MEDIZINISCHE UNIVERSITÄT WIEN

Christian Doppler Laboratory
for the
Diagnosis & Regeneration
of Cardiac and Thoracic Diseases

Diploma Thesis

Alpha-Gal specific humoral immune response after implantation of bioprostheses in cardiac surgery

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Betreuer: Univ.-Doz. Dr. Hendrik Jan Ankersmit

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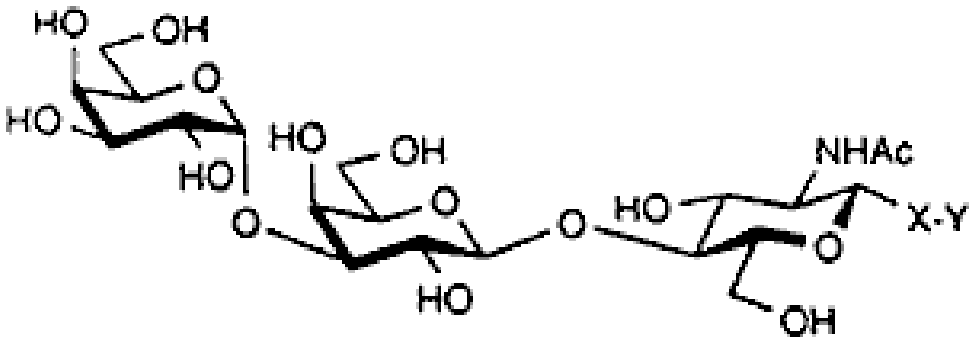
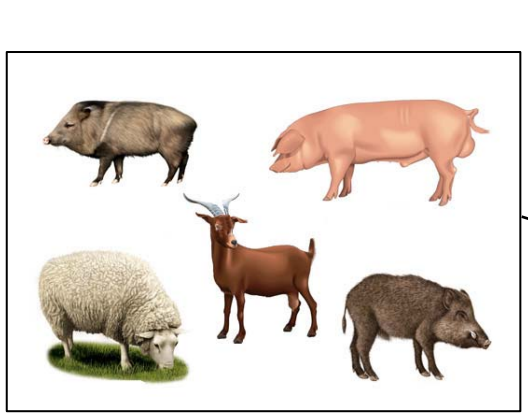
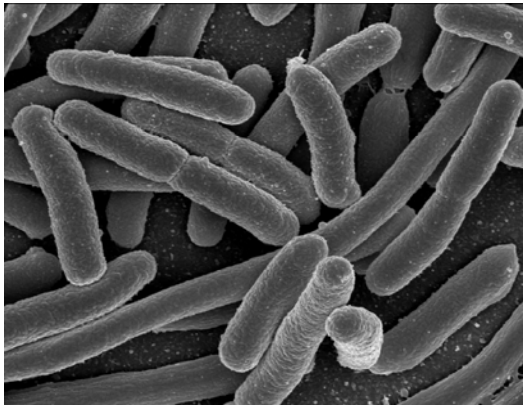
Alpha-Gal

