hemorrhage 30 % of calculated blood volume; MAP ~ 35-40 mmHg over 3-4 hours; thereafter re-transfusion of shed blood**
  - 24-48 h observation

- **Volume resuscitation**
  - Crystalloids 20 mL/kgxh \(\Rightarrow\) 10 mL/kgxh if PAOP \(\geq\) 18 mmHg

- **Noradrenaline**
  - \(\text{MAP}_{\text{target}} \approx \) pre-shock value; maximal heart rate: 160/min
  \(\Rightarrow\) Mean infusion rate 1.0 \(\mu\)g/kg·min

- **Mechanical ventilation**
  - \(V_T\) 8 mL/kg, I/E ratio 1:1.5, PEEP 10 cmH\(_2\)O, PAW\(_{\text{max}}\) 40 cmH\(_2\)O, FiO\(_2\) \(\rightarrow\) SaO\(_2\) 88-90 %, RR \(\rightarrow\) PaCO\(_2\) 35 – 45 mmHg
  - if \(\text{PaO}_2/\text{FiO}_2 < 300\) mmHg \(\Rightarrow\) I/E ratio 1:1, PEEP 12 cmH\(_2\)O
  - if \(\text{PaO}_2/\text{FiO}_2 < 200\) mmHg \(\Rightarrow\) PEEP 15 cmH\(_2\)O

- **Coagulation**
  - Rotem-System
Sepsis: Experimental design

- **Protocol**
  - Instrumentation (4h), recovery period (8h)
  - *Intra-abdominal inoculation of 0.5-1.0 g/kg autologeous feces*
  - 24-48 h observation

- **Volume resuscitation**
  - Crystalloids 20 mL/kgxh $\Rightarrow$ 10 mL/kgxh if PAOP $\geq 18$ mmHg

- **Noradrenaline**
  - $\text{MAP}_{\text{target}} \approx \text{pre-shock value}$; maximal heart rate: 160/min
  - $\Rightarrow \text{Mean infusion rate} \ 0.53 \ \mu\text{g/kg}\cdot\text{min}$

- **Mechanical ventilation**
  - $V_T \ 8 \ \text{mL/kg}, \ I/E \ \text{ratio} \ 1:1.5, \ \text{PEEP} \ 10 \ \text{cmH}_2\text{O}, \ \text{PAW}_{\text{max}} \ 40 \ \text{cmH}_2\text{O}, \ \text{FiO}_2 \ \rightarrow \ \text{SaO}_2 \ 88-90 \ %, \ RR \ \rightarrow \ \text{PaCO}_2 \ 35-45 \ \text{mmHg}$
  - if $\text{PaO}_2/\text{FiO}_2 < 300 \ \text{mmHg} \ \Rightarrow \ I/E \ \text{ratio} \ 1:1, \ \text{PEEP} \ 12 \ \text{cmH}_2\text{O}$
  - if $\text{PaO}_2/\text{FiO}_2 < 200 \ \text{mmHg} \ \Rightarrow \ \text{PEEP} \ 15 \ \text{cmH}_2\text{O}$

- **Coagulation**
  - Rotem-System

- **Mikrobiology**
  - *Intra-abdominal samples: E. Coli, S. Aureus, PSA, Bacteroides*
  - Blood cultures: *E. Coli, S. Aureus, PSA*
Do we need the „Animal ICU“?

Yes!

How long should animal models last?

Pros of pigs?

Cons of pigs?
Do we need the „Animal ICU“?

Age, pre-existing co-morbidity?

How long should animal models last?

Pros of pigs?

Cons of pigs?
Angus D, et al:
Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care.
CCM 2001;29:1303-10
Severe Sepsis and Septic Shock

Derek C. Angus, M.D., M.P.H., and Tom van der Poll, M.D., Ph.D.


“.....For example, options to enrich the pre-clinical portfolio include the study of animals that are more genetically diverse, are older, or have preexisting disease. ....“
Human-like atherosclerosis in minipigs: a new model for detection and treatment of vulnerable plaques

Troels Thim

Pigs with pre-existing atherosclerosis: cEPO 50 μg/kg, rh EPO 5000 IU/kg before aortic occlusion/over 4 h reperfusion, measurements at 8 h reperfusion.

Pigs with pre-existing atherosclerosis: cEPO 50 μg/kg, rh EPO 5000 IU/kg before aortic occlusion/over 4 h reperfusion, measurements at 8 h reperfusion.

