The Critical Role of Preclinical Science in Health Care Innovation

IMMR Accelerating your innovative research

PRECLINICAL RESEARCH | GLP STUDIES | PATHOLOGY | SURGICAL TRAINING

Agenda

- Introduction
  - About IMMR
  - Introduction of the speakers
  - Why preclinical science is an essential component of innovation in health care
- The phases of preclinical research and the unique contributions of each phase
  - Proof of Concept, Feasibility & GLP studies
  - Investigator training
  - Pathology evaluation
- The importance of choosing the right model for preclinical studies
- Considerations for selecting a preclinical science partner
- Q & A

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Value chain

Innovators

University

Start-up

Large strategic

Idea / Innovation

Market study

Intellectual property

Early funding

Engineering

Preclinical Science

Preclinical studies

Pathology evaluation

Investigator training

Approval – First in Human

Clinical Research

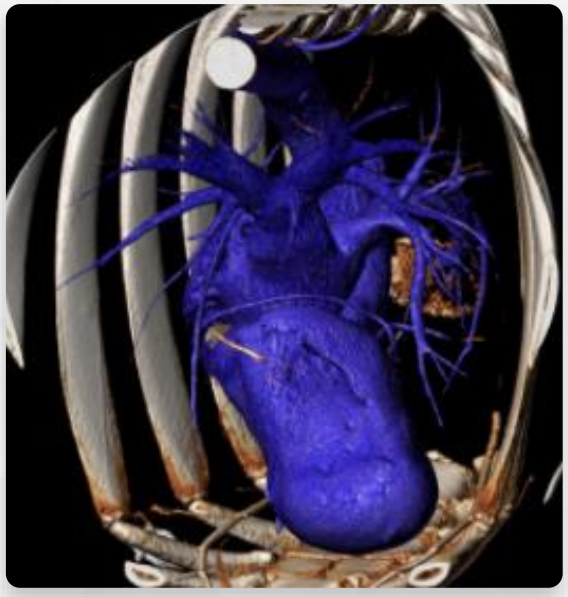
Clinical trials

Approval – Market release

Marketing & Commercialisation

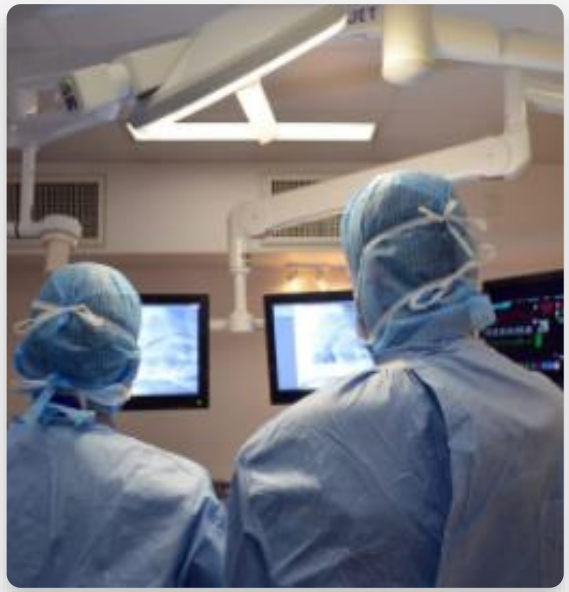
Commercial use

Full range of preclinical services

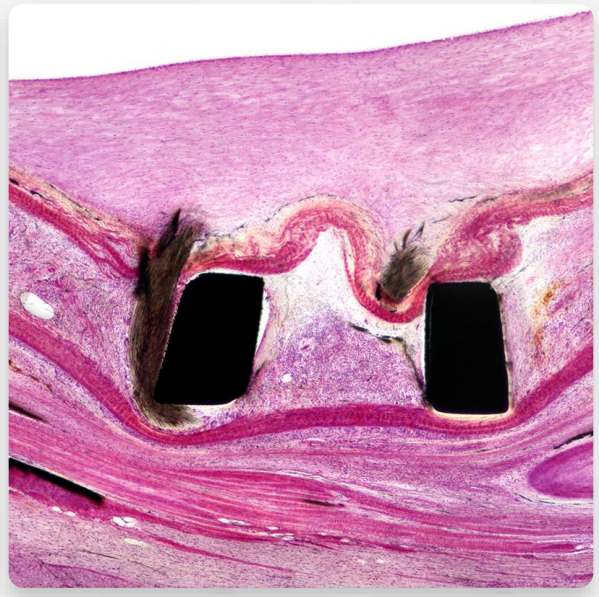


Early research and development studies

Good Laboratory Practices (GLP) compliant studies



Surgical and interventional training



Pathology evaluation of explanted soft and hard tissue

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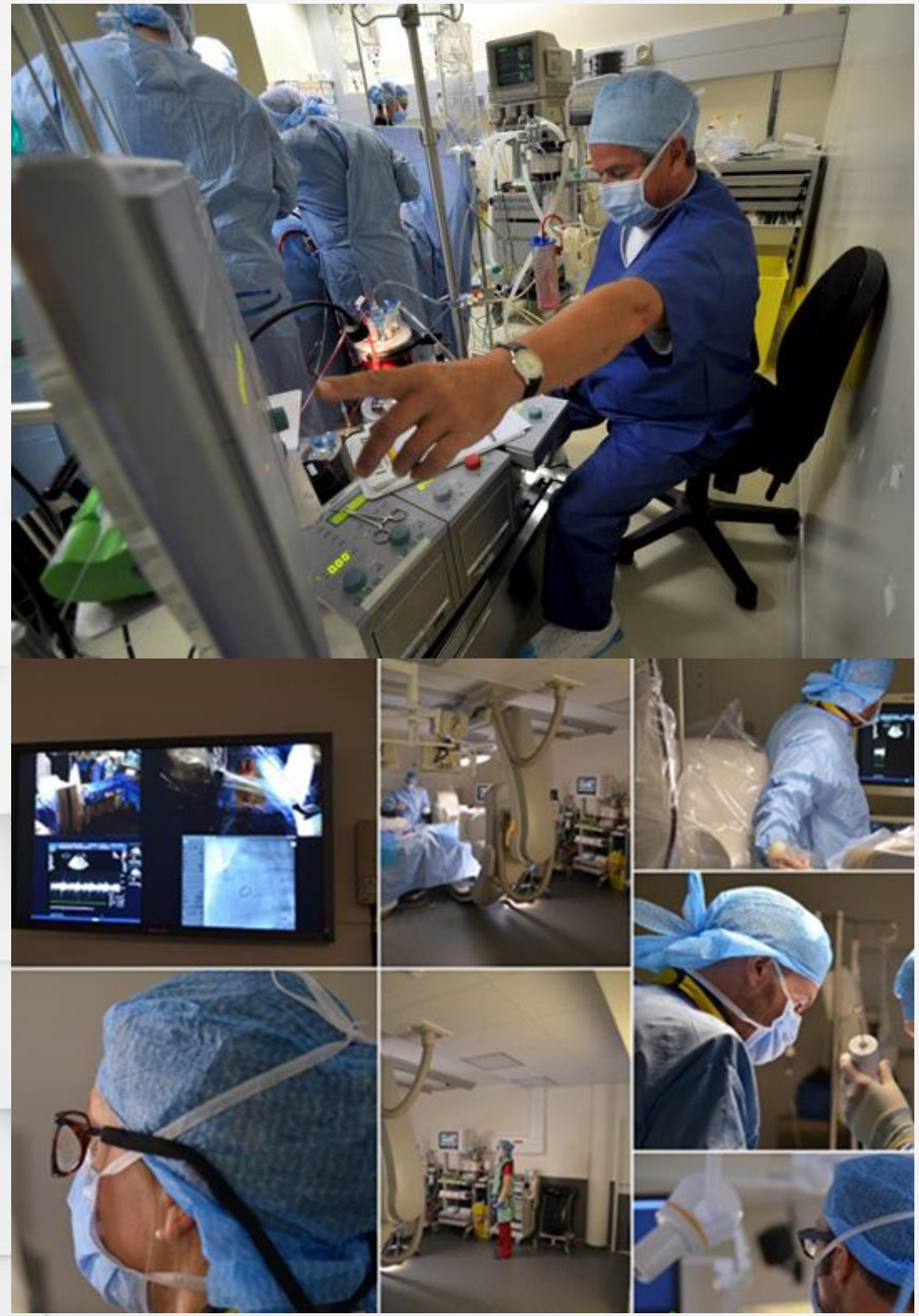
IMMR's Values

- Making substantive contributions to medical innovation and human health
- Providing unparalleled technical excellence in preclinical research
- Providing 100% customer satisfaction
- Remaining impartial (holding no IP)
- Maintaining the highest ethical standards and concern for animal welfare



A high-end technical platform

01/

Cardiopulmonary bypass equipment

02/

5 sophisticated and efficient operating rooms and expanding

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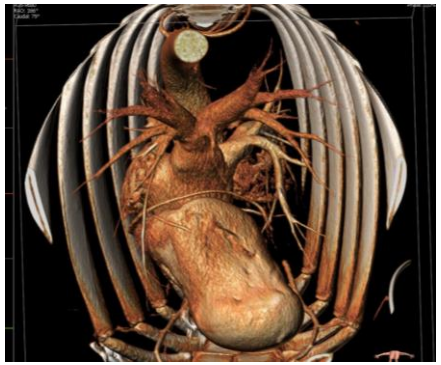
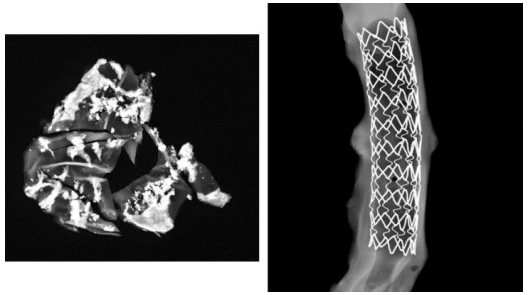
A high-end technical platform

Philips Epiq Ultrasound



CT Scan



Faxitron MX-20

IMMRemote

Track record

Key Figures

Over **1,000,000**

Patients treated to date with medical devices validated at IMMR

2500

Procedures / year

800

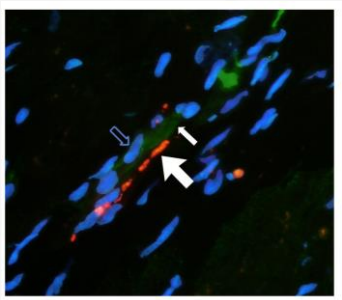
Implantations / year

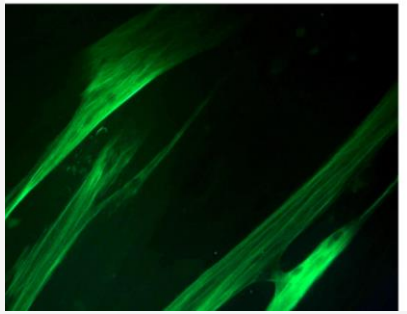
2500

TAVI to date

1400

TMVR to date





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Panelists

Nicolas Borenstein DVM, PhD
Co-Founder & Scientific Director

Luc Behr DVM, PhD
Co-Founder & Scientific Director

Laurence Fiette DVM, PhD, DESAPV, HDR
Head of Pathology

Robert Kieval VMD, PhD
CEO, IMMR, Inc. (USA)

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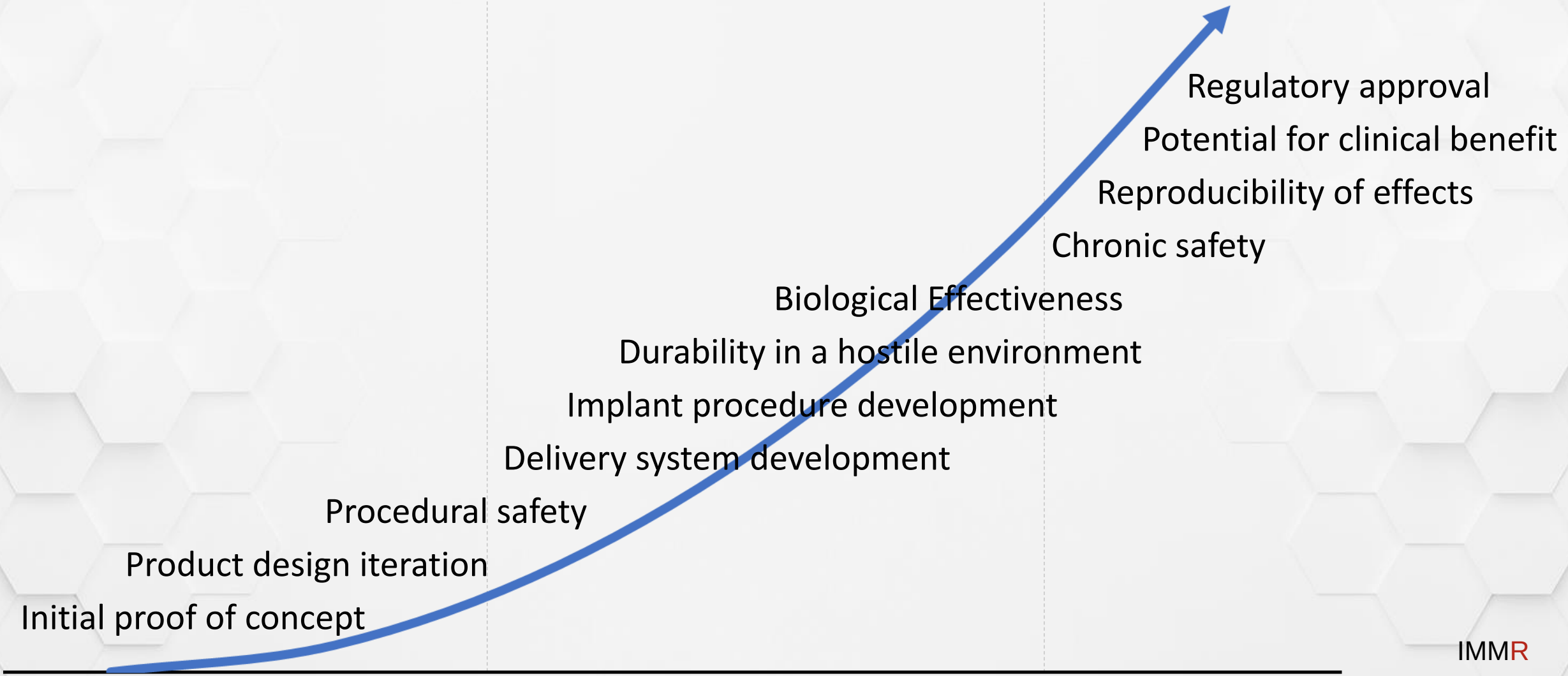
Value creation during the preclinical phase

