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Another report on unfavourable long-term outcome following implantation of the  
Shelhigh No-React™ tube valved graft

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28 Totally biological valved conduits like the Shelhigh No-React™ implant were expected to offer  
29 several advantages for patients requiring aortic root replacement in whom a tissue valve would  
30 be the preferential option. The stentless design of the valve promised a better hemodynamic  
31 performance following implantation of a stented valve. Furthermore traditionally glutaraldehyde-  
32 preserved biological valves tended to calcify, especially in younger patients, whereas the novel  
33 No-React™ detoxification process promised to ensure stable tissue cross-linking, resulting in  
34 less calcification and tissue deterioration. This was demonstrated in the animal model (1).  
35 Finally, availability of the conduit from the bench in the most commonly used sizes as opposed  
36 to self-constructed valved tubes and homografts is considered as additional advantage.

37 In this paper, the group of Zürich's University Hospital reports additional conflicting mid-  
38 to long-term results following implantation of the former Shelhigh conduit in aortic root ±  
39 ascending aortic position (2). Their initial experience, like ours and that of other groups,  
40 was satisfying regarding the implantability of the graft, the postoperative hemodynamics  
41 and the short-term clinical results (3,4). More than 15 years ago, we optimistically  
42 implanted this graft when a tissue valve was found to be the best solution for patients  
43 requiring aortic root replacement. Years ago, we were the first group to describe some  
44 negative experience with the Shelhigh conduit since several patients presented with  
45 sudden disintegration of the graft, leading to unexpected severe complications that  
46 required most difficult redo-operations (5). Unfortunately, we were not able to find which  
47 patients may be at increased risk for such complications: no statistical significant  
48 relationship was found regarding the timing of the operation (planned versus emergency)  
49 nor regarding the underlying pathology (aortic root dilation, acute type A aortic dissection  
50 or aortic valve endocarditis with destruction of the aortic root) or the implantation  
51 technique (interrupted versus continuous sutures). Review of the literature revealed that  
52 other institutions have observed similar singular cases.

53 The present analysis by the Zürich's group confirms our observations and reports similar mid- to  
54 long-term adverse outcome with a relatively high rate of premature death, "a very high rate of  
55 reoperations due to endocarditis, aorto-ventricular disconnection and structural valve failure" (2).  
56 The authors concluded that this may be potentially connected to the nature of the conduit. In  
57 fact looking at the details of this small series, there are several patients that died because of  
58 what the authors called unoperable intraoperative status. A similar case report was published by  
59 Tjan et al. from Münster, where the only solution to the uncontrollable intraoperative situation,  
60 was the removal of the whole heart and the construction of a bi-ventricular assist device as a  
61 bridge to transplantation (6). We have fortunately never encountered an unoperable  
62 intraoperative situs although the amount of destruction of the aortic root was surprising and  
63 technically extremely challenging in all cases we had to re-operate.

65 In that sense, these observations are in line with other reports: the summarized experience of  
66 Calderon presented at the meeting of the Society of Heart Valves Diseases a series of 51  
67 consecutive patients who received the Shelhigh conduit, with a reoperation rate of 13% (7/51)  
68 after Shelhigh conduit implants (7). All patients of this series demonstrated a similar finding to  
69 that described by the Zürich group, with a disintegration of the proximal anastomosis at the level  
70 of the aortic annulus within one year after implantation. The intraoperative findings were very  
71 similar with pseudo-aneurysmal formation and sterile abscess formation. Another group in the  
72 Netherlands published a similar experience in 2011 (8).

73 Extensive work from a Munich group has independently focused on the No-React<sup>®</sup> patch from  
74 the same provider and used for pericardial closure in 127 patients. Also in this location, a high  
75 incidence of sterile abscess formation was found. Bacterial growth was never found and the  
76 underlying mechanism of abscess formation was suspected to be a xenogenic complement  
77 mediated graft rejection (9).

78 To share our experience, we exchanged intensively with the dutch group and presented our  
79 common results at the 2015 EACTS meeting (10). The series included 291 consecutive patients  
80 with a mean age of 69 years. During a mean follow-up of  $70.3 \pm 53.1$  months, 29 patients  
81 (11.1%) died from unknown reasons and the overall rate of re-operation of 8.6% (25 patients)  
82 was worrisome. We found similar causes leading to re-operation: infection of the conduit (n=9),  
83 aorto-ventricular disconnection (n=4), pseudo-aneurysm formation (n=4) and structural valve  
84 degeneration (n=8).

85 The results presented by the Zurich group are even worse than ours with a re-operation rate  
86 close to 20% and a surprisingly high rate of unexplained deaths. For all centers that have  
87 implanted the Shelhigh conduit, we strongly recommend long-term follow-up, especially in  
88 asymptomatic patients, since unexpected findings may be observed independently of structural  
89 valve degeneration.

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