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

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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

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)

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)

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

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


Fig. 1: Isolated heart setup during working mode

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.

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

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