Pigs with pre-existing atherosclerosis: cEPO 50 μg/kg, rh EPO 5000 IU/kg before aortic occlusion/over 4 h reperfusion, measurements at 8 h reperfusion
**Wepler et al:** Effects of the PPAR-β/δ agonist GW0742 during resuscitated porcine septic shock. *ICM Exp 2013;1:9*

Pigs with pre-existing atherosclerosis: GW0742 30 μg/kg vs. vehicle at 6, 12, and 18 h after induction of fecal peritonitis

<table>
<thead>
<tr>
<th></th>
<th>Before peritonitis</th>
<th>12 hours peritonitis</th>
<th>24 hours peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NGAL [ng·L⁻¹]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMSO</td>
<td>65 (55;72)</td>
<td>n.d.</td>
<td>364 (270;400) #</td>
</tr>
<tr>
<td>GW0742</td>
<td>56 (53;61)</td>
<td>n.d.</td>
<td>365 (276;400) #</td>
</tr>
<tr>
<td><strong>Renal venous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>interleukin-6 [ng·L⁻¹]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMSO</td>
<td>96 (77;139)</td>
<td>1710 (1242;4807) #</td>
<td>8405 (2565;23153) #</td>
</tr>
<tr>
<td>GW0742</td>
<td>97 (77;107)</td>
<td>2656 (1186;2910) #</td>
<td>3457 (3348;3489) #</td>
</tr>
<tr>
<td><strong>Renal venous tumor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>necrosis factor-α [ng·L⁻¹]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMSO</td>
<td>34 (28;52)</td>
<td>70 (55;105) #</td>
<td>125 (91;172) #</td>
</tr>
<tr>
<td>GW0742</td>
<td>49 (42;126)</td>
<td>63 (50;84) #</td>
<td>183 (131;239) #</td>
</tr>
<tr>
<td><strong>Renal venous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NO₂⁻+NO₃⁻ [µmol·L⁻¹]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMSO</td>
<td>7 (5;14)</td>
<td>10 (8;15)</td>
<td>14 (12;21) #</td>
</tr>
<tr>
<td>GW0742</td>
<td>9 (6;10)</td>
<td>9 (8;14)</td>
<td>17 (10;21) #</td>
</tr>
<tr>
<td><strong>Renal venous 8-isoprostane [ng·L⁻¹]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMSO</td>
<td>85 (80;131)</td>
<td>96 (78;132)</td>
<td>123 (90;166) #</td>
</tr>
<tr>
<td>GW0742</td>
<td>83 (72;109)</td>
<td>91 (70;113)</td>
<td>123 (87;264) #</td>
</tr>
</tbody>
</table>

Pigs with pre-existing atherosclerosis: GW0742 30 μg/kg vs. vehicle at 6, 12, and 18 h after induction of fecal peritonitis

**PPAR-β/δ expression**
Parrillo et al: Septic shock in humans. 
Ann Intern Med 1990;113:227-42

<table>
<thead>
<tr>
<th></th>
<th>Before sepsis</th>
<th>12 h sepsis</th>
<th>24 h sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac output</strong> [mL·kg⁻¹·min⁻¹]</td>
<td>64 (48;71)</td>
<td>103 # (91;105)</td>
<td>102 # (90;131)</td>
</tr>
<tr>
<td><strong>Stroke volume</strong> [mL·kg⁻¹]</td>
<td>0.6 (0.5;0.9)</td>
<td>0.7 (0.5;0.9)</td>
<td>0.6 (0.5;0.9)</td>
</tr>
<tr>
<td><strong>dp/dt\textsubscript{max}</strong> [mmHg·s⁻¹]</td>
<td>1571 (1363;1947)</td>
<td>4238 # (1926;4585)</td>
<td>3149 # (1847;5905)</td>
</tr>
<tr>
<td><strong>Ejection fraction</strong> [%]</td>
<td>50 (44;58)</td>
<td>49 (36;56)</td>
<td>60 (44;75)</td>
</tr>
<tr>
<td><strong>End-diastolic volume</strong> [ml·kg⁻¹]</td>
<td>1.3 (1.1;1.7)</td>
<td>1.4 (1.3;2.4)</td>
<td>1.3 (0.9;1.6)</td>
</tr>
<tr>
<td><strong>End-diastolic pressure</strong> [mmHg]</td>
<td>11 (9;16)</td>
<td>7 (15;19)</td>
<td>18 (15;21)</td>
</tr>
<tr>
<td><strong>dp/dt\textsubscript{min}</strong> [mmHg·s⁻¹]</td>
<td>-1971 (-2231;-1748)</td>
<td>-2089 (-2387;-1773)</td>
<td>-2180 (-2630;-1654)</td>
</tr>
</tbody>
</table>
Do we need the „Animal ICU“?