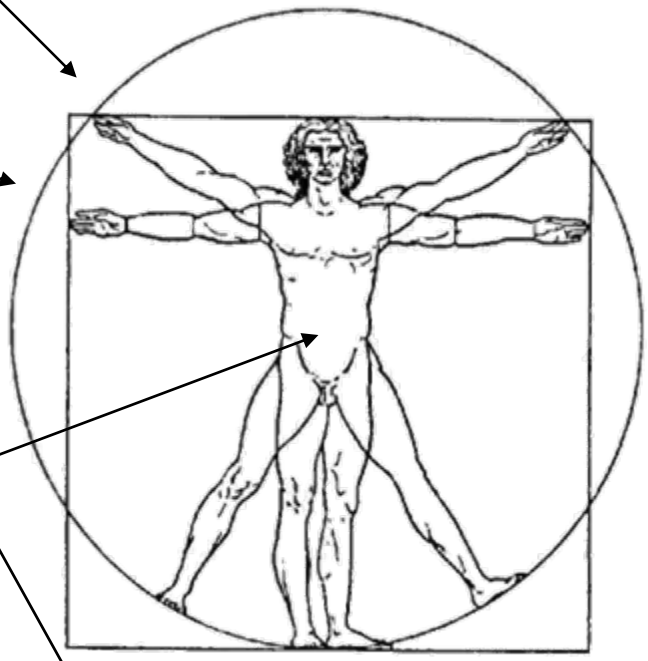


Galα1,3-Galβ1–4GlcNAc-R

Alpha-Gal







Anti-Gal AB (IgM, IgG, IgA) 1-2%

Heart valve replacement

vs

Heart valve replacement

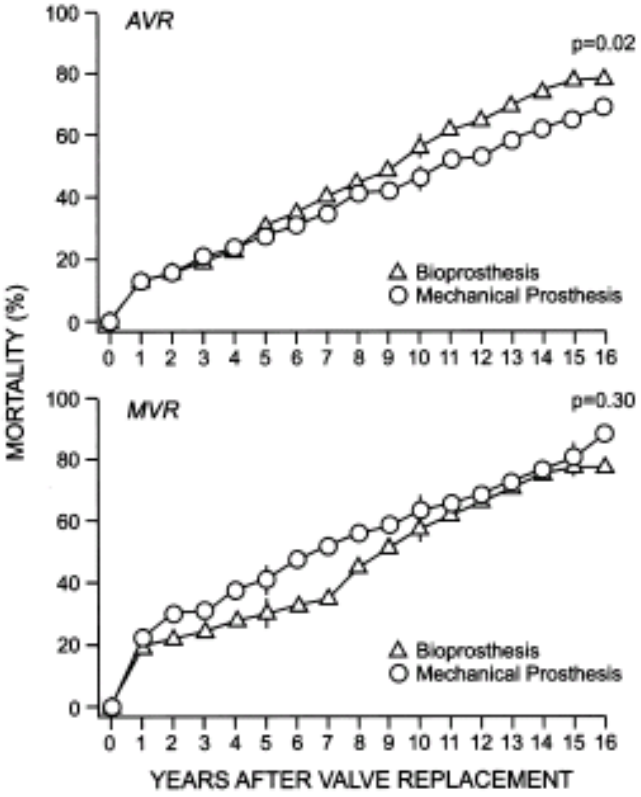


Figure 1. Death from any cause (including operative mortality). AVR = aortic valve replacement; MVR = mitral valve replacement.

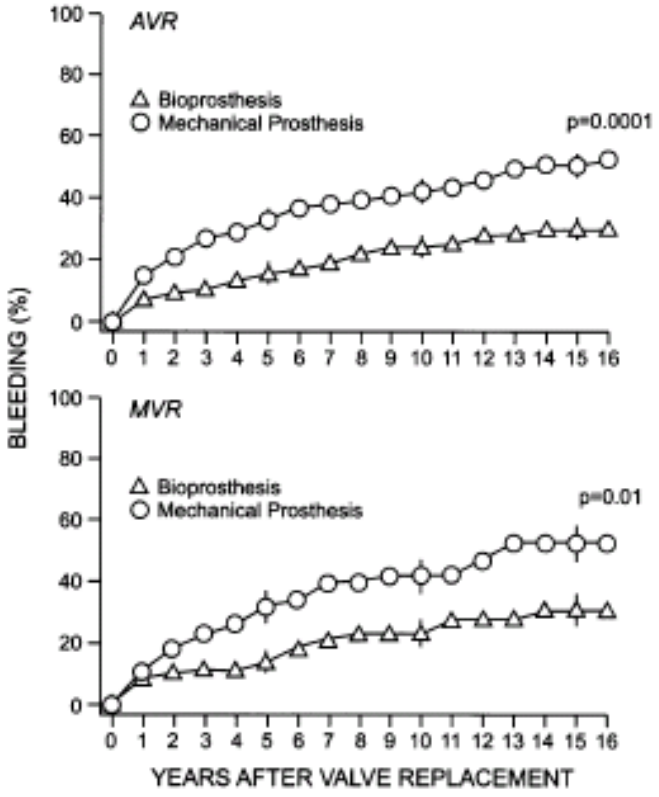


Figure 3. One or more clinically significant bleed(s). AVR = aortic valve replacement; MVR = mitral valve replacement.

Hammermeister et al. J Am Coll Cardiol. 2000 Oct;36(4):1152-8.

Heart valve replacement

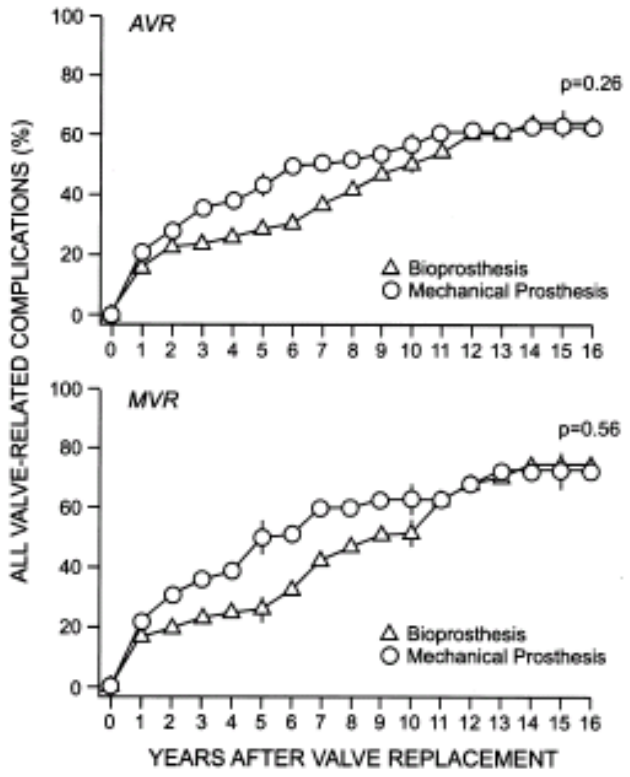


Figure 2. Occurrence of one or more valve-related complications (bleeding, endocarditis, systemic embolism, nonthrombotic valve obstruction, valvular regurgitation or valve thrombosis). AVR = aortic valve replacement; MVR = mitral valve replacement.