Proof of Concept	Feasibility / R & D	Late Stage / GLP



Key stakeholders

Management Team

Regulators

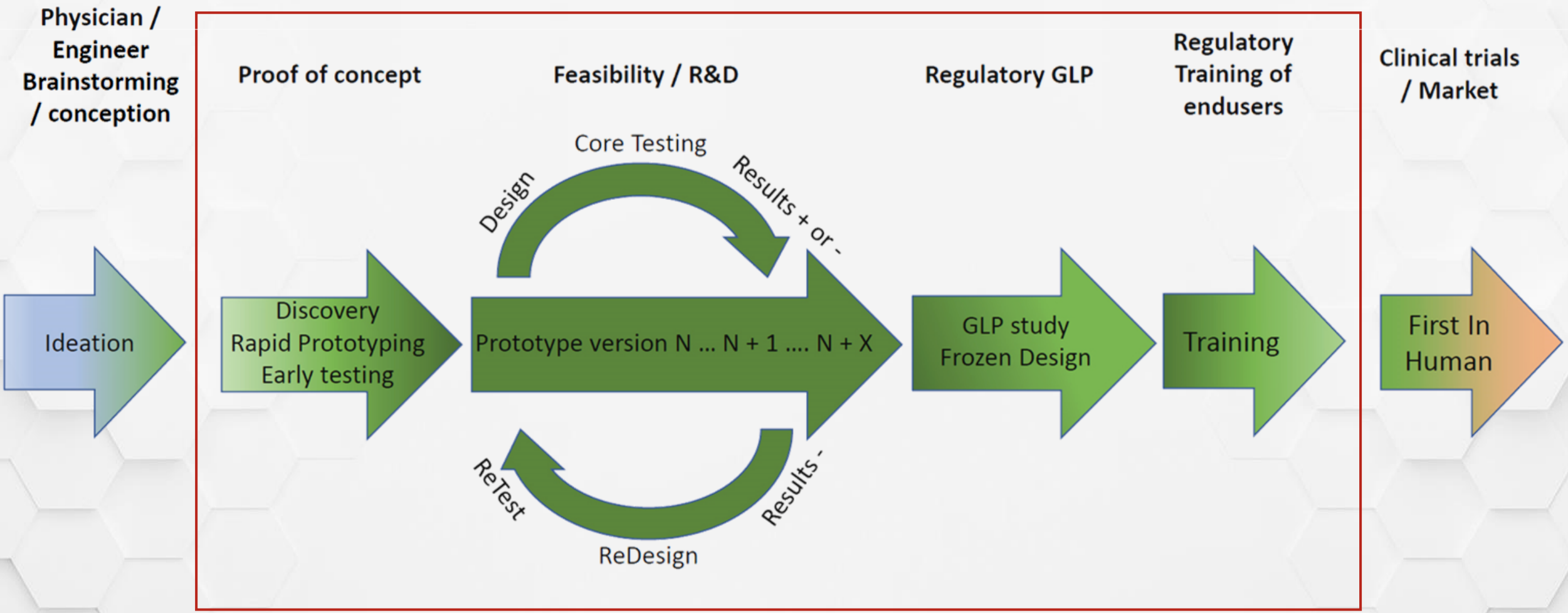
Ethics committees

KOLs & Investigators

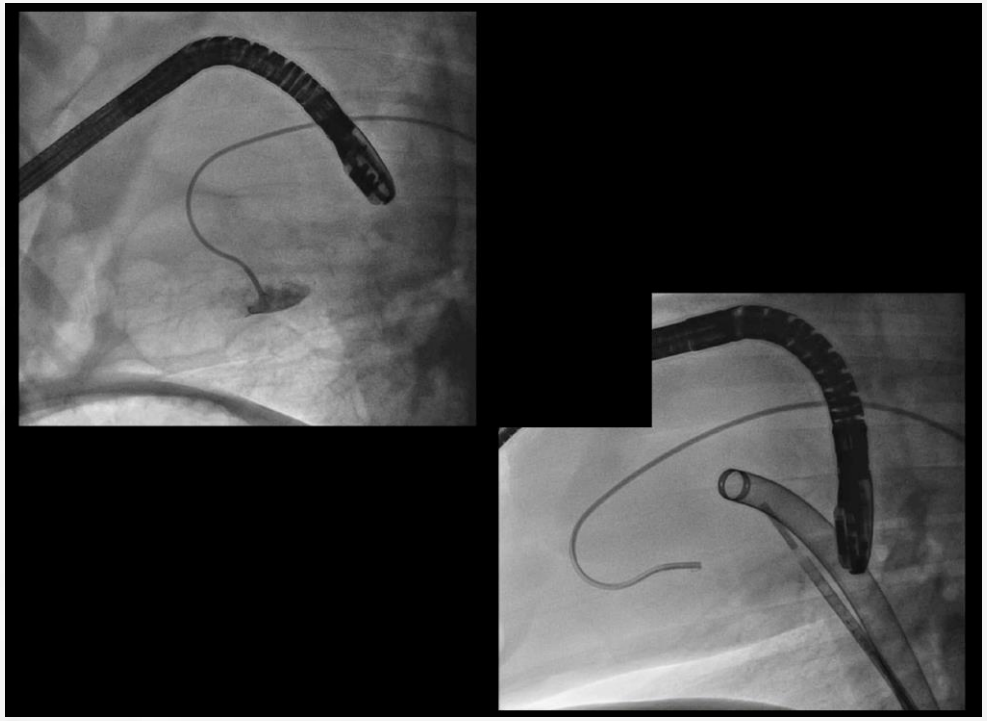
Funding agencies

Investors

The preclinical pathway

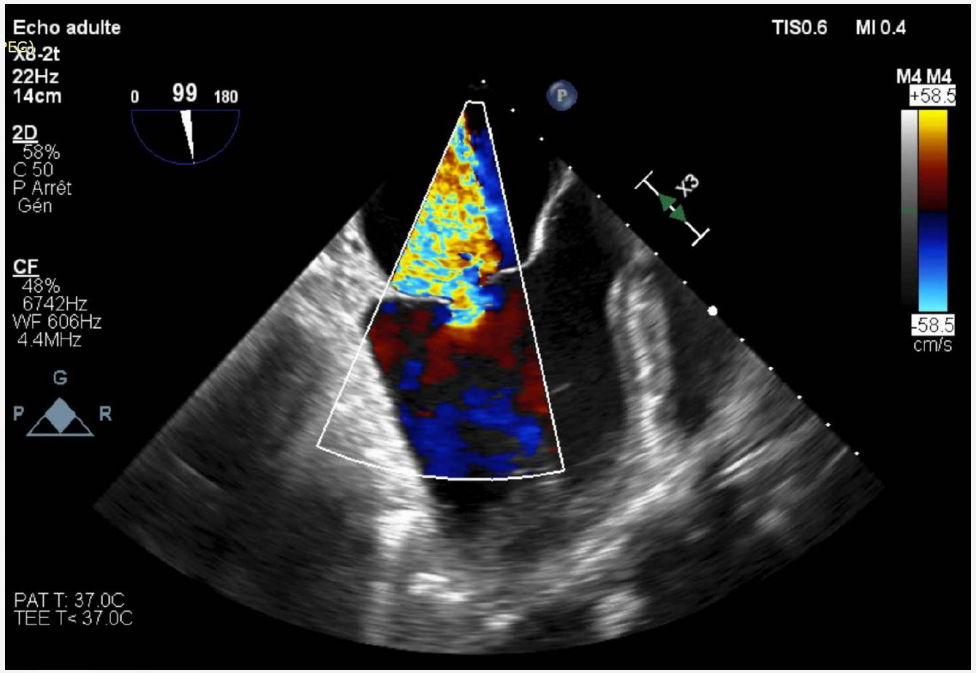


Proof of Concept studies



- First *in vivo* experience
- Scope: 5-10 acute cases
- Key outcomes: Preliminary validation of basic concept, procedural safety
- Key challenges: Utilizes unrefined prototypes and components
- Key lab competencies: Adaptability and real-time problem solving

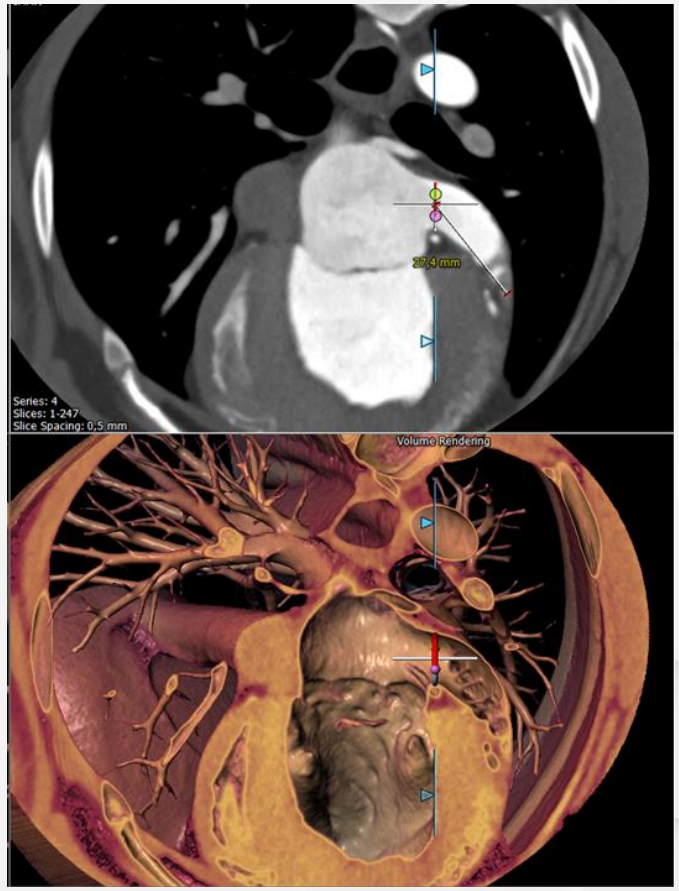
Feasibility / R & D studies



- Iteration of prototypes to refine product design
- Scope: 4-6 cases for each iteration
- Key outcomes: Design freeze, chronic safety
- Key challenges: May require multiple iterations
- Key lab competencies: High procedure volumes, consistency of technical team

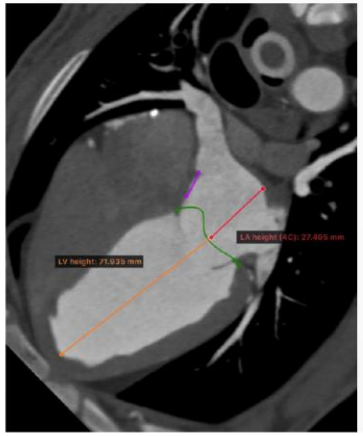
Regulatory / GLP studies

- Require full regulatory compliance according to risk Class (I, II, III)
- Scope
  - 5-6 animal test group + control/predicate group(s) ± disease model
  - Follow-up or sacrifice at several time points up to 180 or 365 days
- Key outcomes
  - Chronic safety and performance
  - Complete data set and full report for regulatory submission
- Key challenges: Rigorous study planning and protocol adherence
- Key lab competencies
  - Pre-screening capabilities
  - Intimate knowledge of the technology
  - Disciplined quality management and documentation

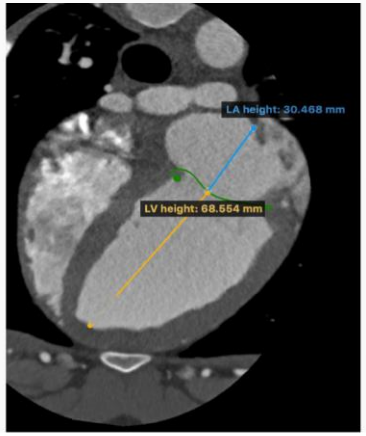


Surgical / investigator training

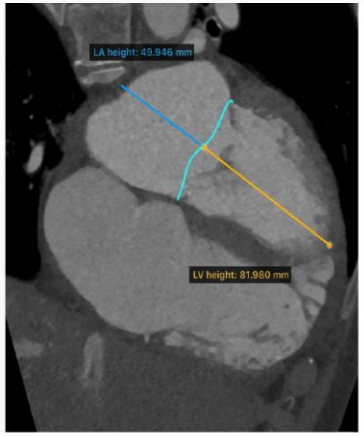
Ovine

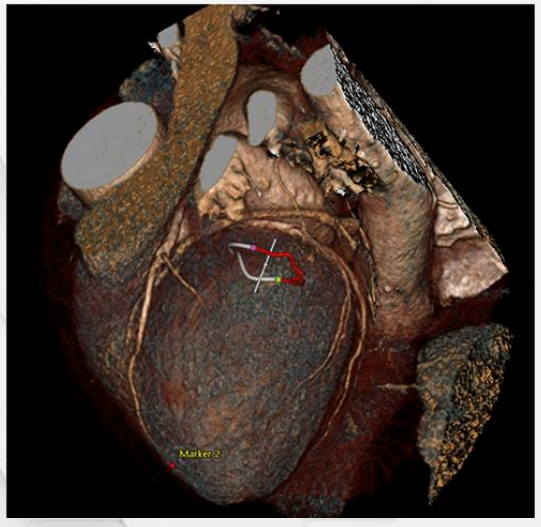


Porcine

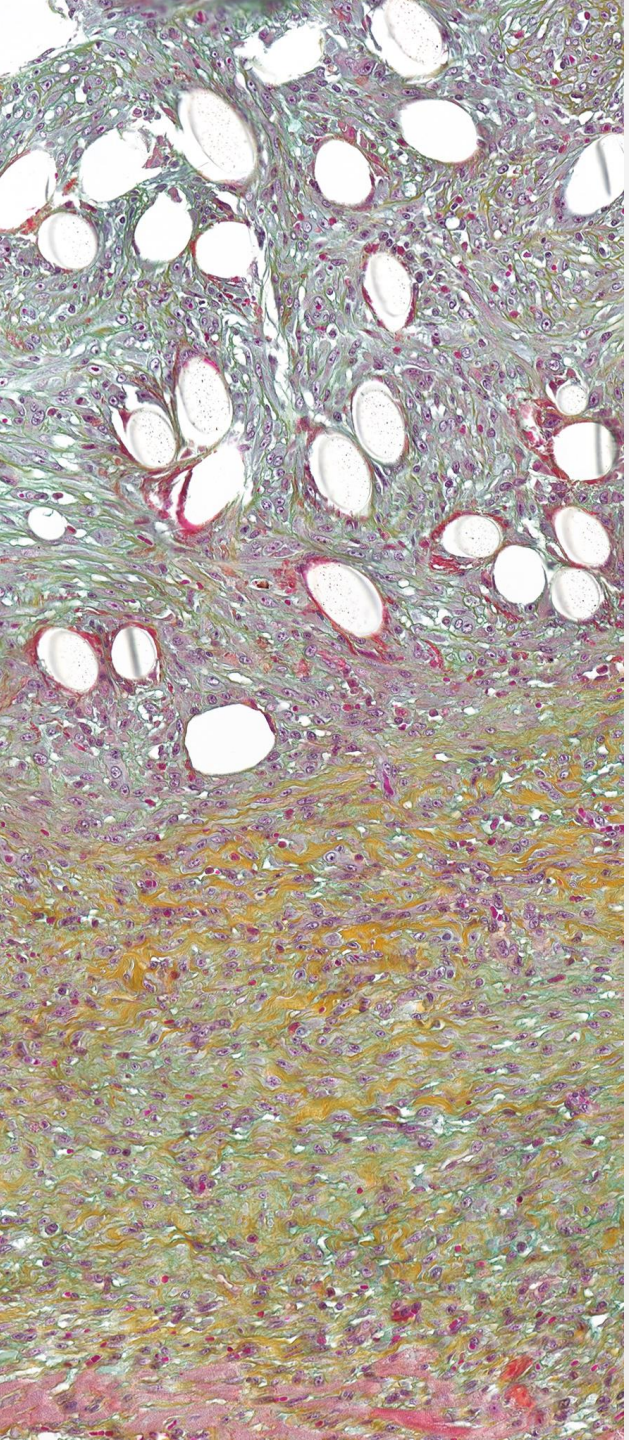


Human





IMMR



Pathology in preclinical studies

- Gold standard for evaluation of the performance & safety
- Required in regulatory studies
  - Local tissue tolerance
  - Systemic effects
- Very informative in feasibility studies
- Validation of an animal model

Macroscopy **Histology**

Evaluate, describe, illustrate

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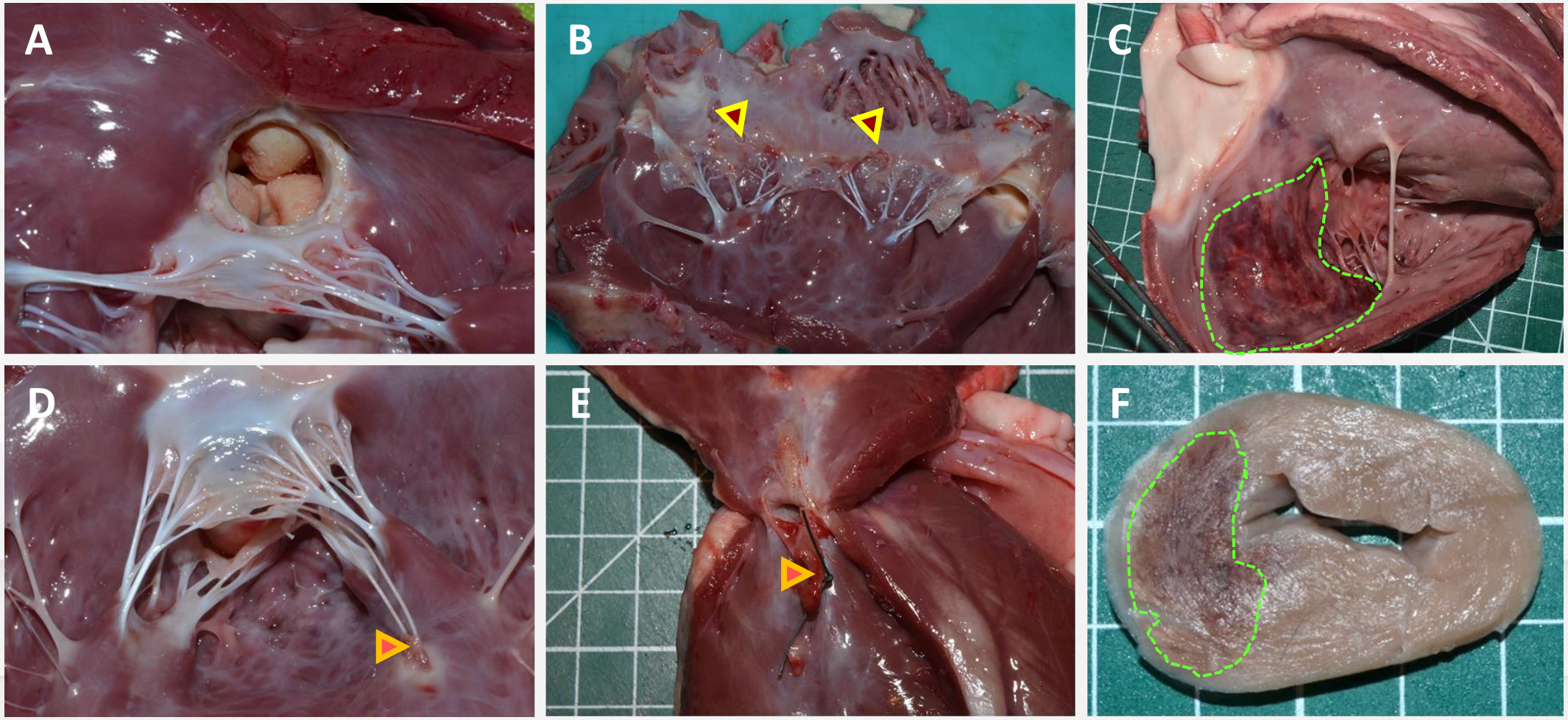
Macroscopic evaluation: Device

- **Implant and site of implantation**
  - **Inspection of the device and surrounding tissues**
    - Implant position
    - Tissue healing & ingrowth (Pannus, neointima)
    - Fibrin deposits
    - Mineral deposits
    - Local effects