Age, pre-existing co-morbidity?

Must be included!

Pros of pigs?

Cons of pigs?
Do we need the „Animal ICU“?
Age, pre-existing co-morbidity?

How long should animal models last?

Pros of pigs?
Cons of pigs?
Severe Sepsis and Septic Shock

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"... Longer experiments with more advanced supportive care would allow better mimicry of the later stages of sepsis and multiorgan failure, permitting the testing of drugs in a more realistic setting ...."
Su et al:
Epidemiology of sepsis in Germany: results from a national prospective multicenter study. Intensive Care Med 2007;33:606-18

ICU length of stay 12 - 19 days
Su et al:
Epidemiology of sepsis in Germany: results from a national prospective multicenter study. *Intensive Care Med 2007;33:606-18*

**ICU length of stay 12 - 19 days**

<table>
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<tr>
<th>Hospital</th>
<th>ICU</th>
<th>Mechanical Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 (19-64)</td>
<td>22 (13-36)</td>
<td>17 (10-29)</td>
</tr>
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</table>

The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation

*Intensive Care Med (2011) 37:1932*
Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok\textsuperscript{a,1}, H. Shaw Warren\textsuperscript{b,1}, Alex G. Cuenca\textsuperscript{c,1}, Michael N. Mindrinos\textsuperscript{a}, Henry V. Baker\textsuperscript{a}, Weihong Xu\textsuperscript{a}, Daniel R. Richards\textsuperscript{d}, Grace P. McDonald-Smith\textsuperscript{a}, Hong Gao\textsuperscript{e}, Laura Hennessy\textsuperscript{f}, Celeste C. Finnerty\textsuperscript{g}, Cecilia M. López\textsuperscript{c}, Shari Honari\textsuperscript{i}, Ernest E. Moore\textsuperscript{h}, Joseph P. Minei\textsuperscript{i}, Joseph Cuschieri\textsuperscript{i}, Paul E. Bankey\textsuperscript{k}, Jeffrey L. Johnson\textsuperscript{l}, Jason Sperry\textsuperscript{l}, Avery B. Nathens\textsuperscript{m}, Timothy R. Billiar\textsuperscript{r}, Michael A. West\textsuperscript{o}, Marc G. Jeschke\textsuperscript{g}, Matthew B. Klein\textsuperscript{i}, Richard L. Gamelli\textsuperscript{p}, Nicole S. Gibran\textsuperscript{i}, Bernard H. Brownstein\textsuperscript{q}, Carol Miller-Graziano\textsuperscript{k}, Steve E. Calvano\textsuperscript{t}, Philip H. Mason\textsuperscript{t}, J. Perren Cobb\textsuperscript{s}, Laurence G. Rahme\textsuperscript{t}, Stephen F. Lowry\textsuperscript{f,2}, Ronald V. Maier\textsuperscript{l}, Lyle L. Moldawer\textsuperscript{c}, David N. Herndon\textsuperscript{g}, Ronald W. Davis\textsuperscript{o,3}, Wenzhong Xiao\textsuperscript{a,t,3}, Ronald G. Tompkins\textsuperscript{t,3}, and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program\textsuperscript{a}

