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In endocarditis Staphylococcus aureus and Staphylococcus lugdunensis can adhere to the heart valve by binding to von Willebrand Factor

Laurens Liesenborghs*[1], Jorien Claes[2], Marijke Peetermans[3], Rafael Veloso[3], Marleen Lox[3], Willy Peetermans[4], Thomas Vanassche[3], Marc F. Hoylaerts[2], Peter Verhamme[3]

[1]*Uz Leuven; Cardiovascular Sciences*

[2]*Ku Leuven; Department of Cardiovascular Sciences*

[3]*Ku Leuven*

[4]*Uz Leuven; Internal Medicine*

Background: Both *Staphylococcus aureus* and *Staphylococcus lugdunensis* are feared causes of endocarditis, but it is insufficiently understood how they are able to infect the heart valves. Bacteria must first bind to the valve endothelium before they can grow to a mature vegation. However, their adhesion is hindered by the high blood flow going over these valves, because this blood flow creates shear stress, a frictional force that bacteria need to overcome. During arterial bleeding or thrombosis, blood platelets adhere under shear stress by binding to von Willebrand factor (VWF), a molecule that only under shear exposes its crucial binding domains. We thus investigated whether *S. aureus* and *S. lugdunensis* also bind VWF to adhere to the heart valves.

Material/methods With flow chamber technology, we studied the adhesion of *S. aureus* and *S. lugdunensis* to VWF and endothelial cells under shear stress. Furthermore, we used a mesenteric microvascular perfusion mouse model to evaluate bacterial adhesion to the vessel wall. In this model we could visualize the interaction between fluorescently labeled bacteria and the vasculature in real time. We also developed a new endocarditis mouse model to study early bacterial adhesion to the aortic valve. In this model we injected fluorescent bacteria in the bloodstream and subsequently activated the valve endothelium by locally infusing histamine through a catheter that was placed in the carotid artery. With confocal microscopy we could measure the adhesion of *S. aureus* and *S.*

lugdunensis to the heart valves. Using VWF knockout mice, we investigated the role of VWF in early bacterial adhesion to heart valves.

Results: Both *S. aureus* and *S. lugdunensis* were able to bind to VWF under shear stress, this in contrast to other staphylococci that seldom cause endocarditis. In case of inflammation or blood vessel damage, activated endothelial cells will release VWF. We could therefore show that *S. aureus* and *S. lugdunensis* adhered to activated endothelial cells by binding to VWF. Also, in the microvascular perfusion model we could prove that VWF release enables bacteria to overcome shear stress and adhere to the vessel wall. In our new endocarditis mouse model we showed that *S. aureus* and *S. lugdunensis* hardly adhered to resting valve endothelium. However, by locally infusing histamine and inducing endothelial activation we could make these bacteria stick to heart valves and induce endocarditis. In VWF knockout mice however binding of both *S. aureus* and *S. lugdunensis* to heart valves was significantly reduced.

Conclusions: *S. aureus* and *S. lugdunensis* overcome shear stress by binding to VWF. This allows them to bind and infect the hearth valves and may explain why *S. aureus* and *S. lugdunensis* are so effective in causing endocarditis, compared to other staphylococci.