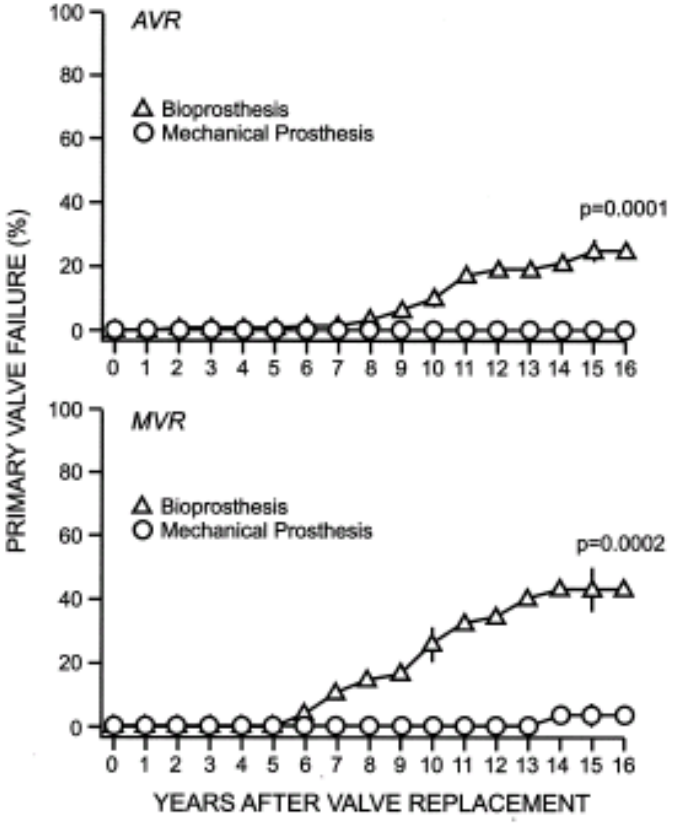


Figure 4. Primary valve failure (nonthrombotic valve obstruction or central valvular regurgitation). AVR = aortic valve replacement; MVR = mitral valve replacement.

Hammermeister et al. J Am Coll Cardiol. 2000 Oct;36(4):1152-8.

Heart valve replacement

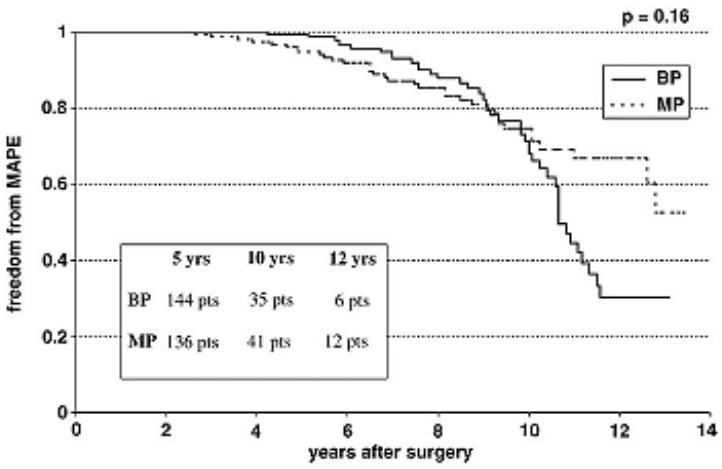


Figure 3 Freedom From MAPE for Patients Who Received Either MP or BP Valves

MAPE = major adverse prosthetic-related events; other abbreviations as in Figure 1.

Table 4 Linearized Rate of Valve-Related Events

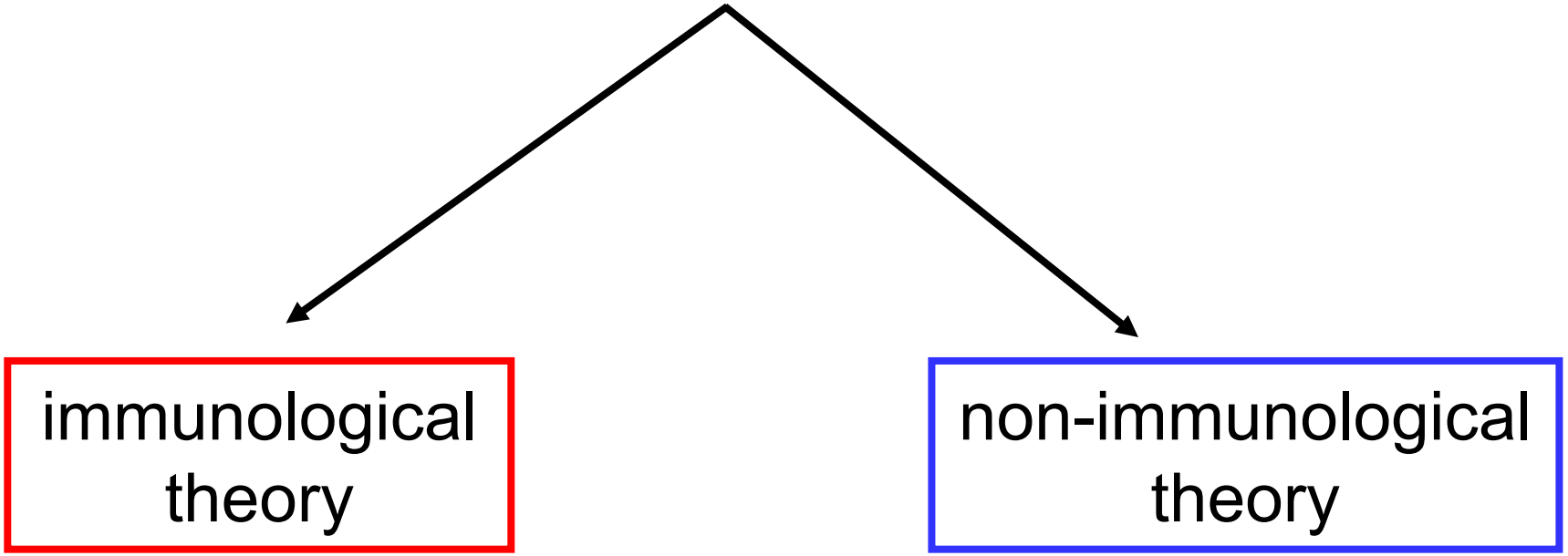
Variables	MP (n = 149) %/pt-yr (95% CI)	BP (n = 147) %/pt-yr (95% CI)	p Value
Thromboembolism	0.54 (0.14–0.94)	0.24 (0.03–0.51)	0.3
Bleeding	1.47 (0.81–2.13)	0.72 (0.25–0.19)	0.08
Endocarditis	0.38 (0.04–0.72)	0.24 (0.03–0.51)	0.7
Valve failure	0	2.17 (1.35–2.98)	0.0001
Valve thrombosis	0.23 (0.03–0.49)	0	0.2
Nonstructural dysfunction	0.23 (0.03–0.49)	0.24 (0.03–0.51)	0.6
Reoperation	0.62 (0.19–1.05)	2.32 (1.48–3.18)	0.0003