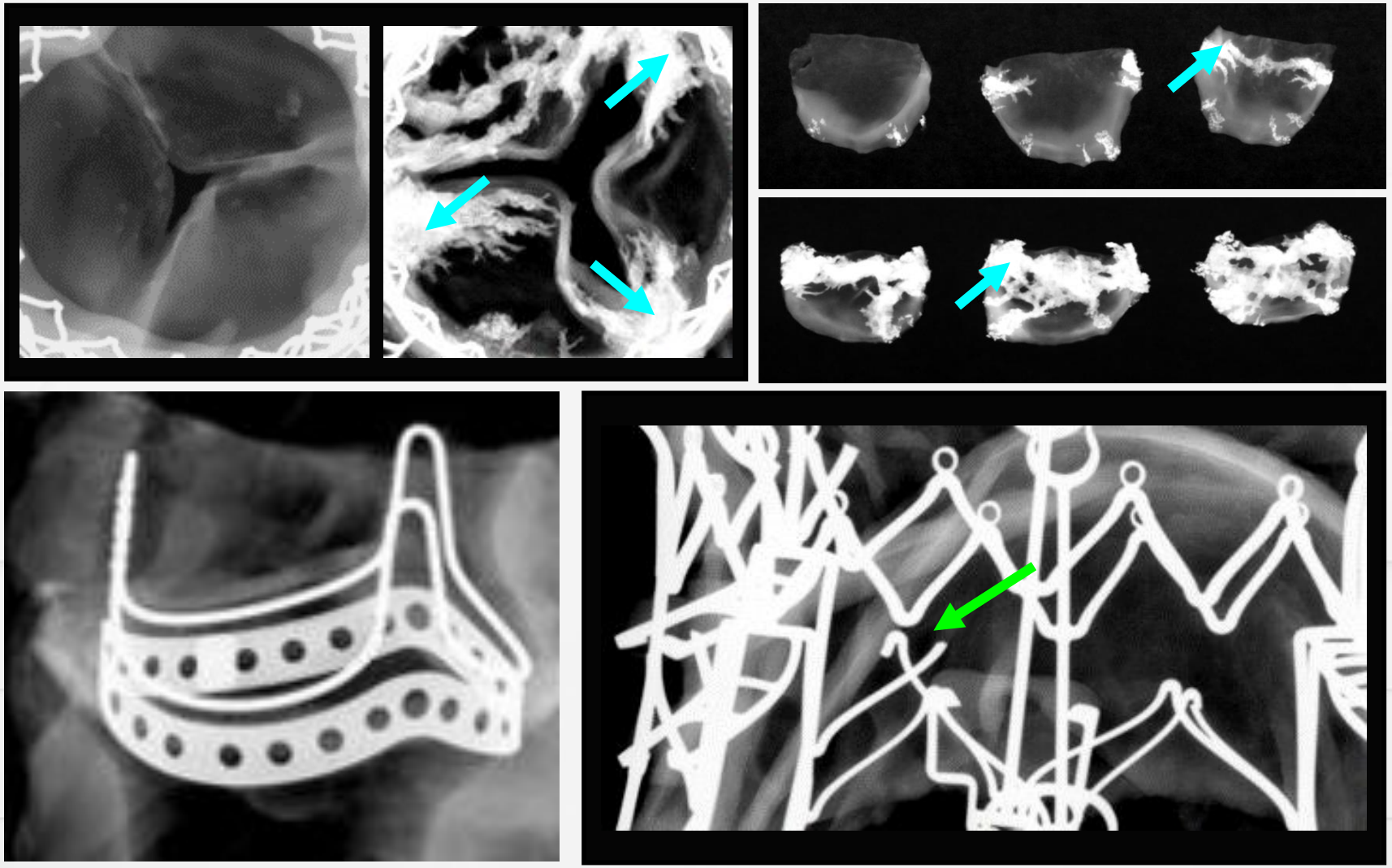
Macroscopic evaluation: Device



Macroscopic evaluation: Faxitron®

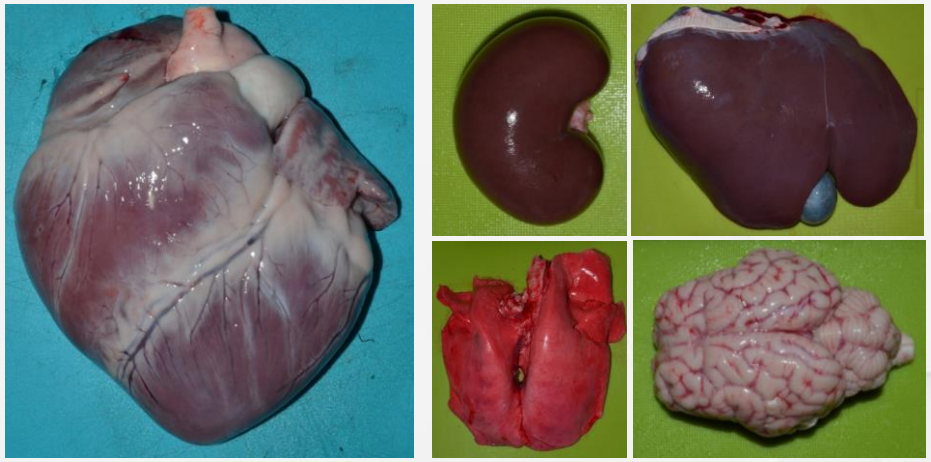
- **Implant and site of implantation**
  - **High resolution radiography (Faxitron®) or Micro-CT**
    - Mineral deposits
    - Fracture or deformation

Macroscopic evaluation: Faxitron®



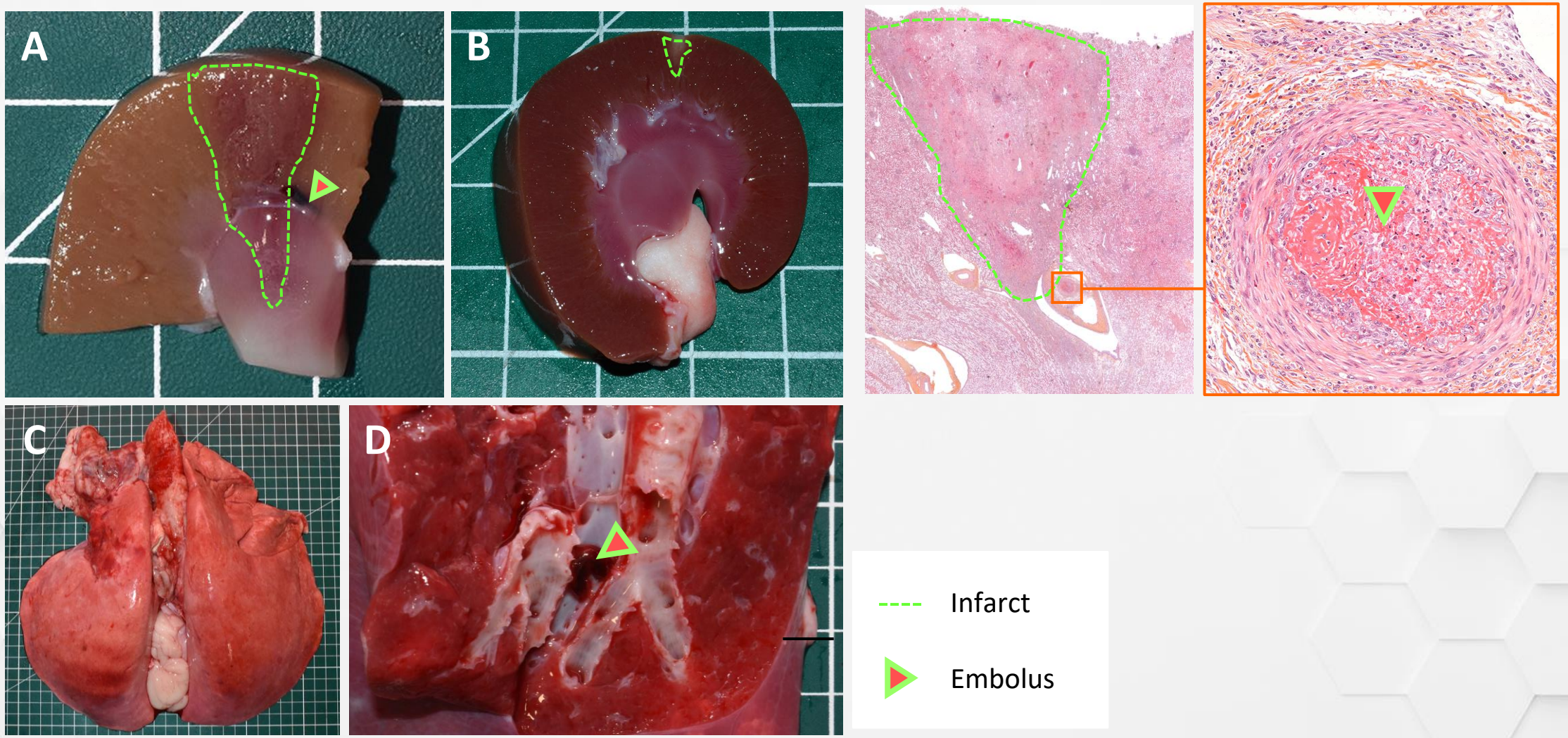
Macroscopic evaluation: Organs

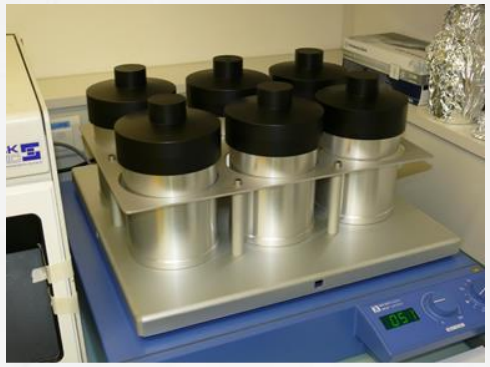
- **Organs**
  - **Full necropsy**
  - **Inspection, weighing & photographs**
    - Heart
    - Lung
    - Liver
    - Kidney
    - Spleen
    - Regional Lymph Node
    - Brain
    - Specific target organs

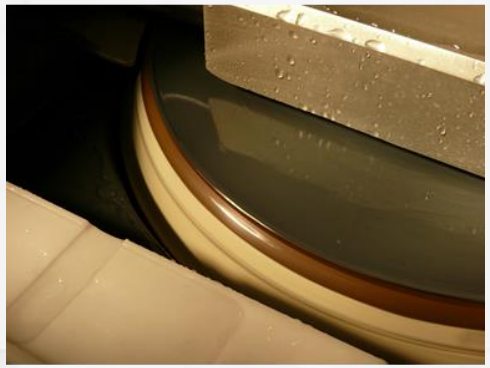


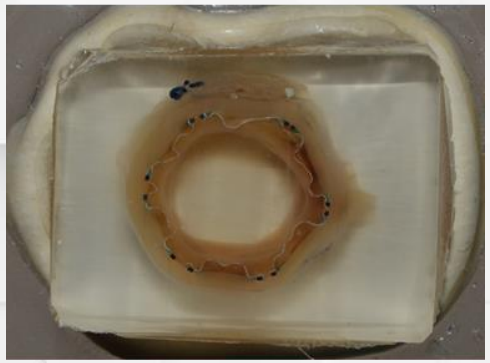
Evaluate, describe, illustrate

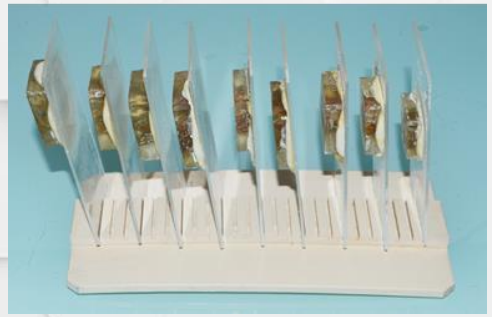
Macroscopic evaluation: Organs





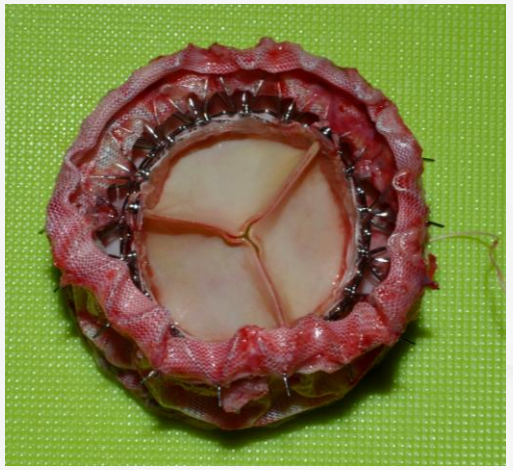


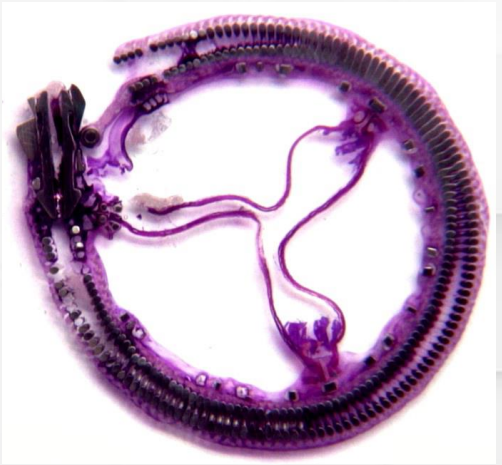




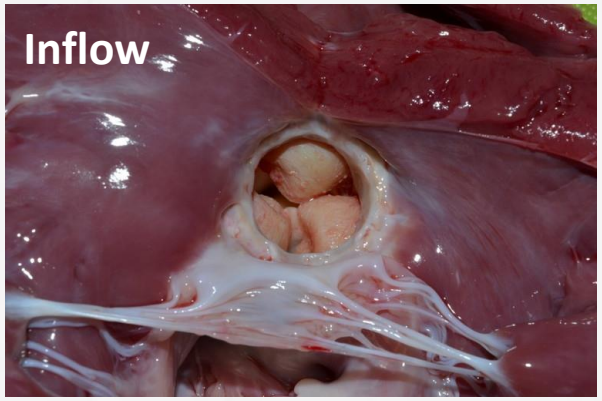
From 2D to 3D

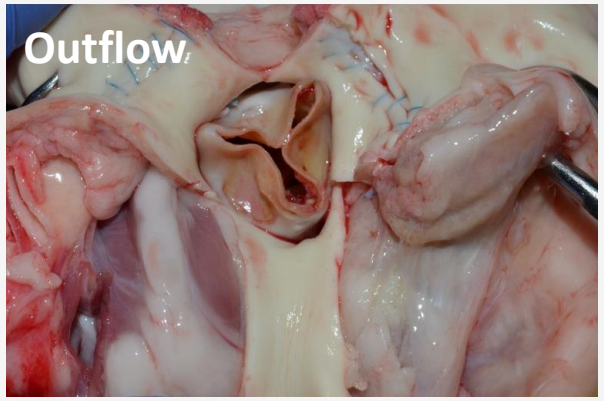
- **Trimming**
  - Preservation of implant-tissue interface
  - Orientated macrophotographs
- **Preparation of sections**
  - Slicing with a band-saw
  - Resin embedding
  - Sectioning & grinding

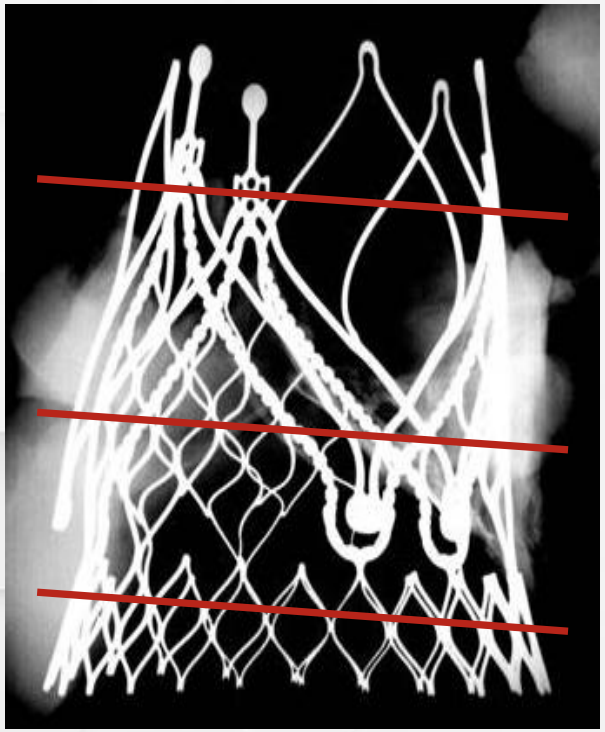




From 2D to 3D







Faxitron®

Aortic valve, PMMA resin sections, H&E stain, x1, Scale bar: 1 mm

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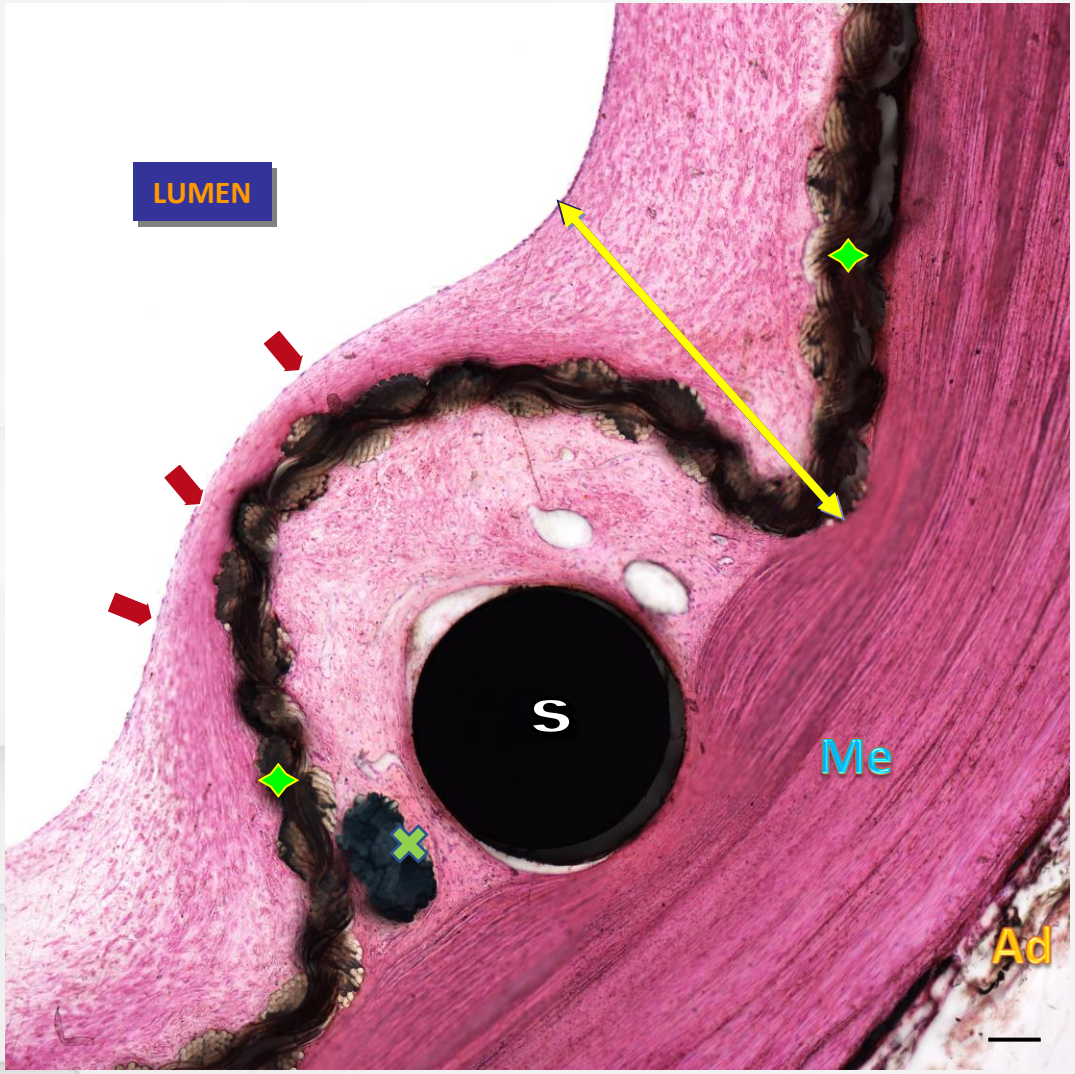
Histopathological evaluation: Parameters

