

PW4-2

Heart valve tissue-engineered matrices attenuate monocyte binding and procoagulant responses in human endothelial cell cultures exposed to *S. aureus*, *S. sanguis* and *S. epidermidis*.

Heying, R. (1,4), Eyskens B. (4), Cools B. (4), Wolf C. (2), Beekhuizen H. (3), Jockenhoevel S. (5), Hoylaerts M.F. (6), Schmidt K.G. (1), Schroten H. (2,7)

Department of Pediatric Cardiology, University Children's Hospital, Duesseldorf, Germany (1), Pediatric Infectious Diseases, Department of General Pediatrics, University Children's Hospital, Duesseldorf, Germany (2), Department of Infectious Diseases, Leiden University Medical Center, Leiden, the Netherlands (3), Department of Pediatric Cardiology, UZ Leuven, Belgium (4), Department of Applied Medical Engineering, RWTH Aachen, Germany (5), Center for Molecular and Vascular Biology, KU Leuven, Belgium (6), Pediatric Infectious Diseases, Department of Pediatrics, University Hospital Mannheim, Heidelberg University, Germany (7)

Introduction: Infective endocarditis (IE) remains a serious complication after heart valve replacement. Autologous valves constructed by matrix-based tissue engineering are under investigation to increase biocompatibility. The impact of the underlying matrix on the risk to develop IE is not known. IE is characterized by bacterial adhesion and subsequent interactions of disseminating bacteria with endothelial cells (ECs) and monocytes, evoking endothelial proinflammatory and procoagulant activity, leading to heart valve destruction.

Methods: In the present study we therefore have seeded human ECs on a fibrin vs. collagen gel matrix, and, at confluence, infected them with *Staphylococcus aureus*, *Streptococcus sanguis* and *Staphylococcus epidermidis*.

Results: Especially *S. aureus* infected ECs grown on fibrin (4.2 % of the inoculum) and collagen (3.7 %) matrices, even more than on ECs grown on non-coated plates (1.2 %; $p < 0.01$). This was associated with higher monocyte adhesion (61% on fibrin and 43% on collagen) than in the control cultures (30%, $p < 0.01$), even when the EC surface expression of ICAM-1 and VCAM-1 remained comparable. The collagen matrix attenuated the *S. aureus* induced MCP-1 expression 2.0 fold, compared to the non-coated control ECs. This reduction prominently coincided with a 4.2-5.0 fold reduction in the procoagulant activity, triggered in ECs grown on non-coated wells, as a consequence of tissue factor expression by ECs, further stimulated by EC-bound monocytes. Moderate responses were seen upon infection with *S. sanguis* and *S. epidermidis* for both gel matrices.

Conclusions: Thus, even when fibrin and collagen gel matrices equally increase bacterial adhesion, and subsequent monocyte adhesion to infected ECs, these matrices modulate EC responses to these stimuli, resulting in attenuated cytokine production and attenuated adherent monocyte-dependent tissue factor production by the ECs. Further investigations will need to confirm that also in vivo, EC-matrix interactions can attenuate EC responses to bacteria and inflammatory cells to reduce IE at infected endovascular sites.