CI = confidence interval; other abbreviations as in Table 1.

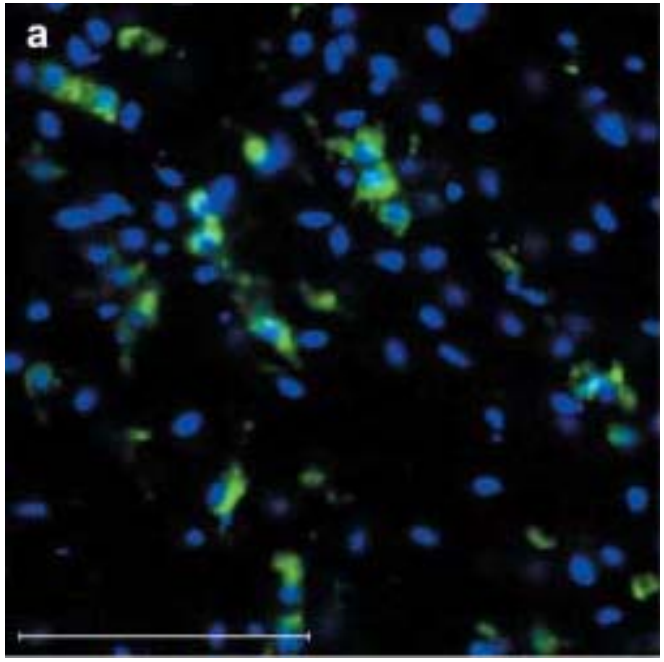
Stassano et al. J Am Coll Cardiol. 2009 Nov;54(20):1862-8.

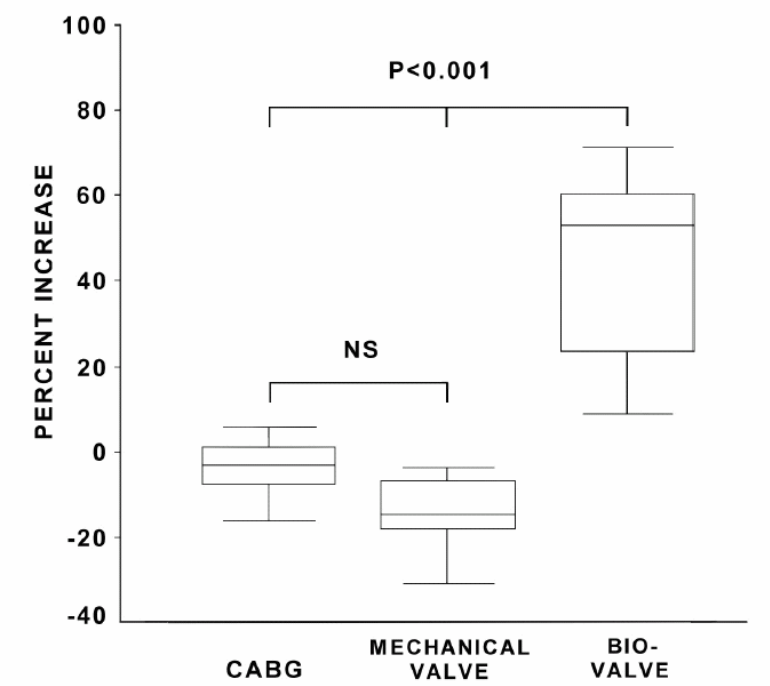
Rationale

Why do bioprostheses fail to function?



Former Work





Konakci et al. Eur J Clin Invest. 2005 Jan;35(1):17-23.

