Modeling Cardiovascular Disease Using Swine Models

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Disclosures

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No Disclosures
Classification

- Phylum: Chordata
- Class: Mammalia
- Order: Artiodactyla
- Family: Suidae
- Genus: Sus
- Species: scrofa
- Subspecies: domestica

- Sus scrofa has 38 chromosomes
- Life span: 15-25 years
FIGURE 21.10 The total use of dog, pig, and NHP in the four regions for the years 2002, 2005, and 2008. From 2002 to 2008, the use of pigs increased by 15% and the use of dogs was more or less constant (down 2%) while the use of NHPs grew 33%. (Numbers above columns are number of animals; numbers inside columns are per cent of a given year; total for each year equals 100%.) (From Ganders, N.C. et al., 2012. International Journal of Toxicology, 31:507–528. With permission.)

Swine in the laboratory. 3rd Ed. 2016, page 534.
Current Review Article Literature Search
Swine and Canine Models of Human Cardiovascular Disease

• Swine Comparative Review
  o Years Covered: 2019 – 2009
  o Number of Review Articles: 111

• Canine Comparative Review
  o Years Covered: 2018 – 2009
  o Number of Review Articles: 64
Sources

- **Purebred registered herds**: Have a known lineage, genetic uniformity, often closed colony, and generally have better management.

- **Commercial production swine**: Readily available, cheap to less expensive.

- **SPF herds**: Some for experimental purposes, some for commercial production.

- **SPF miniature swine herds**: Purpose-bred for research, advantage is small body size of adults (30-50 kg), disadvantage is cost.
Swine in Early Biomedical Research

• Swine have been used in teaching and surgery
  o First published account by Andreas Vesalius in a medical school anatomy text in 1543.
    ✓ *De Humani Corporis Fabrica Libri Septem*

• Vesalius advanced our understanding of the human body through meticulous dissection of human and animal (*Dog, Pig, Ape*) cadavers.

• Since Vesalius, swine have been used in biomedical research.
Swine in Early Biomedical Research

- Swine share characteristics with humans in anatomy and physiology of the cardiovascular system.

- Dr. John Hunter (1728-1793) of Britain recognized the pig as a valid model of physiological research.
Growth

Growth Chart Comparison
Domestic Swine vs Sinclair Miniature Swine

<table>
<thead>
<tr>
<th>Months</th>
<th>Domestic</th>
<th>Micro-Yucalan</th>
<th>Sinclair</th>
<th>Yucalan</th>
<th>Hanford</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>4</td>
<td>4.5</td>
<td>4.5</td>
<td>5.5</td>
</tr>
<tr>
<td>2</td>
<td>10.5</td>
<td>7</td>
<td>7</td>
<td>9.5</td>
<td>9.5</td>
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<tr>
<td>3</td>
<td>14</td>
<td>10.5</td>
<td>11.5</td>
<td>12.5</td>
<td>15.5</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>13.5</td>
<td>14.5</td>
<td>18</td>
<td>23.5</td>
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<tr>
<td>5</td>
<td>22</td>
<td>15</td>
<td>15.5</td>
<td>22</td>
<td>30.5</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>16</td>
<td>21</td>
<td>28</td>
<td>38</td>
</tr>
</tbody>
</table>
Comparative Growth

• Size of Heart and Blood Vessels in mature Hanford minipigs is more analogous to humans than dogs or nonhuman primates.

• Both swine and canine have vessels large enough of instrumentation.

• Growth of swine heart and cardiovascular system from birth to 4 months is analogous to humans into the mid-teens.

Physiological Parameters of Animal Models and Humans

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Human</th>
<th>Pig</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifespan (years)</td>
<td>79</td>
<td>10–15</td>
<td>10–15</td>
</tr>
<tr>
<td>Adult mass (kg)</td>
<td>50–90</td>
<td>150–300</td>
<td>5–70</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>36.5–37.0</td>
<td>38.5–39.2</td>
<td>38–39</td>
</tr>
<tr>
<td><strong>Cardiac anatomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart mass (g)</td>
<td>148–383</td>
<td>250–400</td>
<td>107–500</td>
</tr>
<tr>
<td>Heart:body mass ratio</td>
<td>0.4</td>
<td>0.32</td>
<td>0.64–0.80</td>
</tr>
<tr>
<td><strong>Haemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>120/80</td>
<td>130/75</td>
<td>136/66</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>4,900–16,000</td>
<td>3,000</td>
<td>3,086–3,633</td>
</tr>
<tr>
<td>Respiratory rate (breaths per min)</td>
<td>12–15</td>
<td>15–20</td>
<td>15–25</td>
</tr>
<tr>
<td><strong>Electrocardiogram</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>60–80</td>
<td>68–100</td>
<td>80–160</td>
</tr>
<tr>
<td>P-wave duration (ms)</td>
<td>110</td>
<td>60–80</td>
<td>40</td>
</tr>
<tr>
<td>PR interval (ms)</td>
<td>120–200</td>
<td>50–120</td>
<td>60–130</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>84–110</td>
<td>70–90</td>
<td>50–60</td>
</tr>
<tr>
<td>QT interval (ms)</td>
<td>400–430</td>
<td>260–380</td>
<td>150–250</td>
</tr>
</tbody>
</table>