\textsuperscript{a}Department of Surgery, University of California, San Francisco, San Francisco, CA 94143, USA
\textsuperscript{b}Department of Surgery, University of Pennsylvania, Philadelphia, PA 19104, USA
\textsuperscript{c}Department of Surgery, University of Wisconsin, Madison, WI 53706, USA
\textsuperscript{d}Department of Surgery, University of Washington, Seattle, WA 98195, USA
\textsuperscript{e}Department of Surgery, Stanford University, Stanford, CA 94305, USA
\textsuperscript{f}Department of Surgery, University of Miami, Miami, FL 33136, USA
\textsuperscript{g}Department of Surgery, University of Maryland, Baltimore, MD 21201, USA
\textsuperscript{h}Department of Surgery, University of Michigan, Ann Arbor, MI 48109, USA
\textsuperscript{i}Department of Surgery, University of Colorado, Denver, CO 80262, USA
\textsuperscript{j}Department of Surgery, Harvard Medical School, Boston, MA 02115, USA
\textsuperscript{k}Department of Surgery, University of Tennessee, Memphis, TN 38163, USA
\textsuperscript{l}Department of Surgery, University of Texas, Houston, TX 77030, USA
\textsuperscript{m}Department of Surgery, University of Arizona, Tucson, AZ 85724, USA
\textsuperscript{n}Department of Surgery, University of Iowa, Iowa City, IA 52242, USA
\textsuperscript{o}Department of Surgery, University of Kentucky, Lexington, KY 40536, USA
\textsuperscript{p}Department of Surgery, University of Alabama, Birmingham, AL 35294, USA
\textsuperscript{q}Department of Surgery, University of Pittsburgh, Pittsburgh, PA 15213, USA
\textsuperscript{r}Department of Surgery, University of Nebraska, Lincoln, NE 68588, USA
\textsuperscript{s}Department of Surgery, Ohio State University, Columbus, OH 43210, USA
\textsuperscript{t}Department of Surgery, University of California, Los Angeles, CA 90095, USA

\textsuperscript{1}These authors contributed equally to this work.

\textsuperscript{2}Dr. Lowry's work is supported by the Department of Defense grant W81XWH-10-1-0439.

\textsuperscript{3}Dr. Davis's work is supported by the Department of Defense grant W81XWH-09-1-0439.
# Recurrent Recruitment Manoeuvres Improve Lung Mechanics and Minimize Lung Injury during Mechanical Ventilation of Healthy Mice

Lucy Kathleen Reiss* Anke Kowallik, Stefan Uhlig

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<tr>
<td><strong>Ventilation</strong></td>
<td><strong>Vₜ [ml/kg]</strong></td>
</tr>
<tr>
<td>30 min</td>
<td>7/10</td>
</tr>
<tr>
<td>60 min</td>
<td>8</td>
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<tr>
<td>140 min</td>
<td>30/10</td>
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<td>4 h</td>
<td>25/7</td>
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<td>15/7.5</td>
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<td>12</td>
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<td>6 h</td>
<td>16/8</td>
</tr>
</tbody>
</table>

30 min – 8 h

Vuda et al: Effects of catecholamines on hepatic and skeletal muscle mitochondrial respiration after prolonged exposure to faecal peritonitis in pigs. *Innate Immun* 2011;1-14


Do we need the „Animal ICU“?

Age, pre-existing co-morbidity?

How long should animal models last?

As long as possible!??!

Cons of pigs?
Do we need the „Animal ICU“?
Age, pre-existing co-morbidity?
How long should animal models last?

**Pros** of pigs?

**Cons** of pigs?
Adult $\approx 35$ kg
## Anatomical and Physiological Similarities of the Kidney

<table>
<thead>
<tr>
<th>Mice, rats and rabbits</th>
<th>Pig, monkeys and HUMANS</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Unilobular, unipapillar kidney</td>
<td>● Multilobular, multipapillar kidney</td>
</tr>
<tr>
<td>● Urine empties directly into renal pelvis (no branched calicael network)</td>
<td>● Urine empties into calicael network into renal pelvis</td>
</tr>
<tr>
<td>● Segmental arteries are bypassed</td>
<td>● Interlobular and segmental arteries</td>
</tr>
</tbody>
</table>

*Simmons, J Urol 2008;180:19*
Anesthetized, mechanically ventilated pigs, 40-45 kg

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Portal venous flow [mL/min]</td>
<td>970 ± 300</td>
</tr>
<tr>
<td>Hepatic arterial flow [mL/min]</td>
<td>160 ± 80</td>
</tr>
</tbody>
</table>
Adapted from:
Asfar et al,
*Shock* 2005;23 suppl, 1:85
**Human volunteers:**

- 4 ng/kg bolus (Preas et al, AJRCCM 2001; 164:620)
- 2 ng/kg bolus (Michaeli et al, Clin Nutr 2007;26:70)