Aims of the study

- Does this specific immune response proceed?
- Isotype switch to IgG?
- Which subclass is affected?
- Dynamics of α-Gal-bearing cells in the valve matrix?

Demographics

Biological valve group

n=19

mean age 74 ± 1.1 years

serum samples pre OP, 10d and 90d post OP

Mechanical valve group

n=8

mean age 56 ± 7.8 years

serum samples pre OP, 10d and 90d post OP

Bioprosthetic tissue samples

explantation due to valve malfunction or death

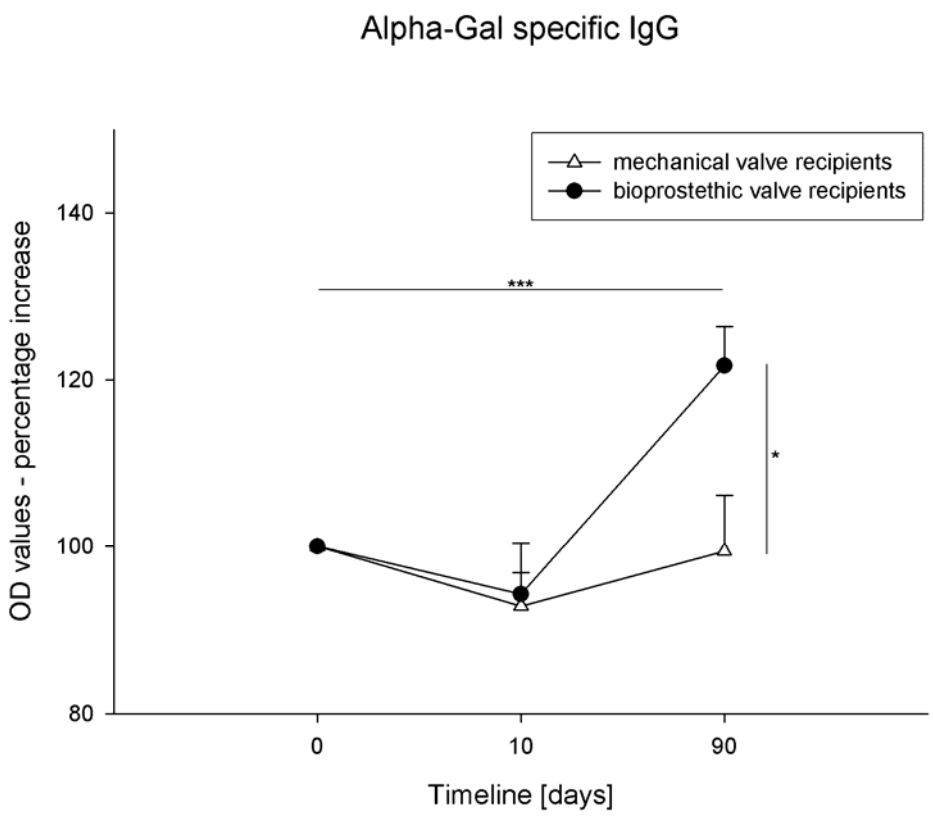
explantation after 1 week n=1