Nat Rev Cardiol. 2019 Mar 20. pii: 10.1038/s41569-019-0179-0
Physiological Parameters of Animal Models and Humans

<table>
<thead>
<tr>
<th>Feature</th>
<th>Goat\textsuperscript{299–303}</th>
<th>Dog\textsuperscript{224,297,304}</th>
<th>Pig\textsuperscript{224,305–312}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac anatomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart size\textsuperscript{a}</td>
<td>(=) smaller</td>
<td>(+) similar</td>
<td>(+ +) similar</td>
</tr>
<tr>
<td>Heart:body mass ratio\textsuperscript{a}</td>
<td>(=) lower</td>
<td>(=) higher</td>
<td>(+) similar</td>
</tr>
<tr>
<td>Coronary anatomy\textsuperscript{a}</td>
<td>(+) fairly uniform coronary anatomy</td>
<td>(−−) extensive collateral circulation</td>
<td>(+ +) similar</td>
</tr>
<tr>
<td>Coronary circulation</td>
<td>(=) left dominant</td>
<td>(=) left dominant</td>
<td>(+) balanced</td>
</tr>
<tr>
<td><strong>Electrophysiology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Anatomy of the conduction system and ion currents\textsuperscript{a} | (=) networks of Purkinje fibres across the entire ventricular wall | (+) all major ion currents found in humans are present (except $I_{to}$) | • (=) shorter bundle of His (more rapid AV conduction)  
• (=) transmural distribution of Purkinje fibres  
• (=) marked autonomic innervation leading to increased excitability  
• (=) $I_{to}$ is absent  
• (+) all major ion currents found in humans are present (except $I_{to}$) |
| Resting heart rate (bpm) | (+) 70–90 | (+) 80–140 | (+) 68–100 |

*Nat Rev Cardiol. 2019 Mar 20. pii: 10.1038/s41569-019-0179-0*
Cardiovascular System

- Coronary artery system similar to humans- coronary anatomy
  - Blood supply from coronary artery is right side dominant
  - Doesn’t have preexisting collateral circulation
- Left azygous vein (hemiazygous) drains intercostal vessels into coronary sinus
- Vasa vasorum in the aortic wall
- Large external jugular vein

DD Myers, Jr., et. al, Chapter 9, Figures 9.9, 9.17, 9.28
Swine in the Laboratory, 3ed. M. Swindle, A. Smith, CRC Press, 2016
Coronary Circulation Comparisons

• Swine have little preexisting collateral circulation
  • Prolonged occlusion of coronary arteries results in myocardial infarct
  • Thus, young human heart may be “Pig Like”

• Canine coronary circulation can have extensive collateral circulation
  • Prolonged occlusion of coronary arteries results in inconsistent myocardial infarct
  • Thus, older human heart may be “Dog Like”
Why the pig?

- Close to the human in size, especially miniature pigs
- Similar physiology to humans
- Similar digestive tract and cardiovascular system to humans
- Similar disease progression
  - Metabolic syndrome (e.g., obesity and heart disease)
    - Ossabaw swine fed excess atherogenic diet
  - Infectious diseases - numerous organisms can cause infections across species
Why the pig?

- Long life span

- Can have multiple litters per year, with reproductive life span of 7-8 years

- Better community acceptance as a laboratory animal

- Miniature breeds have been derived as laboratory animals

- Future availability more certain than companion animals
Common Research Usage and Animal Models

- **Cardiovascular**
  - Atherosclerosis
  - Myocardial infarction
  - Congenital heart disease
  - Grafts, stents, and interventional devices
  - Cardiopulmonary Resuscitation (CPR)
Atherosclerosis

- Pigs naturally develop this condition and aortic streaks are seen in young pigs within a few weeks when diets are high in fat and cholesterol.
  - There is evidence of inheritance as in humans.

