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The isolated large animal heart as a tool to refine and reduce animal experiments in cardiovascular research

Katharina Vellguth, Simon Sündermann, Andreas Escher, Tim Bierewirtz, Tanja Schmidt, Alessio Alogna, Ulrich Kertzscher, Leonid Goubergrits, Katharine H. Fraser and Marcus Granegger

C3R-funding line: Refinement

Motivation and Background

- Animal models are inevitable to assess physiologic effects of cardiovascular implants
- The isolated large animal heart may refine and reduce animal experiments by
  - Reusing hearts from other experiments
  - Outstanding accessibility for advanced measurement and imaging modalities
  - High success rates and enhanced data quality

Aim and Hypothesis

- Development of isolated heart permitting the investigation of complex relationship between flow structures, hemodynamic parameters and cardiac mechano-energetics after
  - Edge-to-edge mitral valve repair
  - Rotatable bicuspid mitral valve prosthesis
- Flow features and their interaction with mechano-energetics could play important role for optimal recovery after mitral valve therapy

3R Goals

- Reuse animal organs from other experiments
- Reduce thereby total number of animals for experiments
- Refine the experimental approach to minimize animal suffering by fast explantation under anesthesia and experiment performance ex-vivo

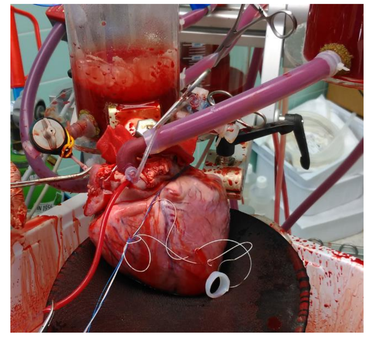

Fig. 1: Isolated heart setup during working mode

Materials and Methods

- Isolated heart setup from *Granegger et al. 2019* and *Aigner et al. 2020* adapted for needs of this study (Fig. 1)
- Five hearts explanted from dedicated animals
- Hearts were treated with
  - edge-to-edge mitral valve repair, mimicking a MitraClip® implantation (Fig. 2a)
  - a bicuspid mechanical mitral valve prosthesis (OpenPivotTM, 25 mm; Medtronic, Ireland), modified to enable leaflet rotation (0-90°) during the experiments (Fig. 2b and Fig. 3)

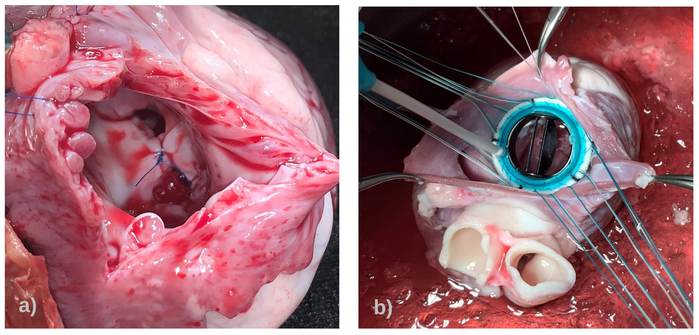

Fig. 2: a) View on the stitched and connected mitral valve leaflets through the left atrium. b) Implantation of rotatable bicuspid mitral valve prosthesis.

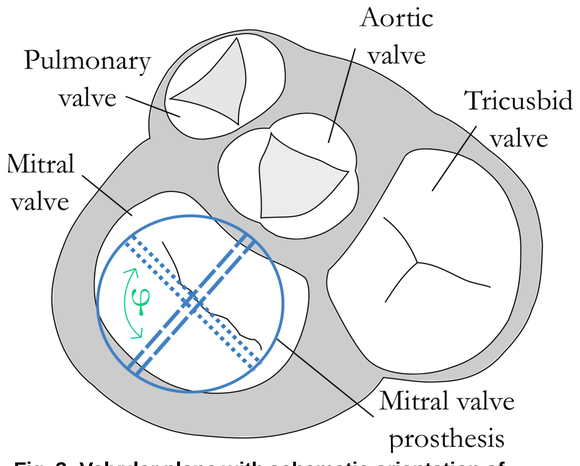

Fig. 3: Valvular plane with schematic orientation of the mechanical mitral valve prosthesis in anatomical (dotted) and anti-anatomical (dashed) position.

Study Protocol

- Continuous measurement of left atrial pressure, aortic pressure, arterial and coronary flow, left ventricular pressure volume loops in working mode after reanimation
- Qualitative flow visualization with ultrasound particle image velocimetry (*Aigner et al. 2020*) on B-mode ultrasound images with 150-200 frames/s and air-bubbles as tracers; applied for native and clipped mitral valve
- Quantitative measurements of hemodynamic parameters with prosthesis in anatomical (baseline) and anti-anatomical position (Fig.3), each held for 1 min before switching

Results

- Eight measurements in two hearts with rotatable prosthetic valve
- No considerable changes in mean arterial pressure (MA) and cardiac output (CO), see Fig. 4
- Trend towards decrease in left atrial pressure (LAP) and external work (EW) observed with valve in anti-anatomical position
- However, not statistically significant applying Wilcoxon signed-rank test (p-value<0.05)

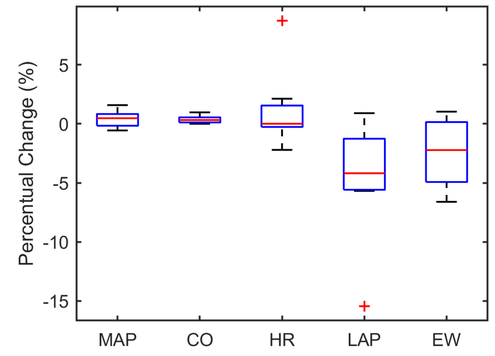

Fig. 4: Percentual changes in hemodynamic and cardiac mechano-energetic at a rotation of the mechanical valve from anatomical to anti-anatiomical position.

- Different flow structures during entire heart beat visible after edge-to-edge procedure (Fig. 5)
- Vortex formation shows more fractured pattern and remaining small vortices in apex area (Fig. 5b)

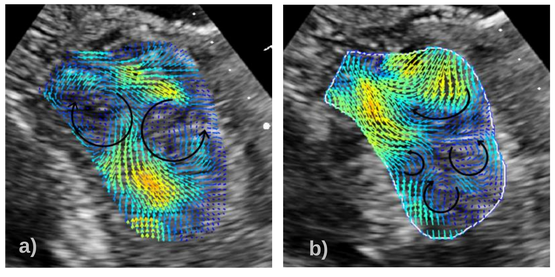

Fig. 5: Late diastolic left ventricular flow apatterns with a) native and b) clipped mitral valve

Discussion

- Feasibility of isolated heart setup for investigations of flow after valve clipping and mechano-energetics after rotatable valve implant shown
- Next step: measurement of both qualitative flow analysis and mechano-energetics simultaneously to delineate interaction between the two

contact: katharina.vellguth@charite.de

Source of images: Vellguth, K., Sündermann, S., Escher, … Granegger, M. (2020). Intraventricular flow features and cardiac mechano-energetics after mitral valve interventions – feasibility of an isolated heart model. Current Directions in Biomedical Engineering, 6(1). https://doi.org/10.1515/cdbme-2020-0028