explantation after 12-15 months n=2

Methoden

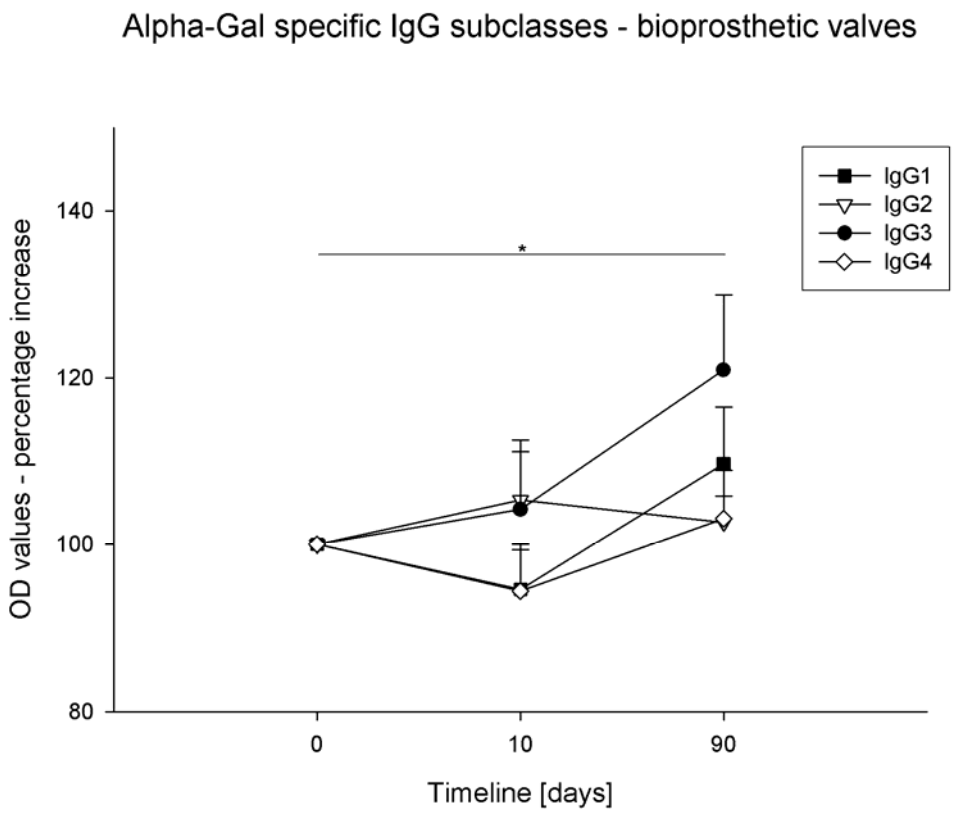
- ELISA
- CLSM
- SPSS

Results



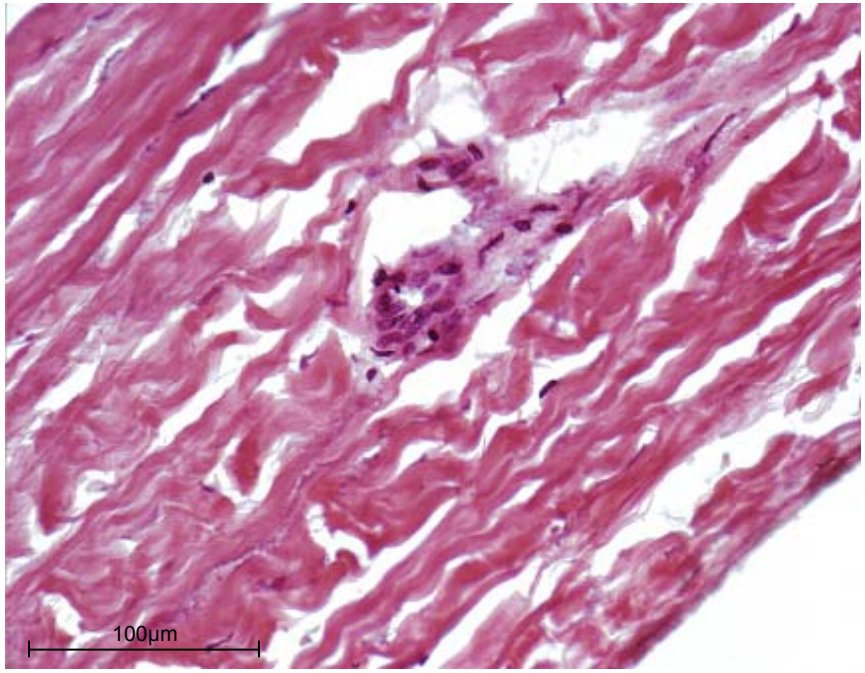
α-Gal specific IgG increase 3 months after bio valve implantation (n=19, ***p<0.001) compared to preoperative values and compared to a control group (n=8, *p < 0.05)

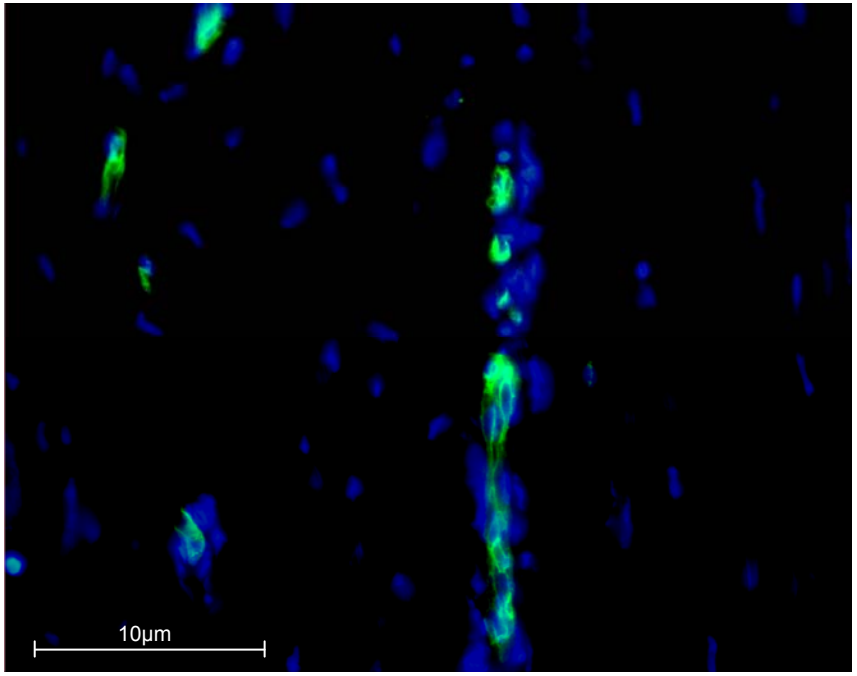
Results



IgG3 subclass levels are significantly increased (*p<0.05) compared to other subclasses and to control group (p < 0.01, data not shown)