**Mice, endotoxin-induced acute lung injury:**

- 0.4 mg/kg bolus nasal (Dreymüller et al, EMBO Mol Med 2012;4:412)
- 1.5 mg/kg bolus i.v. (Mangalmurti et al, Blood 2009;113:1158)
- 4 mg/kg bolus intratracheal (Mekontso-Dessap et al, AJRCBM 2012;46:541)

**Pigs, endotoxin-induced „septic“ shock:**

- 10-40 ng/kg/min infusion (Hauser et al, CCM 2005;33:2034)
Bacteremia, LPS, Ischemia-Reperfusion

PMN activation

\[ \text{O}_2^-, \text{H}_2\text{O}_2, \text{OH}^- \]

DNA single strand breaks

PARP activation

\[ \text{NAD}^+, 4 \text{ATP} \]

poly-ADP-ribosylated proteins

\[ \text{ONOO}^- \]

Nitration and nitrosative stress

Inhibition of mitochondrial respiration

Open K+ ATP channels

Oxidative and nitrosative stress

Lactate \(\uparrow\)

ATP \(\downarrow\)

H+ \(\uparrow\)

Hypotension

Vasodilation

\[ \text{cGMP} \uparrow \]

\[ \text{CO} \uparrow \]

\[ \text{H}_2\text{S} \uparrow \]

Adapted from:
Asfar et al,
Shock 2005;23 suppl, 1:85
**Human septic shock:**

- 47 (28-77) µM (Watson et al, CCM 2004;32:13)

**Mice, CLP-induced septic acute lung injury:**

- 102 (47-121) µM (Barth et al, CCM 2006;34:307)
- 161 ± 23 µM (Wang et al, Am J Pathol 2012;180:505)

**Pigs, fecal peritonitis-induced septic shock:**

- 17 (11-30) µM (before shock: 21 (12-48) µM) (Simon et al, Crit Care 2009;13:R113)
Bacteremia, LPS, Ischemia-Reperfusion

- PMN activation
- iNOS activation
- HO-1 activation
- CBS, CSE activation

- O₂⁻
- H₂O₂
- OH⁻
- DNA single strand breaks

- NO·↑
- ONOO⁻

- PARP activation
- Poly-ADP-ribosylated proteins
- NAD⁺
- 4 ATP

- Nitration
- Oxidative and nitrosative stress

- Inhibition of mitochondrial respiration

- Open K⁺ATP channels

- cGMP↑
- NO·↑
- CO↑
- H₂S↑
- Vasodilation

- Lactate↑
- ATP↓ H+↑

- Hypotension

- Organ dysfunction

Adapted from:
Asfar et al,
Shock 2005;23 suppl, 1:85
Noradrenaline infusion rates

**Human septic shock:**
- 0.23 (0.02-10.0) µg/kgxmin  (Watson et al, CCM 2004;32:13)
- 0.27 ± 0.27 µg/kgxmin  (Russell et al, NEJM 2008;358:877)

**Mice, CLP-induced septic acute lung injury:**
- 1.32 (0.22-5.00) µg/kgxmin  (Wagner et al, Shock 2011;35:396)

**Pigs, fecal peritonitis-induced septic shock:**
- 0.53 (0.20-0.72) µg/kgxmin  (Simon et al, Crit Care 2009;13:R113)
George E.P. Box, FRS (1919-2013):
'All models are wrong, but some are useful'
Do we need the „Animal ICU“?
Age, pre-existing co-morbidity?
How long should animal models last?

Pros of pigs?
Cons of pigs?
**Tucker A, et al:**
Lung vascular smooth muscle as a determinant of pulmonary hypertension at high altitude.
*Am J Physiol 1975;228:762*

<table>
<thead>
<tr>
<th>Species</th>
<th>Control (days)</th>
<th>Altitude (4500m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep</td>
<td>20 ± 1</td>
<td>23 ± 2</td>
</tr>
<tr>
<td>Dog</td>
<td>26 ± 2</td>
<td>28 ± 1</td>
</tr>
<tr>
<td>Pig</td>
<td>27 ± 1</td>
<td>72 ± 7</td>
</tr>
</tbody>
</table>
Kuriyama, et al:
Role of collateral ventilation in ventilation-perfusion imbalance.
*J Appl Physiol* 1984;56:1500

Dogs, pigs; isolated lung region $\text{FiO}_2$ 13 %, remainder 30 %: Presence or not of alveolar collateral ventilation