- **Local tolerance**
  - Tissue ingrowth (pannus or neointima)
  - Endothelialization
  - Inflammation
  - Fibrin deposits/thrombosis
  - Mineralization
  - Resorption of material
  - Etc.
- **Systemic effects**
  - Thrombo-embolism and infarcts
  - Any changes in the organs/tissue

- **Qualitative**
- **Scoring**
- **Histomorphometry**

Aortic stent as an example



Me Media

Ad Adventitia

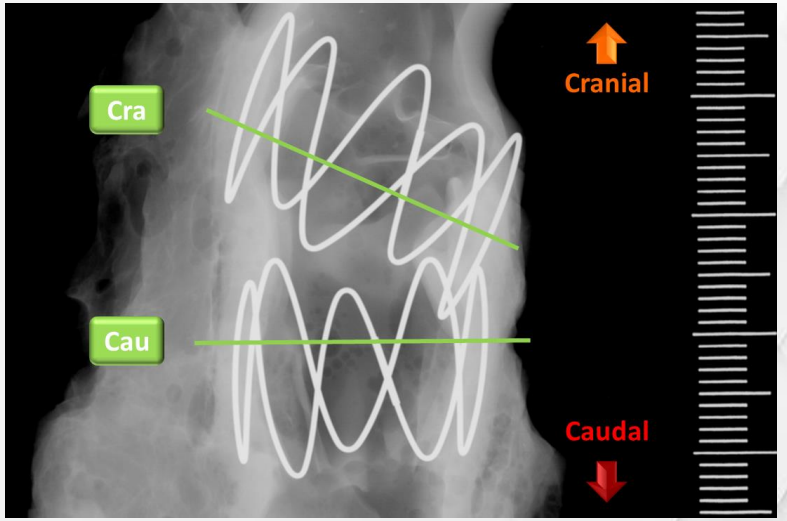
S Stent strut

Fabric skirt

Suture material

Fibrous pannus

Endothelium



Pig, Aortic stent, PMMA resin section, H&E stain, Scale bar: 100 µm.

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Aortic valve as an example

Ao Aortic wall

S Stent strut

Skirt

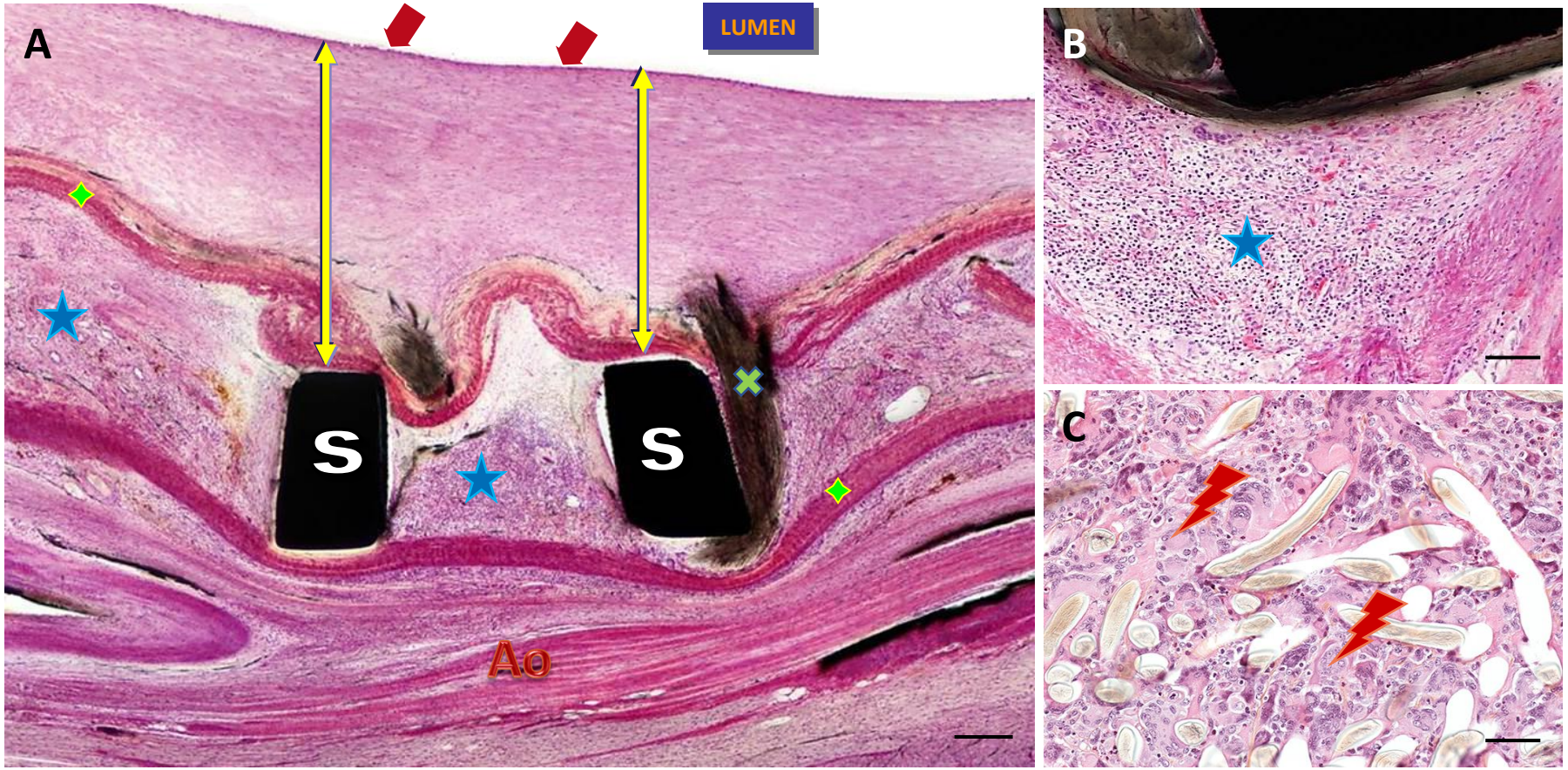
Suture material

Fibrous pannus

Mononuclear inflammation

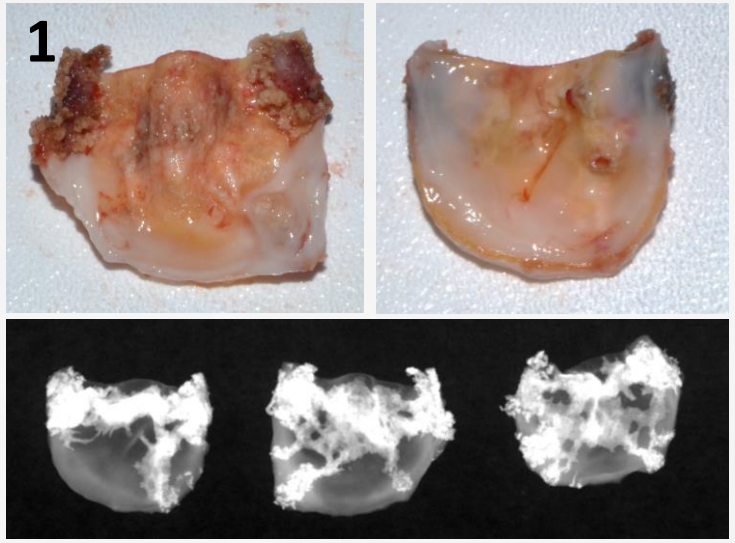
Multinucleated giant cells

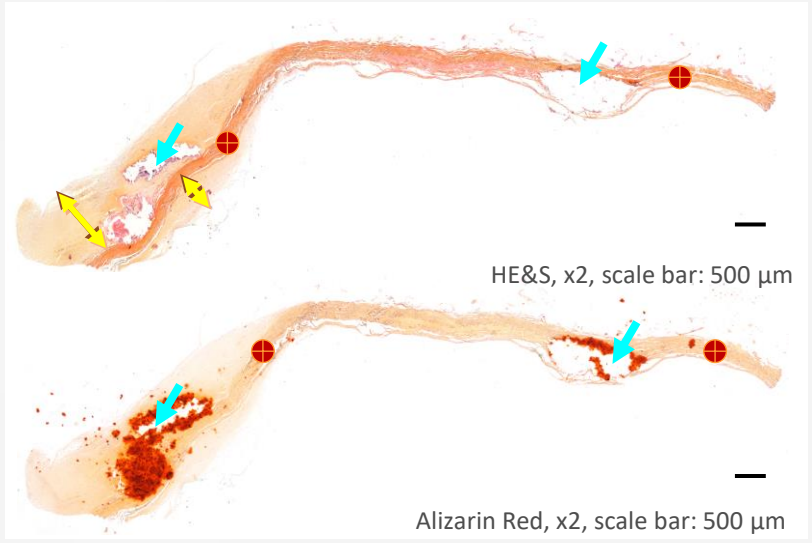
Endothelium

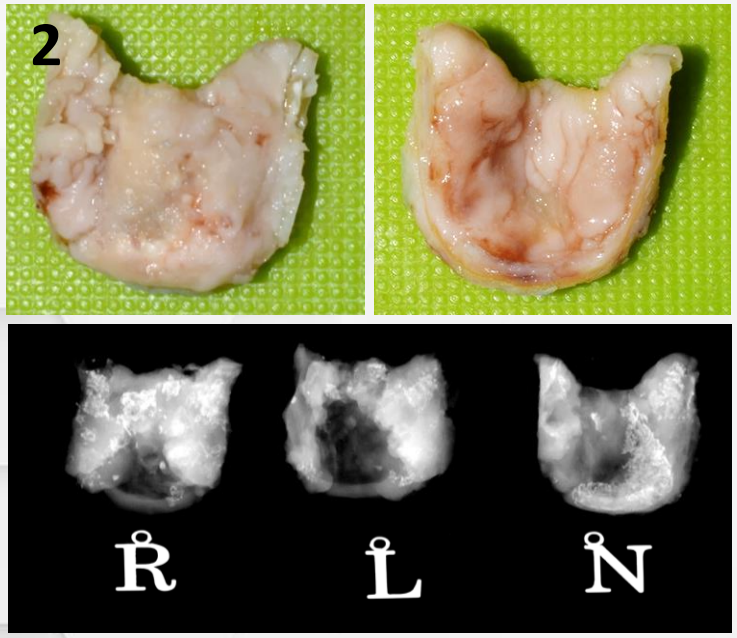


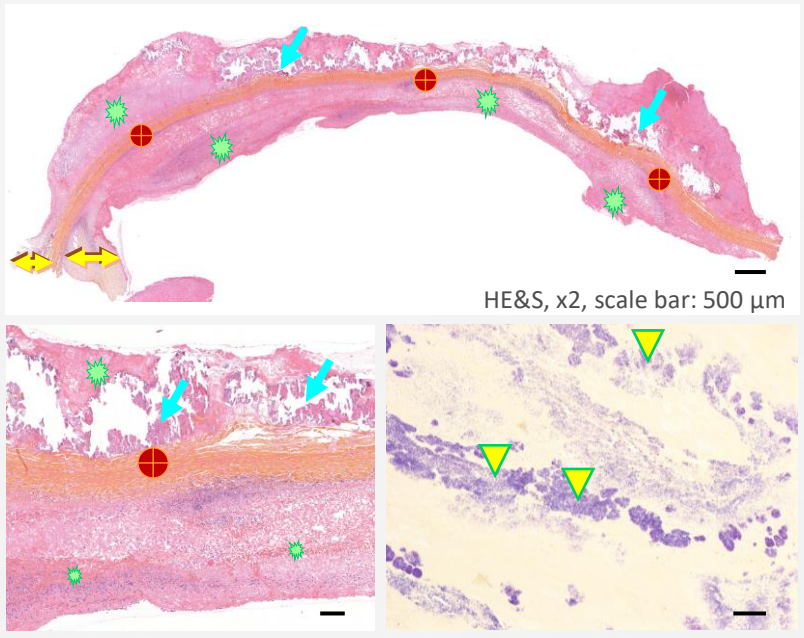
Ovine, Aortic valve, PMMA resin sections, H&E stain, Scale bar: 1 mm (A), 50 µm (B) and 25 µm (C).

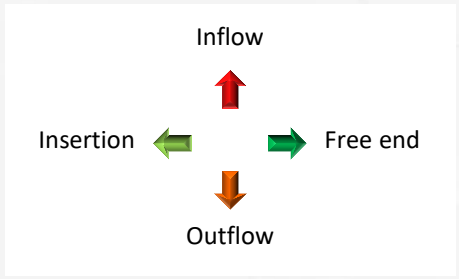
Bioprosthetic cusps
as an example











- Bioprosthetic cusp
- Fibrous pannus
- Mineral deposits
- Fibrin deposits
- Bacterial colonies

Ovine, Aortic valve, Paraffin sections

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Histological report

- Narrative report: description & summary of findings for groups
- All individual data (*Appendix A)*
- Annotated microphotographs *(Appendix B)*
- Morphometric data *(Appendix C)*

Conclusion / Histological report :

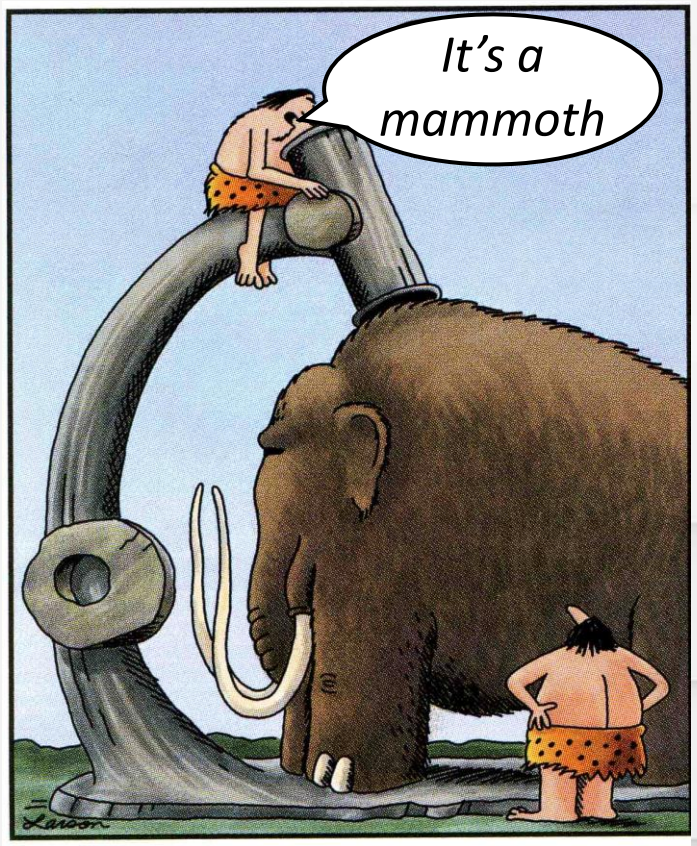
Local & General tolerance

Device-related findings

Expected findings

Very Important Pathologists

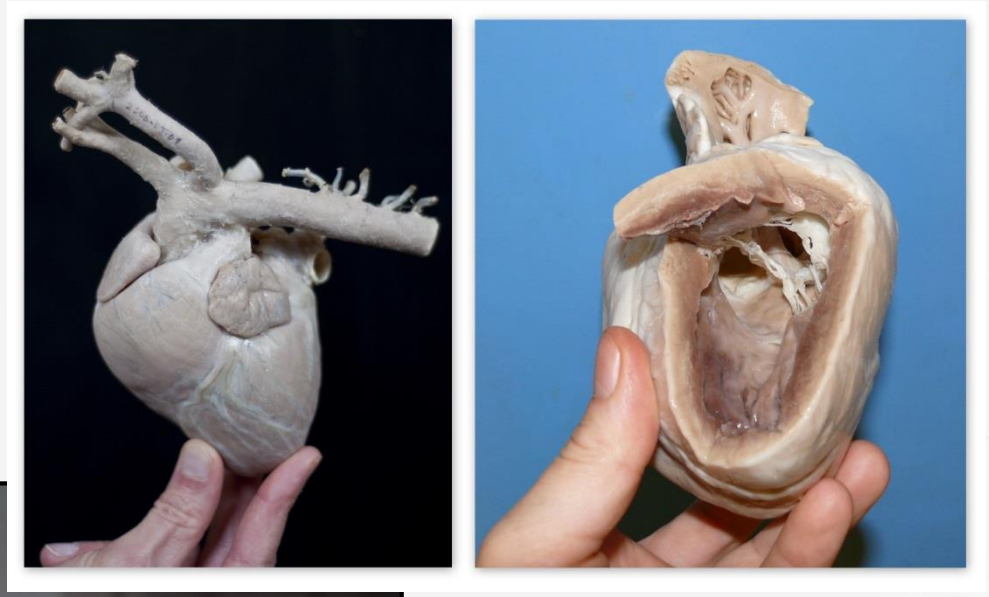
- **Critical role of pathological evaluation**
  - Pathologist: full member of a team of experts
  - Correlation with clinical, biological, imaging data
  - Interpretation based on the animal model



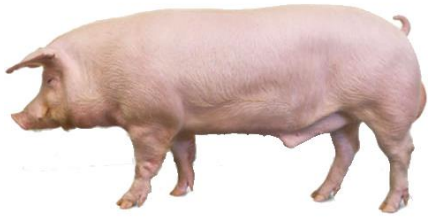
Different large animal models

Size is not everything

- Scientific considerations
- Technical considerations
- Practical considerations



