No-React® Injectable BioPulmonic™ valves re-evaluated: discouraging follow-up results

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Received 26 May 2015; received in revised form 2 July 2015; accepted 6 July 2015

Abstract

OBJECTIVES: The No-React® Injectable BioPulmonic™ valve (BioIntegral) was introduced for minimally invasive off-pump replacement of the pulmonary valve almost 10 years ago. We present our mid- to long-term follow-up results.

METHODS: We conducted a retrospective analysis of all 7 patients treated at our institution at the median age of 9 (range 1–24) years. The children underwent cardiac catheterization when worsening strain on the right heart was suspected after examining their medical history and/or observing significant changes on echocardiography.

RESULTS: After a median follow-up period lasting 5.2 (range 0.7–6.7) years, all patients presented the indication for recatheterization, particularly because the maximum instantaneous velocity measured by Doppler had revealed systolic gradients of a median 63 (dP 18–74) mmHg across the right ventricular outflow. Catheterization confirmed severe stenosis in 2, and moderate stenosis together with moderate insufficiency in 4 patients. We observed two principal failure mechanisms: technical problems resulting from poor alignment to the right ventricular outflow tract and structural problems leading to neointimal proliferation even in cases with appropriate prosthesis positioning. At median of 5.7 (0.7–7) years after implantation, 6 of the 7 patients underwent valve rereplacement. Redo surgery was necessary in 3, and percutaneous valve-in-valve implantation in the remaining 3 patients. Histological analysis of two explanted valves confirmed significant neointima proliferation and thickened valve cusps leading to stenosis of the graft.

CONCLUSIONS: These mid-term results after implantation of the No-React® Injectable BioPulmonic™ valve are disappointing. Graft failure was mainly due to neointimal formation and valve malposition.

Keywords: No-react injectable valve • Stented valve • Congenital heart disease • Minimally invasive revalvulation • Valve-in-valve

INTRODUCTION

The No-React® Injectable BioPulmonic™ valve (BioIntegral Surgical, Inc., Mississauga, ON, Canada) was introduced almost 10 years ago as a helpful tool for minimally invasive off-pump replacement of the pulmonary valve [1, 2]. The acute and initial results were encouraging [1–5], and have been recently updated by another short-term series [6]. We carefully followed our patient cohort to evaluate the mid- to long-term performance of this stented type of No-React® valve.

PATIENTS AND METHODS

All data were analysed retrospectively. The pulmonary valve was replaced with the No-React® injectable valve in 7 patients with a median age of 9 (range 1–24) years at our institution between 2006 and 2010. Our implantation strategy and technique have been reported [3, 5]. Our outpatient department followed all these 7 patients carefully. We considered re-evaluating them via cardiac catheterization when worsening strain on the right heart was suspected and when their medical history and/or significant changes on echocardiography justified it. After obtaining written informed consent, the patients underwent cardiac catheterization under deep sedation or general anaesthesia. We considered a borderline peak-to-peak gradient and right ventricle (RV)-to-systemic-pressure-ratio an indication for a stress-test with dobutamine when the medical history had revealed recurrent chest pain and/or tightness during physical exertion. This was performed via intravenous infusion of dobutamine maintaining a rate of 8–12 µg/kg/min aiming to raise the systemic blood pressure to systolic 180–200 mmHg as a reference for a normal blood pressure response, while measuring simultaneously the peak-to-peak gradient between the RV and main...
The pulmonary artery (MPA), as well as estimating the RV-to-systemic-pressure ratio. The decision for percutaneous pulmonary valve-in-valve implantation (PPVI) or surgical pulmonary valve replacement (PVR) was made in the interdisciplinary team conference.

**Histological examination**

After surgical removal, the tissue specimens containing the valved conduit were fixed in formalin. After that, the specimens were embedded in the hard resin methyl methacrylate (Technovit 9100, KULZER & Co, Wehrheim, Germany), hardened and subsequently sectioned in slices of 0.5 mm using a diamond cutter (300 CP, Exakt GmbH, Norderstedt, Germany). These slices were ground down to 10–30 µm using a rotational grinder (400 CS, Exakt GmbH, Norderstedt, Germany). Standard staining was performed with Richardson blue.

**Statistics**

Data were processed using Prism 6.0 (GraphPad Software, Inc.) and are expressed as median (range). Freedom from valve replacement is presented in a Kaplan–Meier Curve.