- In pigs the predominant blood borne cholesterol transporter is LDL, as in humans.
  - Pig have been used to successfully study the regression of atherosclerotic plaques.

- Pig develop atherosclerosis in anatomical locations that are relevant to the human condition (Brodala et al. 2005; Hasler-Rapacz et al. 1995).

- Pigs develop atherosclerotic lesions that recapitulate the histopathology seen in humans (Brodala et al. 2005)
Myocardial infarction

• An adult porcine model of chronic heart failure after myocardial infarction that is amendable to current invasive and noninvasive imaging techniques
  o Valuable for evaluating electrophysiologic devices and regenerative therapies.

• The Gottingen minipig model of chronic LV failure.

• Slower growth rate than Yorkshire
  o More accurate clinical picture of adult heart failure, reduced LVEF (Shuleri et al., 2008).
Cardiopulmonary Resuscitation

• The Landrace-Large White Swine.

• Suitable breed for Cardiopulmonary Resuscitation (CPR) research.

• Close similarity of hemodynamic values to those of humans (Xanthos et al., 2007).
Spontaneous Ventricular Septal Defect

• Heritable ventricular septal defect (VSD) model has been produced in Yucatan and Micro-Yucatan miniature swine.

• Angiography, echocardiography, and cardiac catheterization techniques.

• Left to right shunts are consistently demonstrated.
  o Subset of the animals develops pulmonary hypertension over time.
  o Some animals develop a failure to thrive syndrome associated with reduced stroke volume due to end-diastolic volume failing to increase adequately.

https://sinclairresearch.com/bio-resources/animal-models/spontaneous-ventricular-septal-defect/
Spontaneous Ventricular Septal Defect (VSD)

• VSD model shares many important similarities to human VSD.
  o Preclinical treatment applications, including diagnosis and treatment of
    the condition or closure of the defect.

• Potential applications include the study of environmental and
  genetic interactions with the occurrence of the defect.

• Studies that require manipulation of cardiac function.

https://sinclairresearch.com/bio-resources/animal-models/spontaneous-ventricular-septal-defect/
Research Uses

- Interventional Radiology
  - PDA (Patent ductus arteriosus)
  - ASD (Atrial septal defect)
  - Occlusion
  - Angioplasty
  - Coronary artery catheterization
  - Catheter ablation techniques
  - Stent placement
  - Surgical robotics training
Surgical and Interventional Catheterization

• Swine are a favored model for interventional catheterization and medical device implantation.

• Similarity to humans in wound healing and development of collateral circulation and neointimal proliferation.

• Blood vessels continue to grow in mini and domestic swine
  o Best suited for acute studies.
  o The stabilized growth of dogs suite them for chronic or longitudinal studies.

• Domestic farm pig vessel diameter increase can be approximately 35-40% over a six months.
  o Medical devices can be dislodged, perforate the vessel, or change the vessel architecture.
Surgical and Interventional Catheterization

- Unlike dogs, swine have a vascular rete mirabile at the base of the brain.
  - Inhibits the passage of catheters through the carotid vessels into the cerebral vessels.

- Black arrows highlight on this cerebral angiogram of the rete mirabile and the Circle of Willis at the base of the brain.

Can swine replace dogs as the preferred model for cardiovascular disease going forward?

• Advantages
  o Similarity in anatomy and physiology
  o Size of vessels and cardiovascular anatomy
  o Medical device testing and instrumentation
  o Similarity of swine and human myocardium
  o Similarity in coagulation system to humans
  o Less societal concerns regarding their use in cardiovascular research.

• Disadvantages
  o Significant growth of blood vessels-need for canine or miniature swine for longitudinal studies.
  o Availability of reliable molecular assays like dogs.
  o Brain vascular anatomy does not allow for catheterization like dogs.
Would replacing dogs with another species compromise the quality or timelines of future advances?

• Possibly
  o Canines are a well characterized surgical model (pre-, op- and post-op anesthesia protocols).
  
  o Canines are well suited for long term studies.
  
  o Canine heart, myocardium, and brain vascular anatomy very similar to humans.
  
  o Pre-clinical computer modeling and translational studies have been built from data obtained from dogs.
Thank you
References

References


• Sinclair Bio-Resources: https://sinclairresearch.com/bio-resources/animal-models/spontaneous-ventricular-septal-defect/