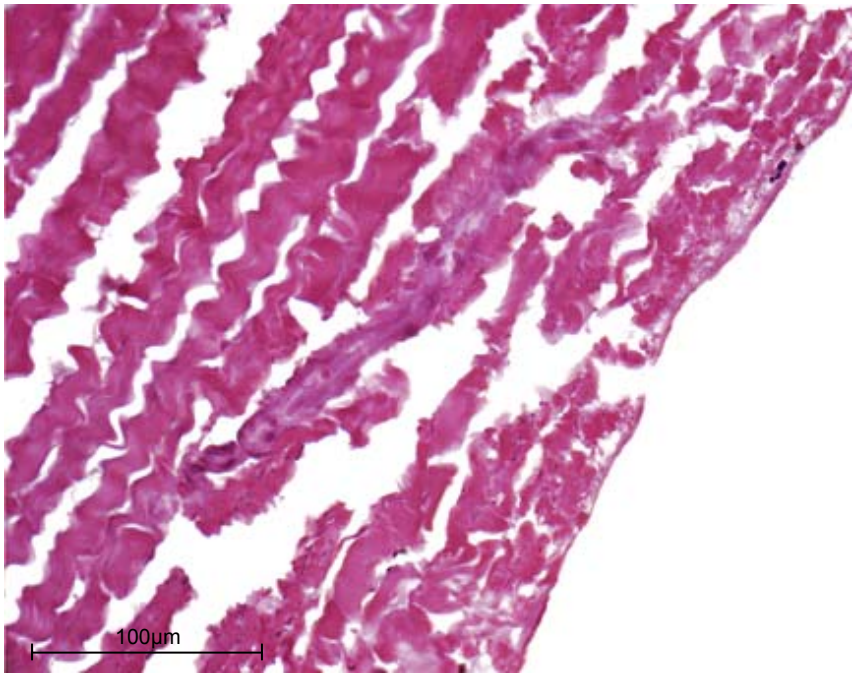
Results

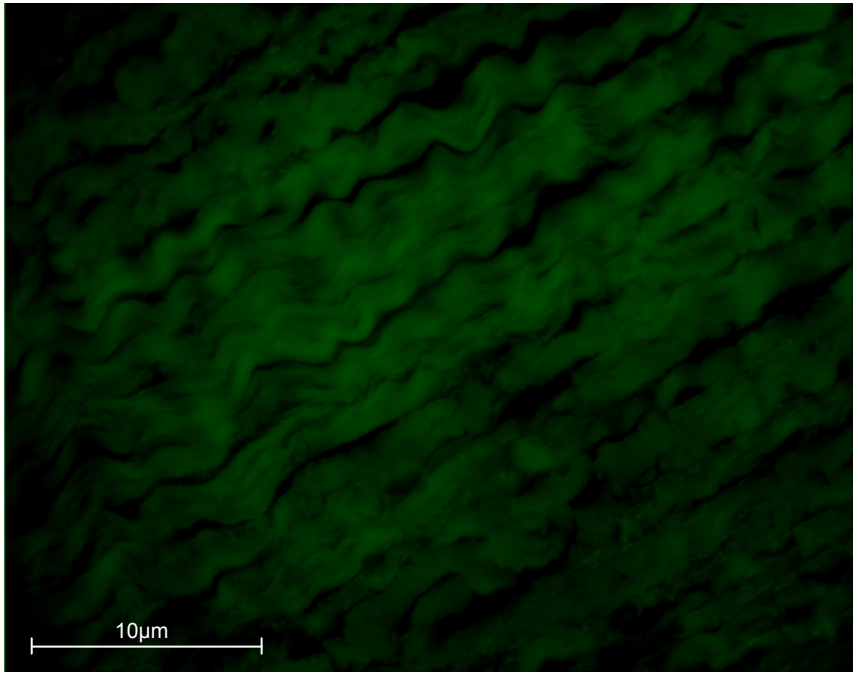




bioprosthesis explanted after 1 week

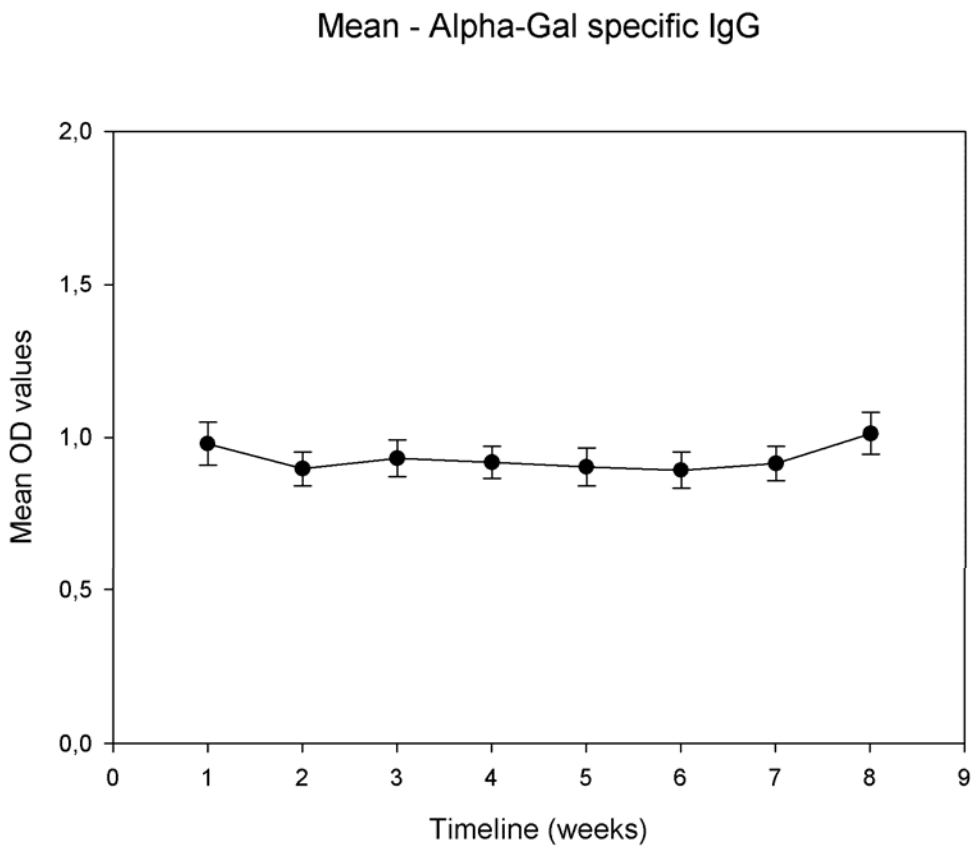
Results





bioprosthesis explanted after 1 year

Anti-Gal titers in healthy adults



n=21

Conclusion

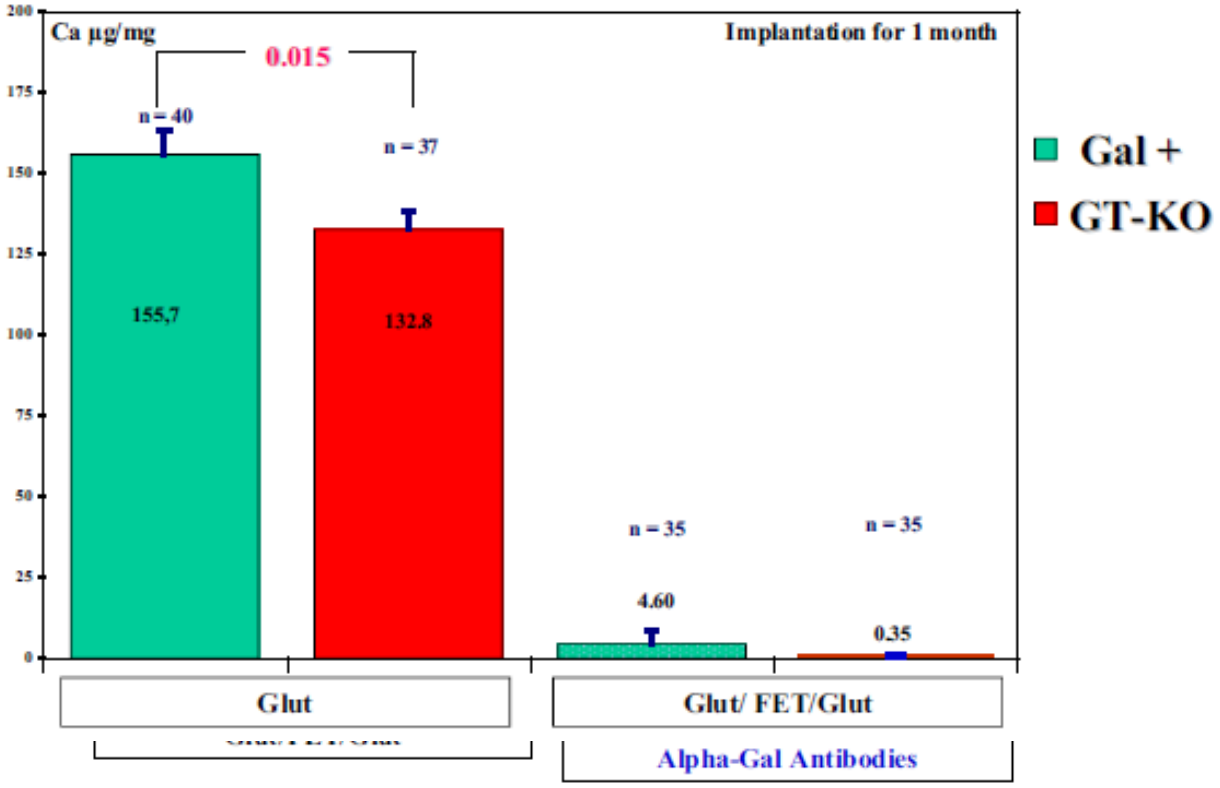
- Antibody opsonization
- Activation of macrophages → MMPs
- Activation cascade → APC → Th-cell → cytokine/chemokine release, cell recruitment, B-cell differentiation →
- Mild IgM / IgG response

Discussion

- J Heart Valve Dis. 2010 Jan;19(1):124-30. **Anti alpha-gal immune response following porcine bioprosthesis implantation in children.** Park CS, Park SS, Choi SY, Yoon SH, Kim WH, Kim YJ.

- J Heart Lung Transplant. 2010 May;29(5):538-43. Epub 2009 Dec 29. **Gal knockout pig pericardium: new source of material for heart valve bioprostheses.** Lila N, McGregor CG, Carpentier S, Rancic J, Byrne GW, Carpentier A.

Discussion



Lila et al. J Heart Lung Transplant. 2010 May;29(5):538-43.

Herzlichen Dank!