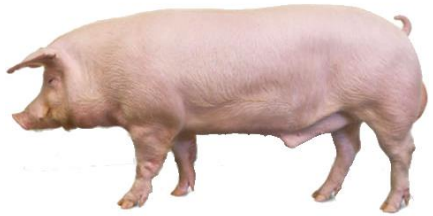
Which model: Advantages



- Heart anatomy is closer to human
  - *valves, cords, coronary system right heart dominant*
- Valve leaflets thicker
- Transesophageal echography is better
- Easily sourced at any weight
- Monogastric (per os…)

- Valve orifices & function similar to human
- More space around the mitral annulus
- Growth compatible with long-term studies
- Very robust & docile animal
- Prone to calcification in juvenile

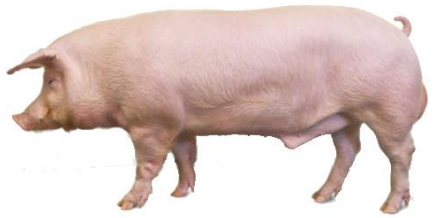
Which model: Limitations



- Rapid growth
- More susceptible to infection, especially thorax
- High incidence of arrhythmia (anesthesia)
- More difficult to handle
- Brawny animal (surgery)
- Hypertrophic ventricles
- Inflammation (more marked)

- Heart anatomy less similar to human
- Leaflets thin and fragile
- NO aortic-mitral curtain
- Fibrillation is difficult to overcome
- More difficult to source at a given weight
- More expensive
- Ruminants (per os…)

Choice of species: Overview



- Any study
- Acute studies
- Effect of growth on the device
- Skin studies, urinary system, laparoscopy

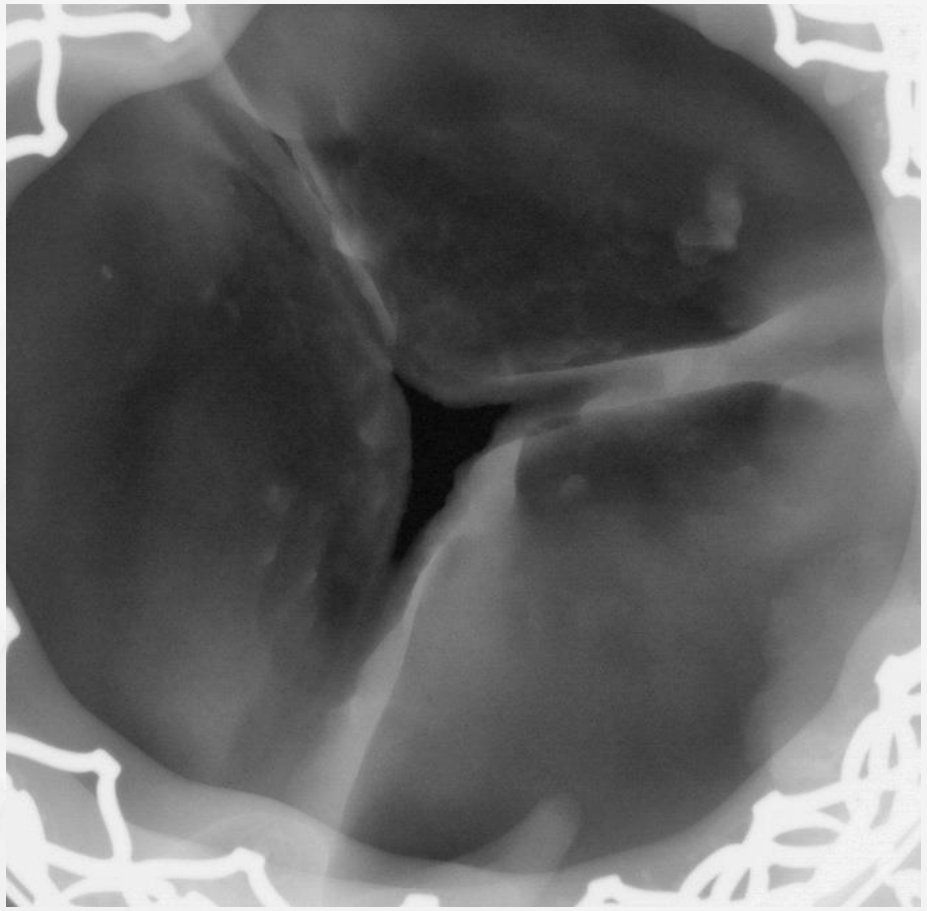
- Any study
- Chronic studies
- Gold standard of valve studies namely for calcification

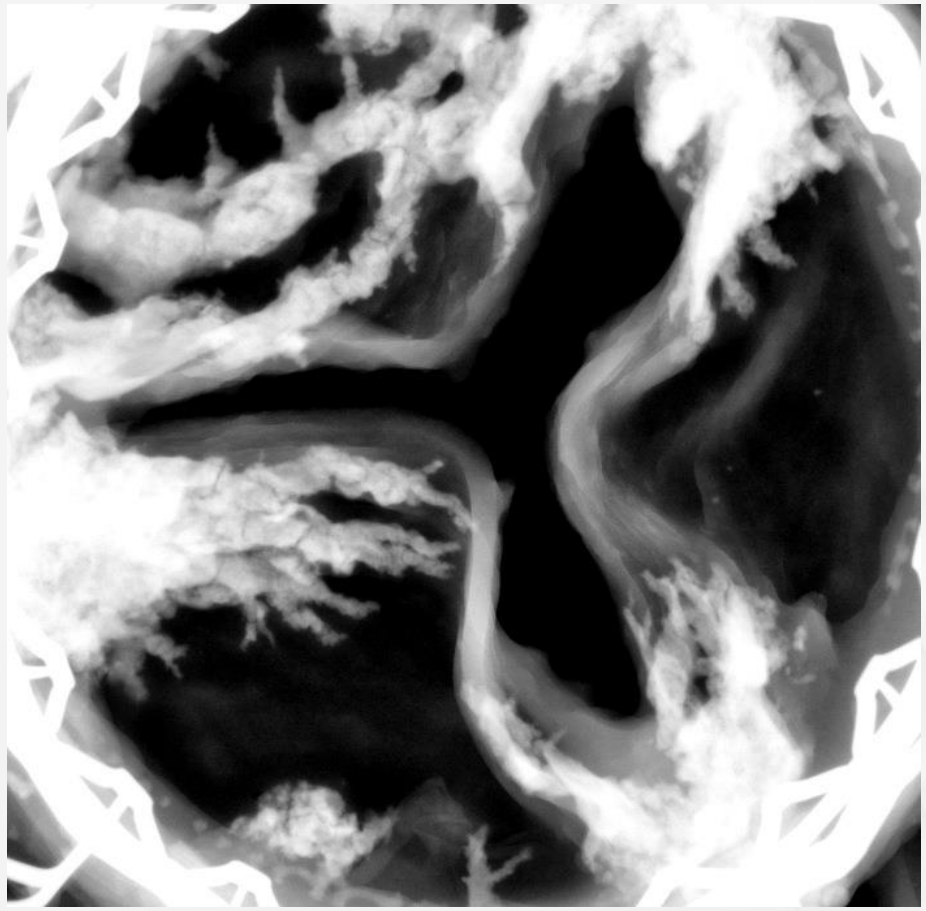
Other species

- Left atrial appendage ablation
- EP studies
- Renal/urinary
- Neuro

- LVAD
- Total artificial heart

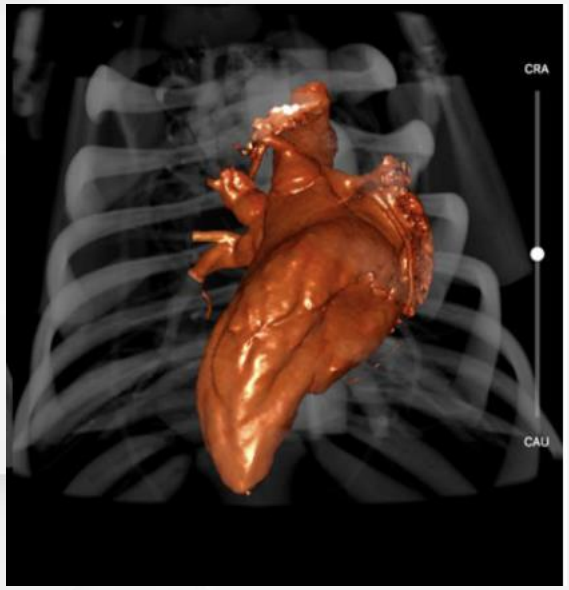
Faxitron analysis of calcifications



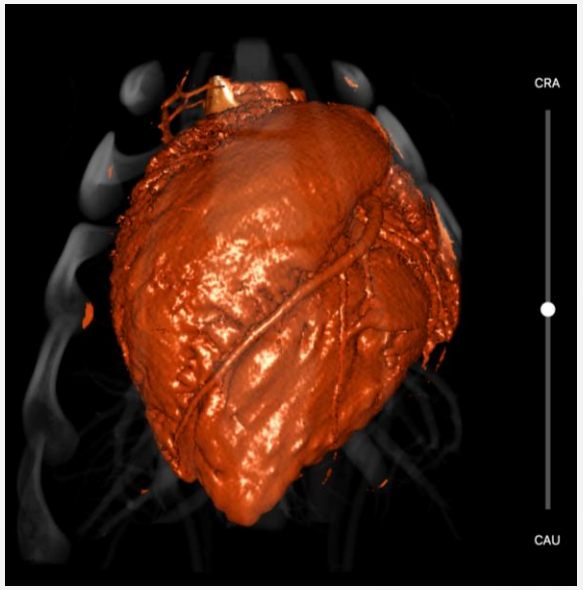


Comparative anatomy and comparative imaging
Heart orientation – “mirror images”

Sheep



Swine



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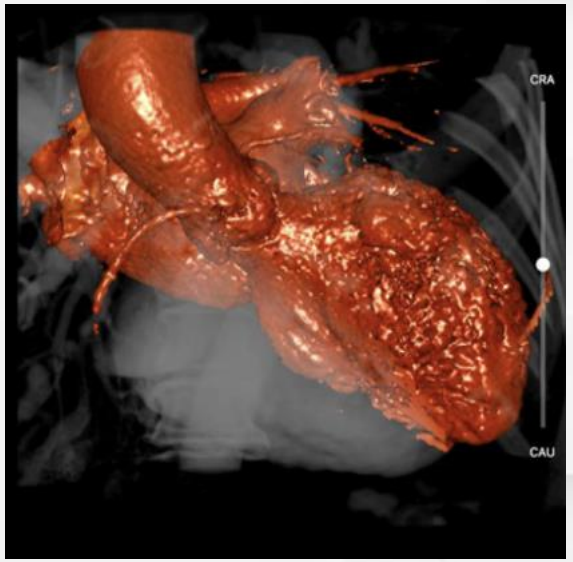

Images, Nicolo Piazza MD, PhD, FRCPC, FESC, FACC, Montreal

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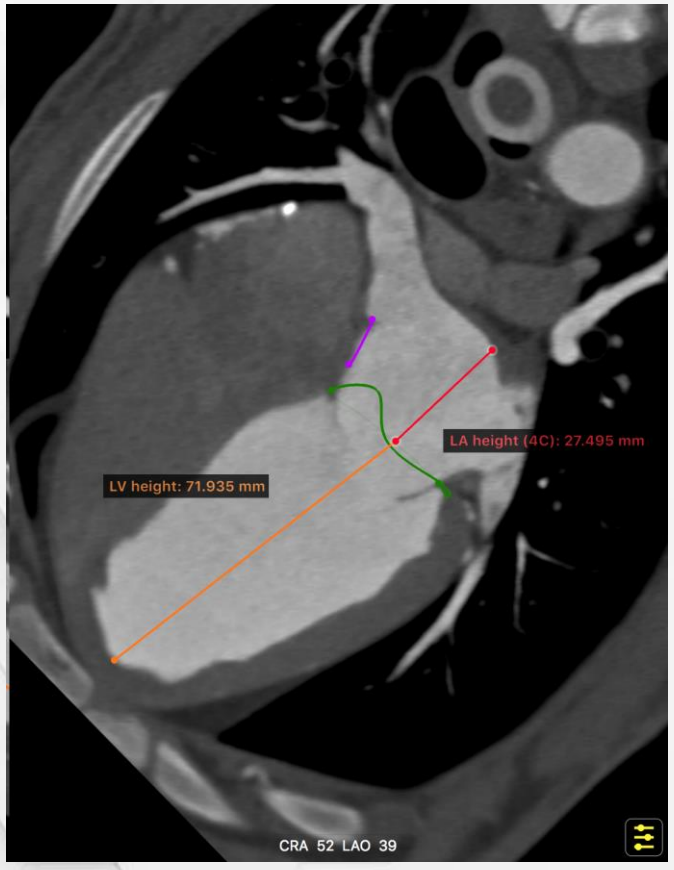
Left atrial and ventricular height

Sheep



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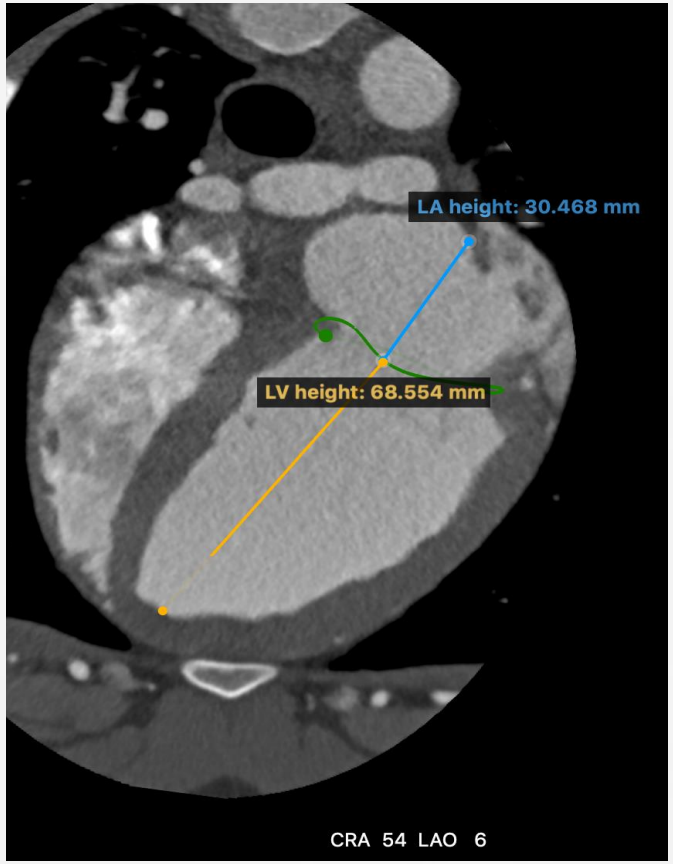

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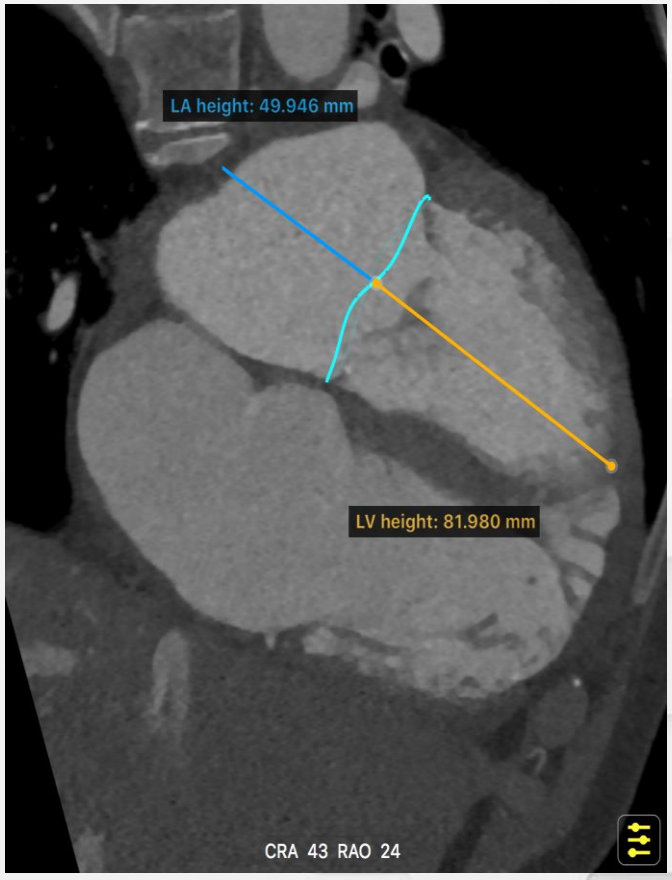


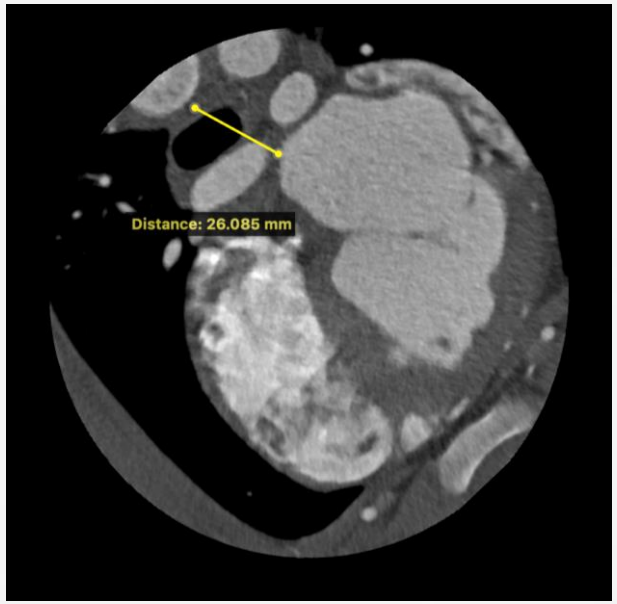
Images, Nicolo Piazza MD, PhD, FRCPC, FESC, FACC, Montreal

IMMR

Limitations of animal models:
Left atrial to esophageal distance, implications for imaging

Sheep

Swine



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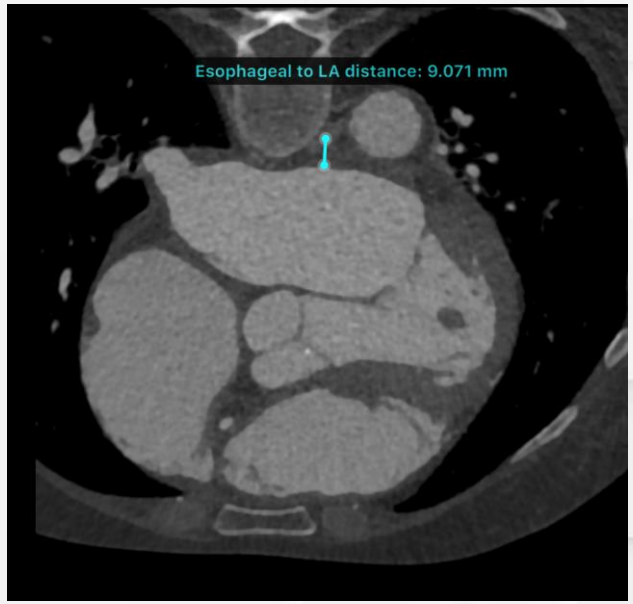

Images, Nicolo Piazza MD, PhD, FRCPC, FESC, FACC, Montreal

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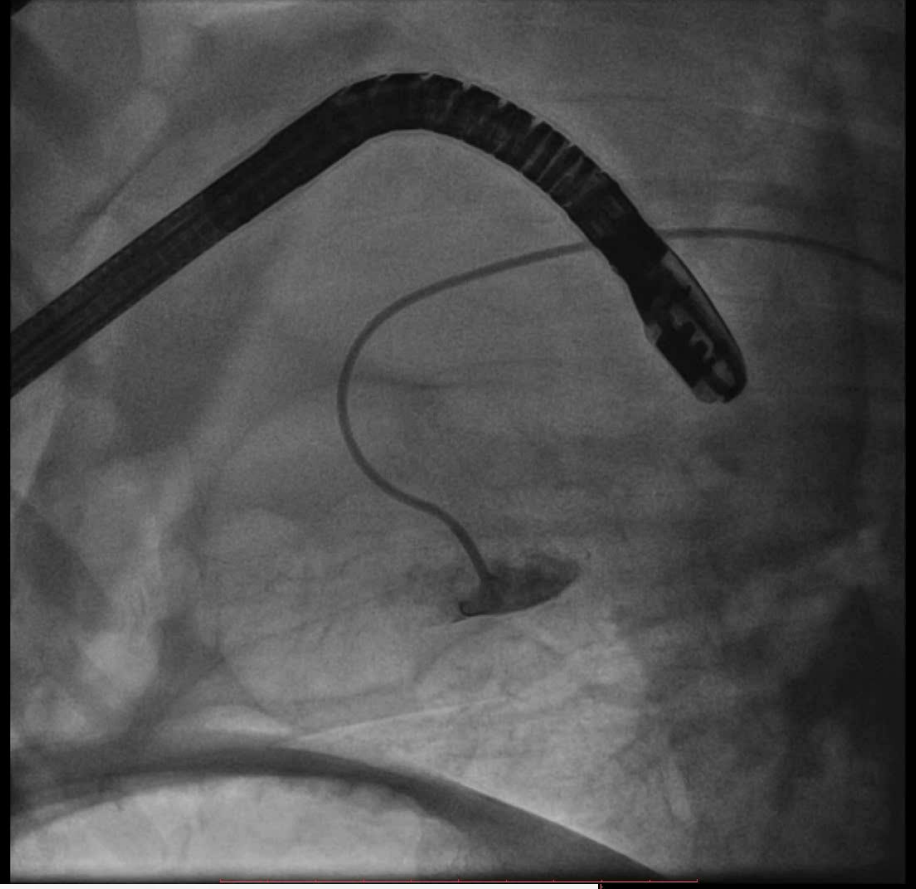

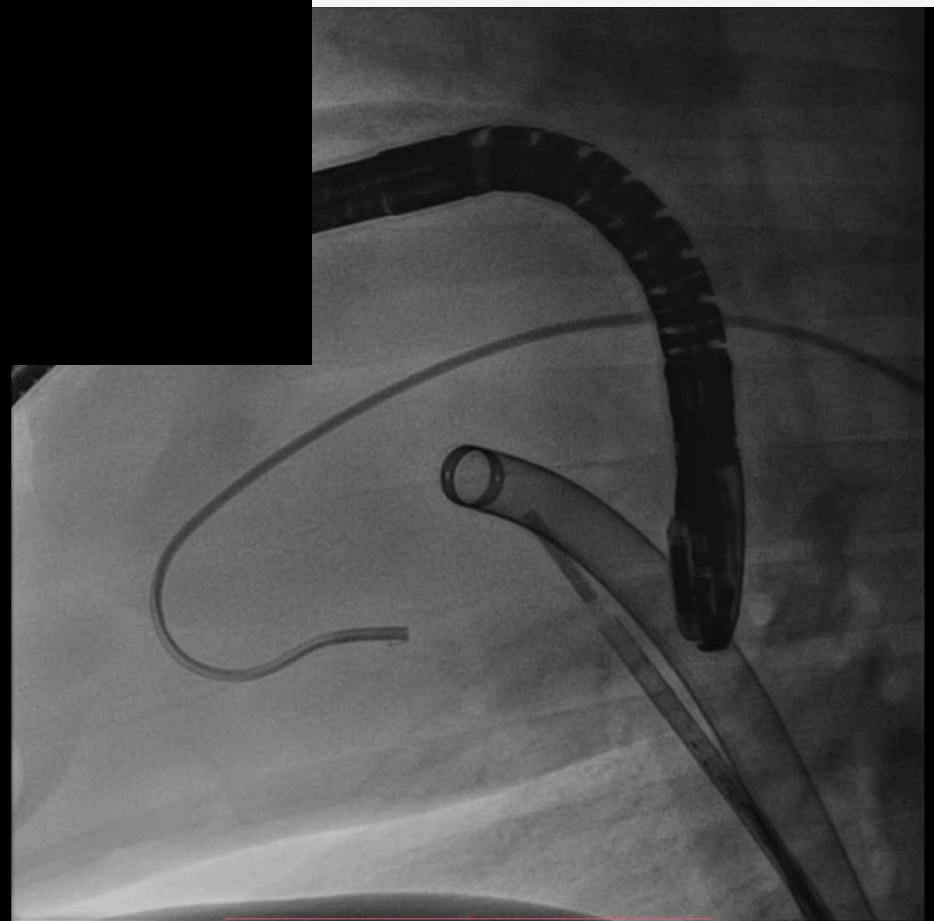

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Coro 7.5i/s Dose Reduite

IMMR

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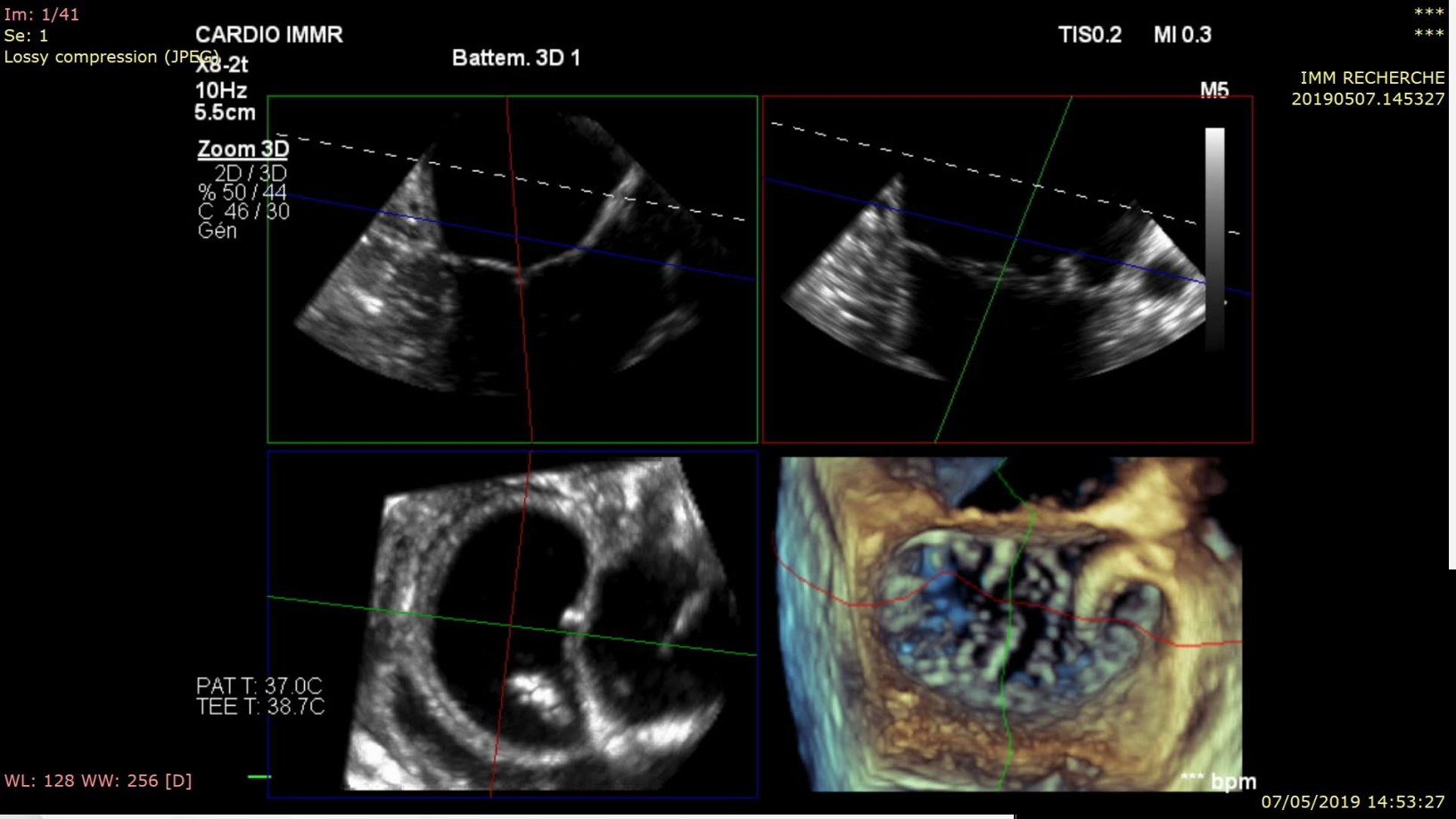
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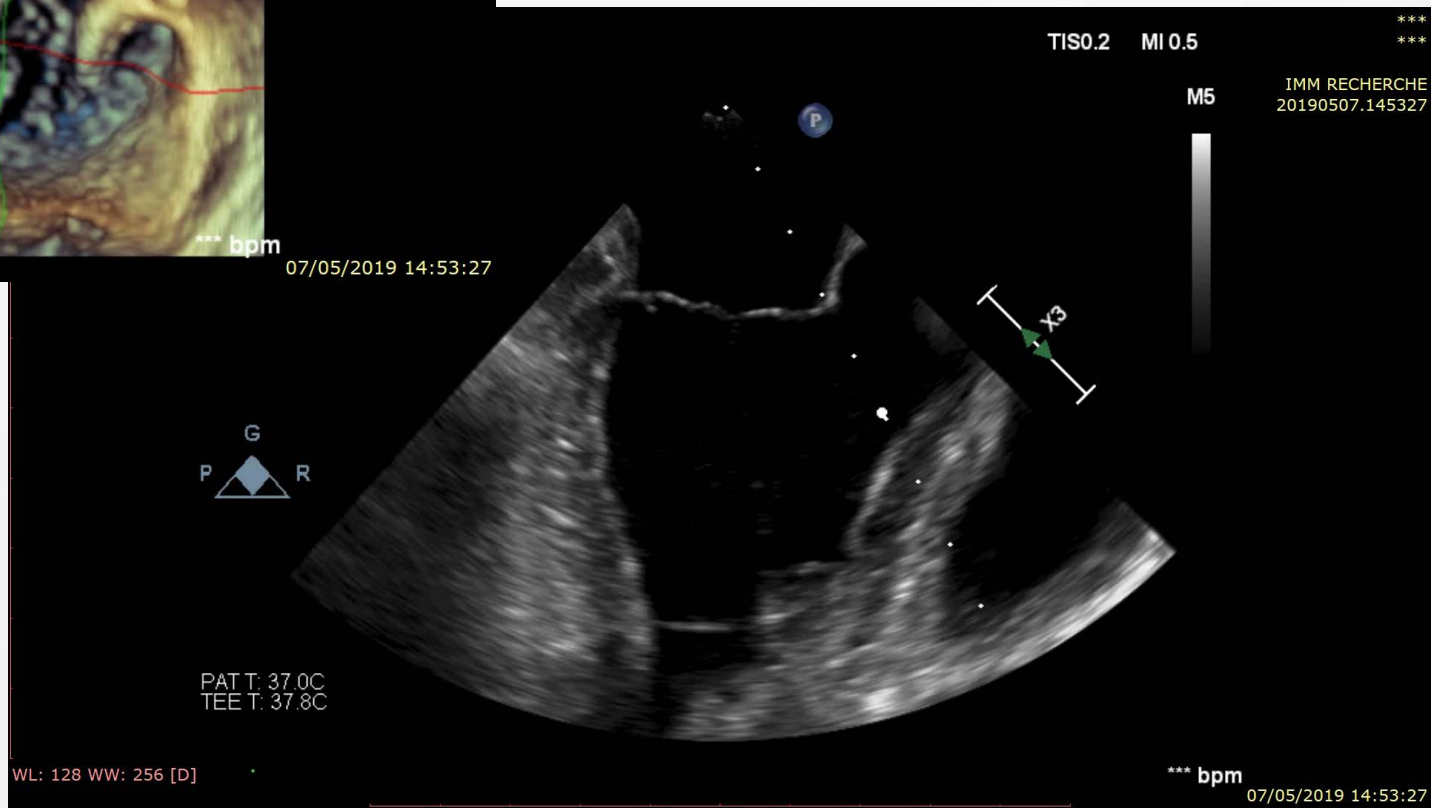
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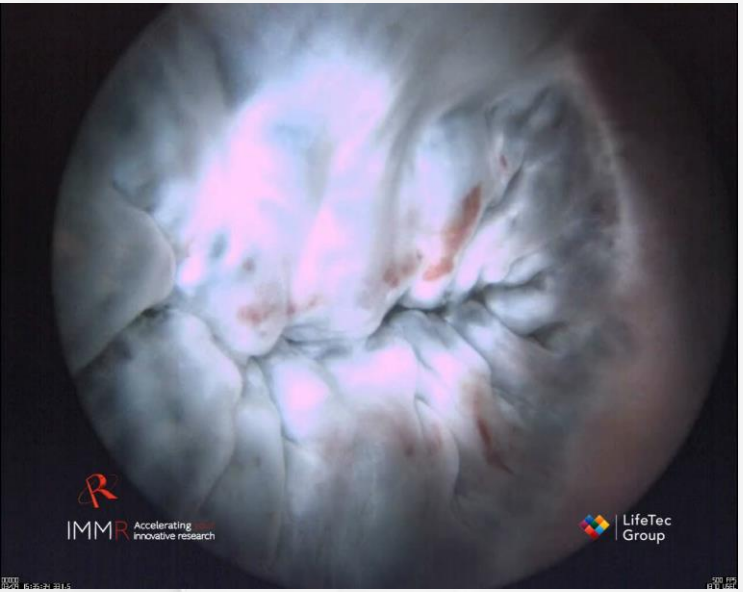
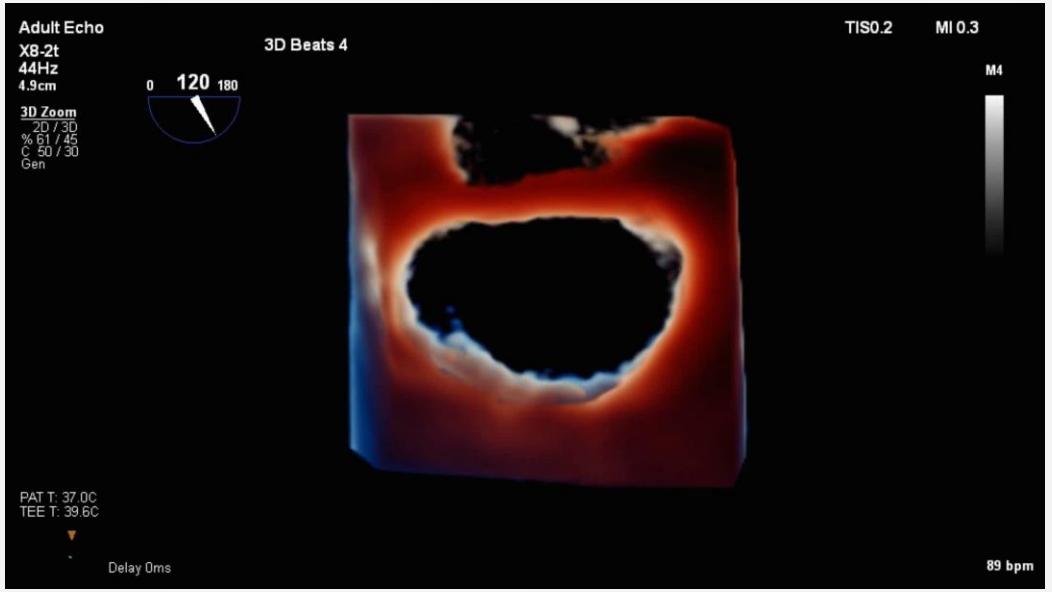

IMMR Accelerating innovative research
LifeTec Group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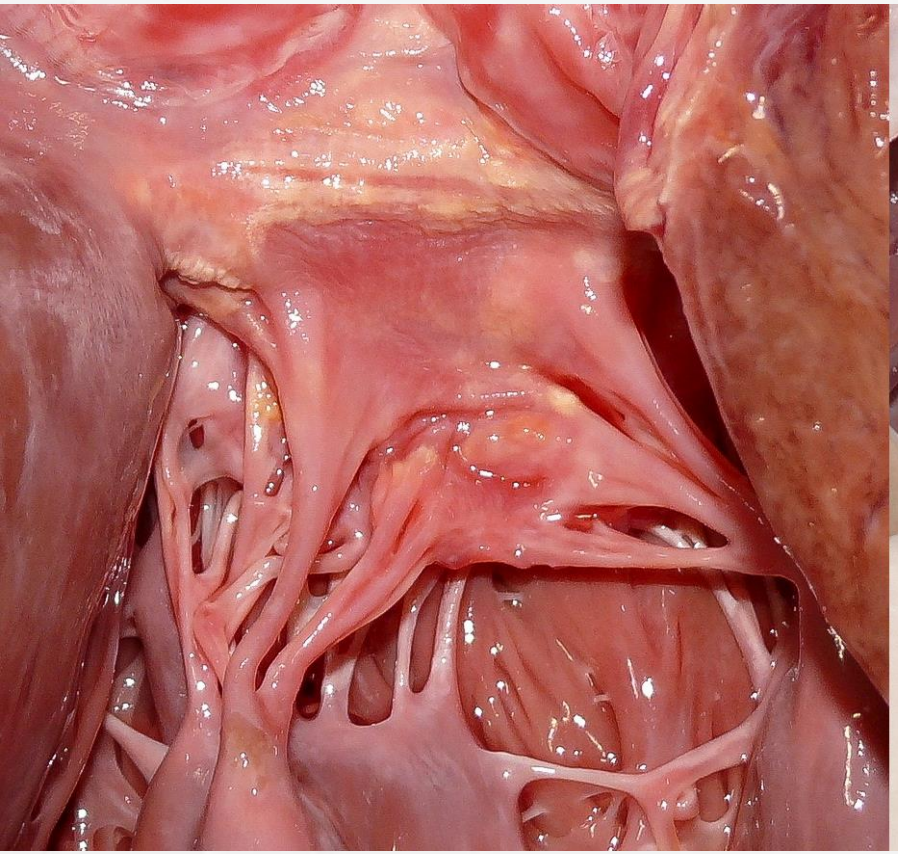
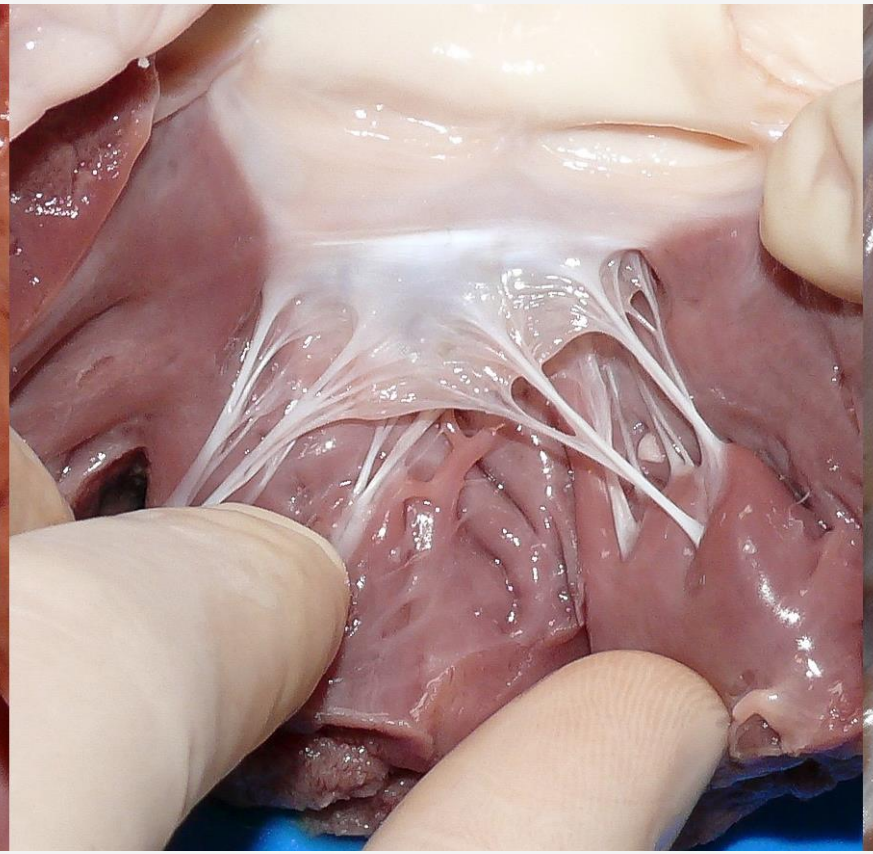
LifeTec Group

Limitations of animal models: Aorto-mitral continuity

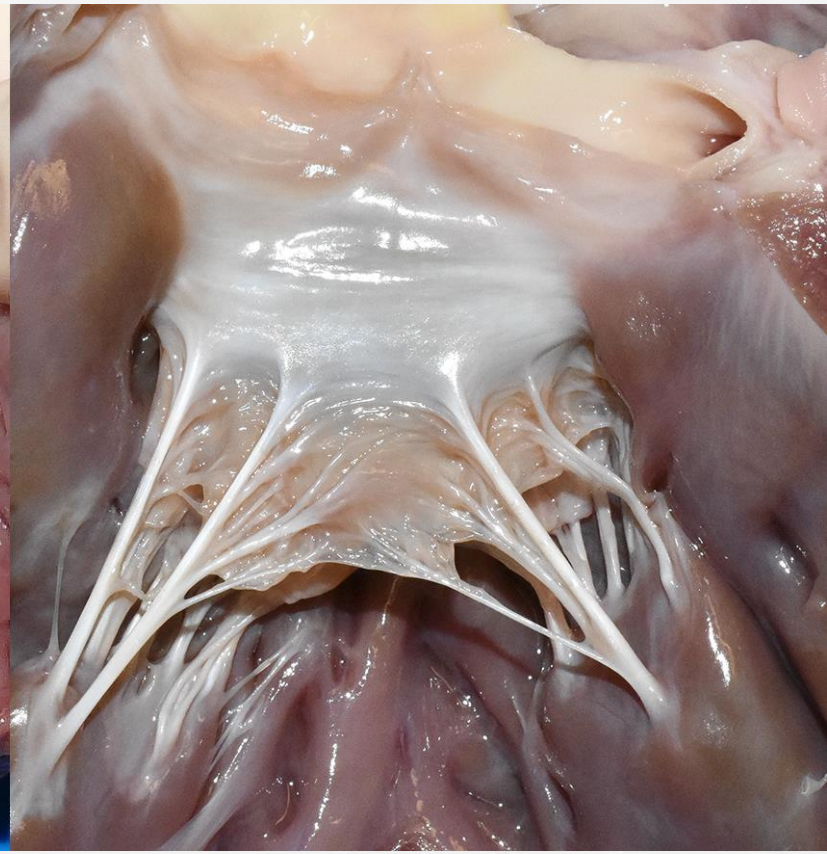
HUMAN

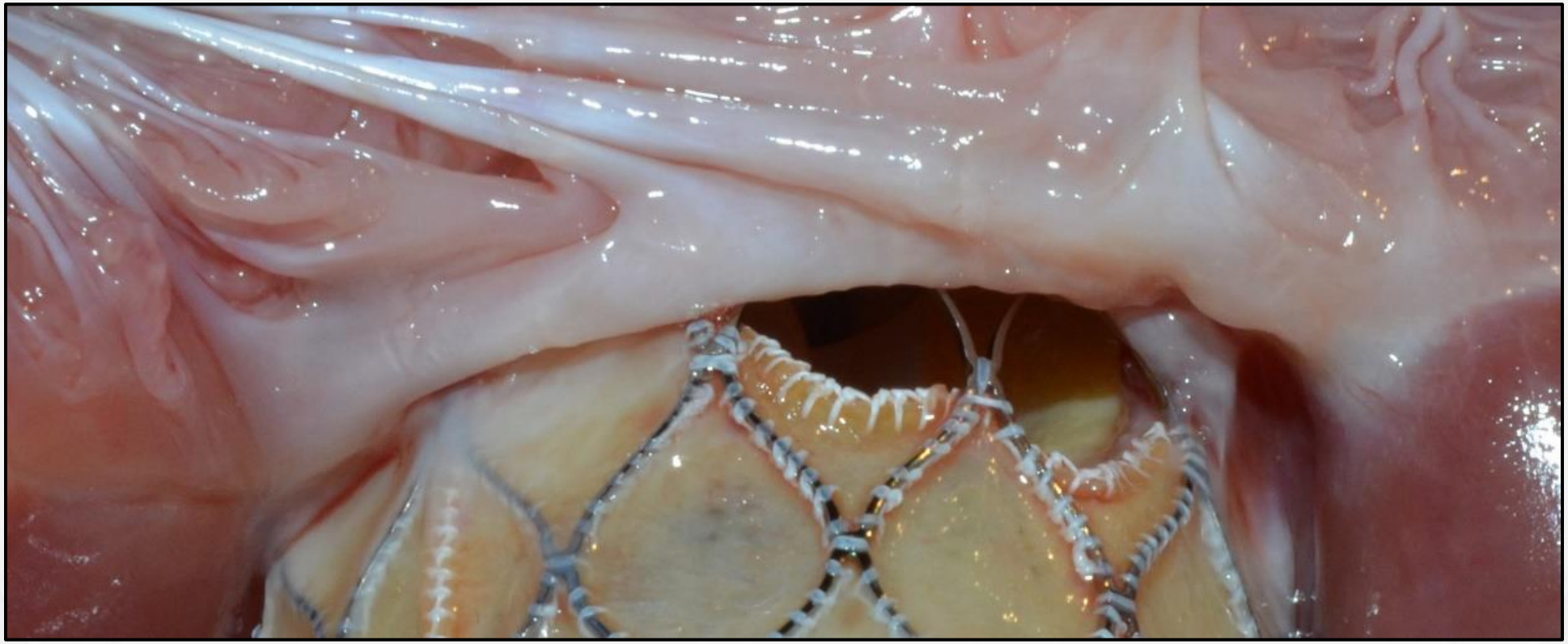


SHEEP

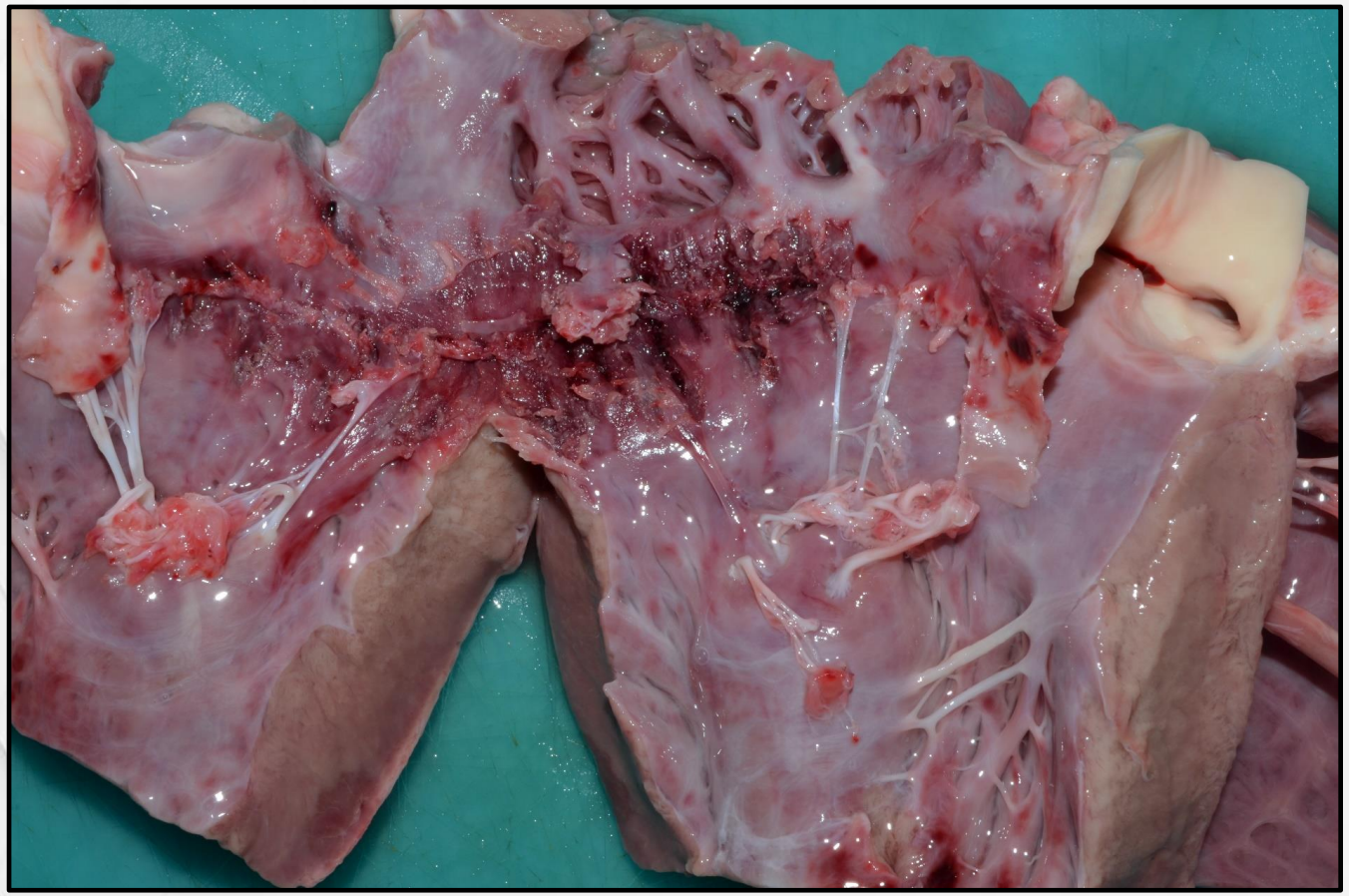


SWINE





Limitations of animal models: Frailty of tissues



Left ventricular hemodynamics

Sheep vs. Human

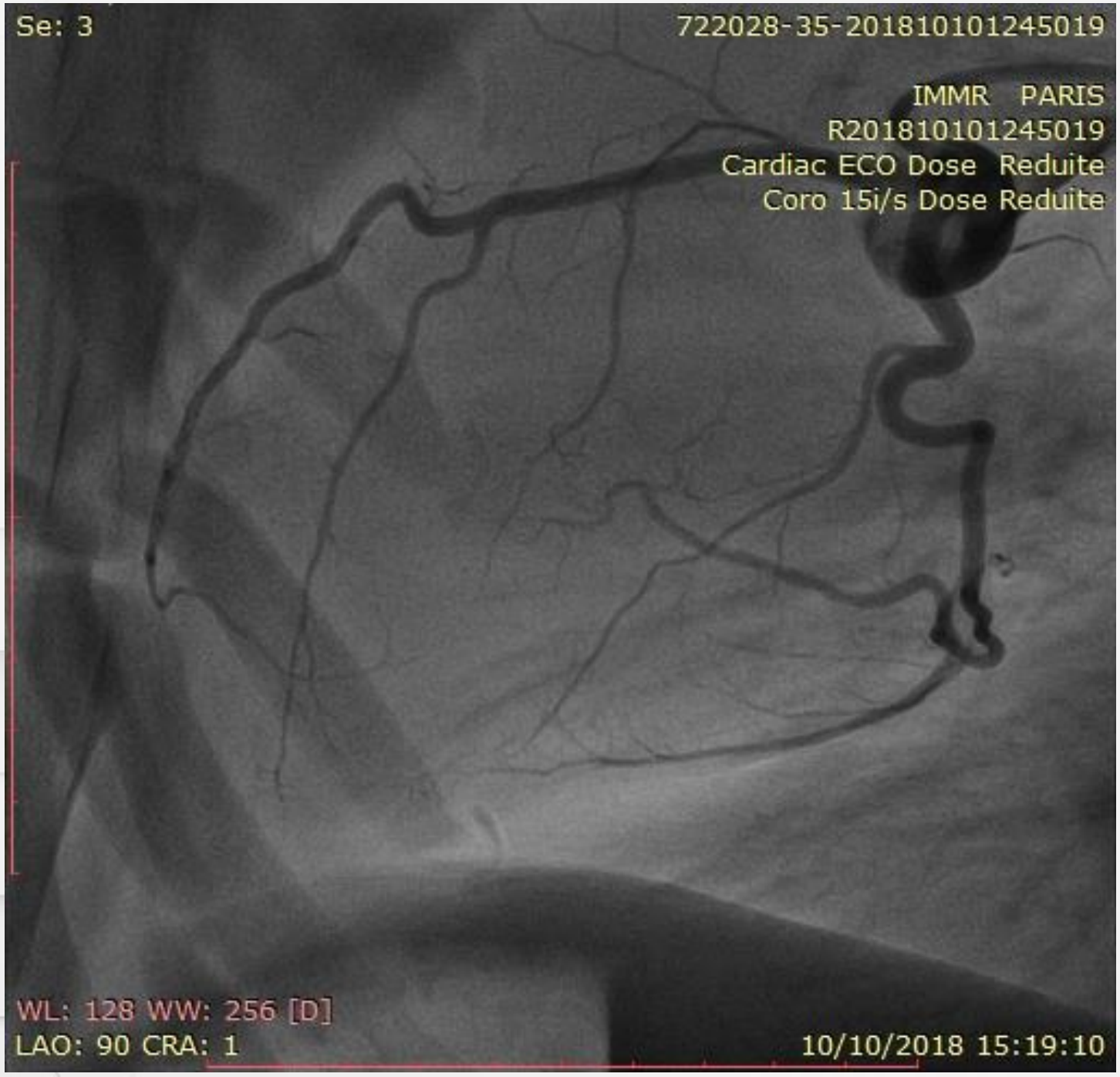
Parameter	Sheep[a]	Human[b]	Ratio Sheep/Human
LVSP (mmHg)	117	115	1.02
LV τ (ms)	28	43	0.65
LV dP/dt_{max} (mmHg/s)	2,119	1,491	1.42
LV dP/dt_{min} (mmHg/s)	−1,959	−1,869	1.05

Swine vs. Human

Parameter	Swine[a]	Human[b]	Ratio Swine/Human
LVSP (mmHg)	119	115	1.03
LV τ(ms)	-	43	-
LV dP/dt_{max} (mmHg/s)	3,290	1,491	2.21
LV dP/dt_{min} (mmHg/s)	−2,750	−1,869	1.47

Pharmacol Ther. 2014 March ; 141(3): 235–249. doi:10.1016/j.pharmthera.2013.10.007

Stent fractures



Working with pathologic models

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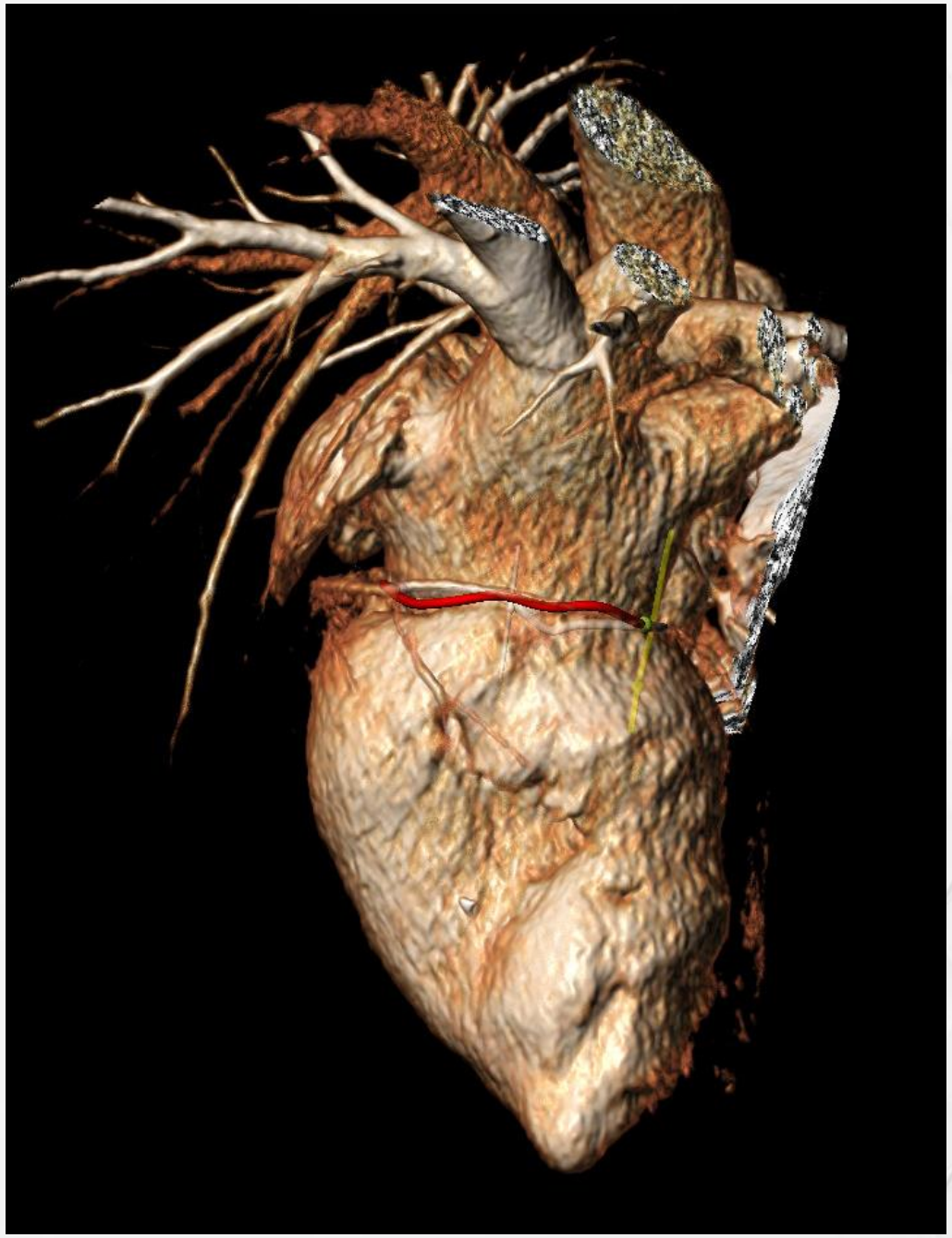
Working with pathologic models

- In theory, diseased animal models should be the best platform for assessing the safety and efficacy of novel devices
- Reliable pathologic model in large animals is extremely challenging
- Creating lesions is never an issue
- Challenge: Enough dysfunction to make it relevant and not too much in order to make it cost-prohibitive and more importantly ethically acceptable
- Survival rates in disease models can be unacceptably low

Working with pathologic models: Example of ischemic mitral insufficiency

- Serial transcatheter intracoronary embolizations
- 1,5-2 months duration
- +/- 80% success rate depending on anatomy and age
- No clinical sign of heart disease (animals are treated with ACE inhibitors and diuretics)

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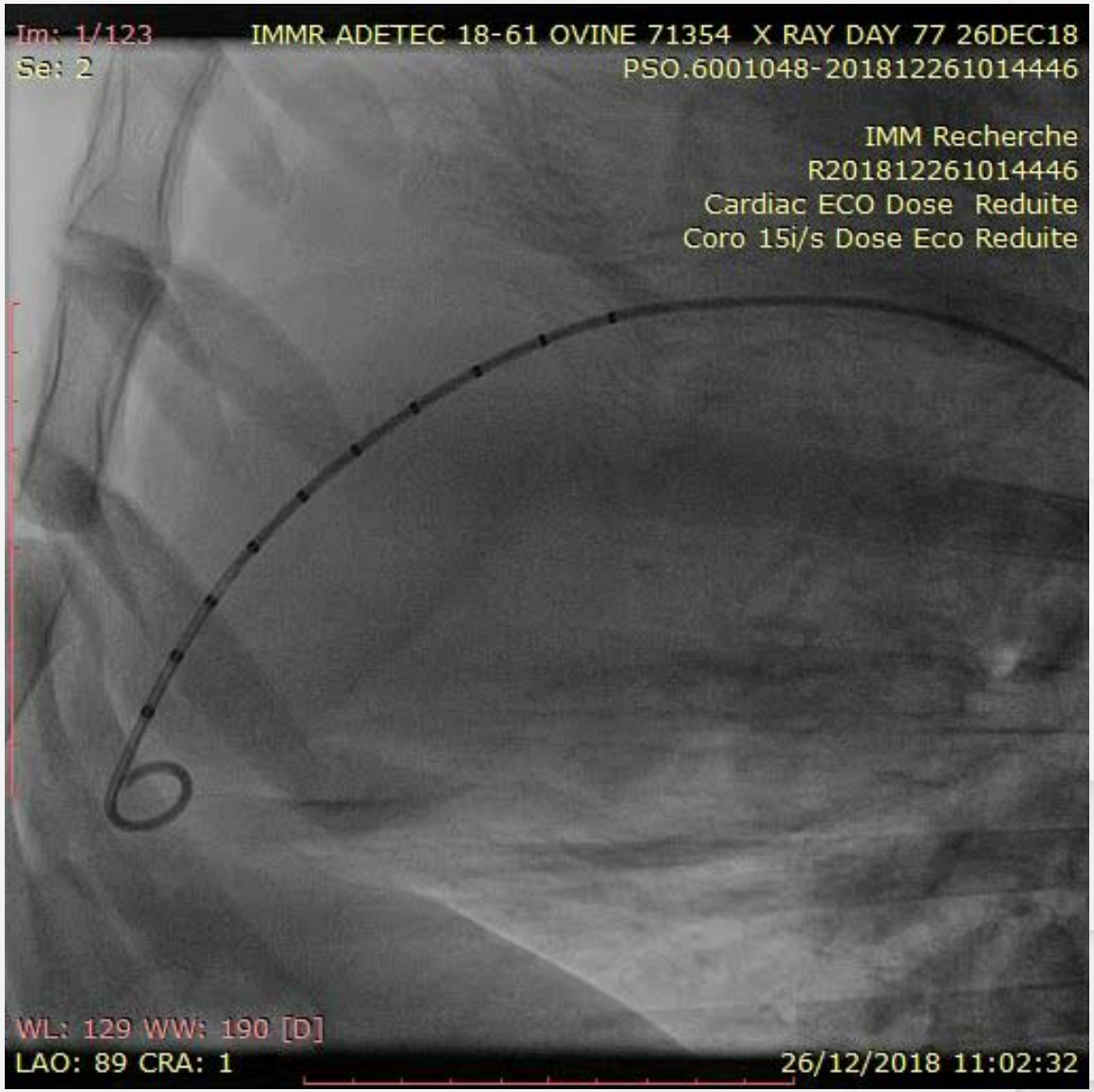
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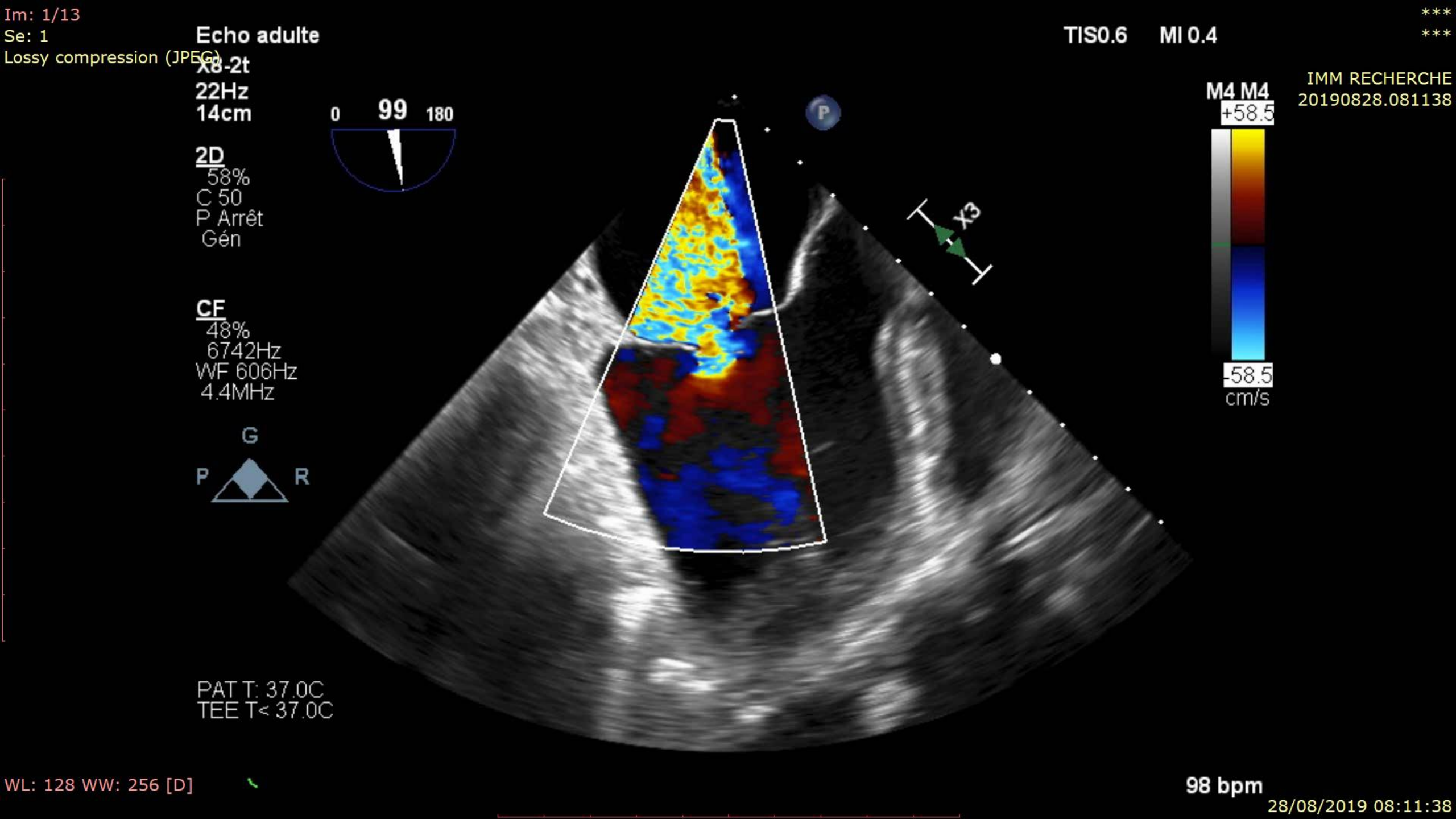
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MI 0.4
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-58.5
cm/s
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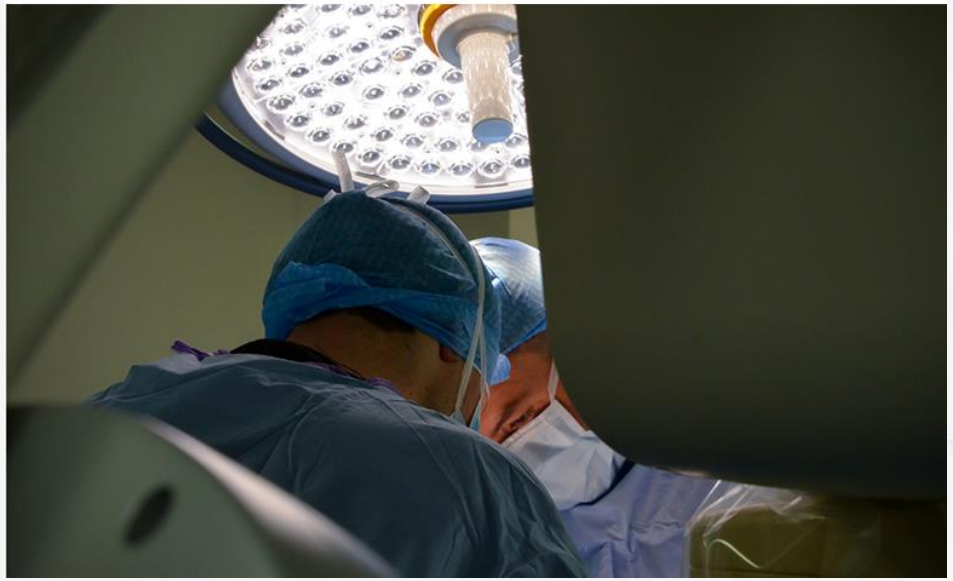
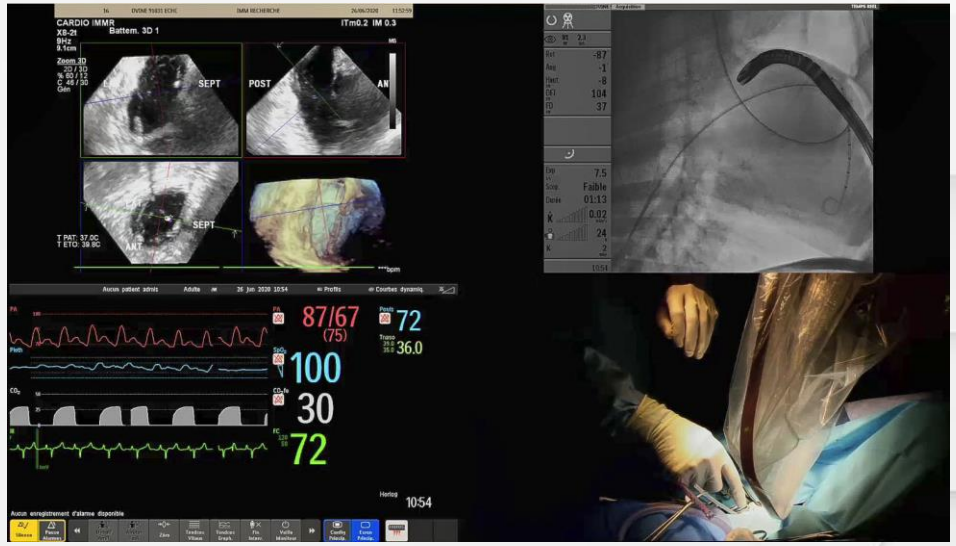
P
WL: 128 WW: 256 [D]
98 bpm
28/08/2019 08:11:38

Considerations for selecting a preclinical science partner

- Highest ethical standards, integrity and commitment to animal welfare
- Complete respect for confidentiality
- Scientific independence free of bias
- Thorough knowledge of comparative anatomy and physiology to select the best model while understanding their limitations
- Problem-solving abilities
- State-of-the-art technical platform
- Facility conditions familiar to surgeons and interventionalists who will carry their experience into the human clinical arena





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The pivotal role of preclinical science in medical technology innovation

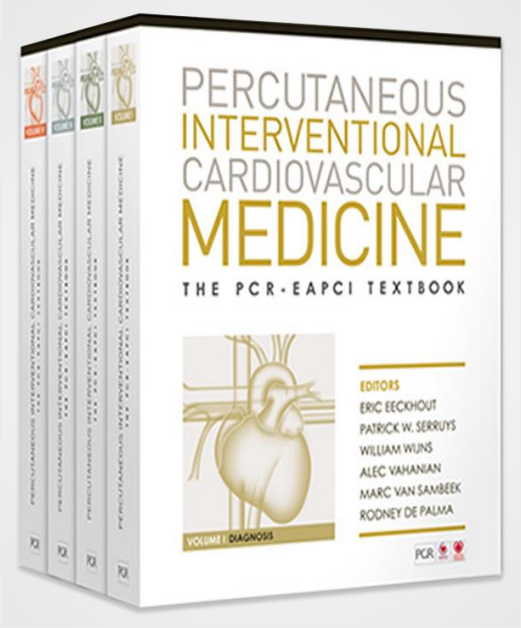
Preclinical science provides essential information about product design and performance at the scale of human anatomy, and it is critical for insuring that human clinical trials can be performed safely, correctly and with compelling outcomes

Critical elements for preclinical studies

- Designed with appropriate scientific rigor to be able to yield actionable results
- Conducted in appropriate models so that they can provide predictive information
- Are conducted in laboratories that have requisite expertise and technology
- Provide familiar conditions to surgeons and interventionalists
- Are completed with close post-operative care
- Are followed by expert and comprehensive gross and histopathology evaluation

PCR – EACPI Textbook

August, 2020



PART IV

Large animal models for the interventional cardiologist: a comparative anatomy, imaging, histopathology and regulatory perspective

Nicolas Borenstein, Luc Behr, Alexis Morlet, Olivier Chevènement, Robert Kieval, Angélique Ente, Laurence Fiette

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Thank You

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