**RESULTS**

The patients’ primary diagnoses, valve size and age at implantation as well as relevant follow-up data are shown in Table 1.
patients had received antiplatelet ASS monotherapy for the initial 6 months (Patients 4 and 6), 1 patient with an artificial aortic valve needed anticoagulation with phenprocoumon (Patient 5). Valve-related adverse events did not occur. None of the patients presented apparent mechanical dysfunction of the sub-pulmonary RV. At a median age of 15 (range 2–28) years, all patients presented a reasonable indication for cardiac catheterization, particularly because of the maximum instantaneous velocity measured by Doppler revealing systolic gradients of median 63 (range dP 18–74) mmHg across the right ventricular outflow (RVOT). The

Figure 2: A 25 mm No-React® Injectable BioPulmonic™ valve 6 years after implantation (Patient 2): significant reobstruction due to an impressive neointimal built-up; stent-struts anchored deeply (A/B). RVOT-ballooning including left coronary artery angiography simultaneously (C/D). After pre-stenting (one Covered CP Stent (TM) and one CP Stent (TM) 39 mm, NuMed), revalvulation (Melody TPV, Medtronic) and redilatation with a 24/20 mm ultrahigh pressure balloon inflated up to max. Twenty-two bar (Atlas gold, Bard) final result w/o residual gradient (E/F). RVOT: right ventricular outflow.
systolic gradient was markedly elevated in all patients but one. The one exception (dP only 18 mmHg) had suffered recurrent episodes of stabbing pectoral pain and palpitations which led to invasive re-evaluation, especially to rule out any coronary artery compression by the valved stent. Moreover, we detected moderate pulmonary insufficiency (PI) in 4 of these 6 patients.

These findings were confirmed by catheterization after a median follow-up period of 5.2 (range 0.7–6.7) years; data are illustrated in Table 2. All procedures were performed in intervention-al standby under either deep sedation or general anaesthesia. Five of the 7 patients had an RV-to-systemic-pressure ratio rising to at least 50%. In this setting, dobutamine stress unmasked borderline

Figure 3: Macroscopic view of the partially thickened valve cusps (A patient 1; B patient 4). Histology (Richardson blue stain) demonstrates significant thickening and retraction of valve cusps (C patient 1; D patient 4) and significant pseudointima proliferation containing fibromuscular cells embedded in abundant extracellular matrix without accumulation of inflammatory cells (E patient 1; F patient 4).
RV-to-MPA gradients in three patients (with additional PI), and explained their medical history, with symptoms occurring during physical exertion.

Given these diagnostic findings, 6 of the 7 patients underwent surgical or interventional valve replacement after a median interval after No-React valve implantation of 5.7 (range 0.7–7) years (Fig. 1). We observed varying degrees of intimal reaction in all No-React® valves on fluoroscopy. Two patients revealed severe thickening as a striking example of overshooting neointimal built-up (Fig. 2). On histological analysis, the narrowing of the lumen was caused by significant pseudo-intima proliferation and remarkable thickening of valve cusps (Fig. 3). Nevertheless, we detected no accumulation of inflammatory cells locally or in the surrounding tissue, thus excluding acute infection as a possible cause for proliferation.

The valved stent’s tilt was a concern. We observed an imperfect alignment with the axis of the RVOT (RVOT-to-MPA axis) in 3 of our patients most likely attributable to the initial implantation process (‘injection’) and leading to a detrimental orientation (Figs 4–6). Those 3 patients presented sub-valvular narrowing, an asymmetric flow pattern and considerable paravalvular leakage.

While the valved stent may provide a stable landing zone for a valve-in-valve procedure, its stiff struts and hooks anchor deeply when attached to the vessel wall, creating a considerable risk for perforation, whereas the self-expandable nitinol-frame enables the edges to be reshaped and flared (e.g. to adjust a covered stent in case of perforation or paravalvular leakage).

Finally, we observed the immediate proximity of the strut-jags to the left coronary artery, especially the left-anterior descending, in 3 patients—fortunately with no obvious coronary narrowing in any of them. However, if the stent was significantly tilted at the same time, the risk for coronary compression after altering the RVOT geometry via additional stenting was greater, thus we opted for surgery in 2 of the patients (Fig. 5).

PVR by redo surgery was uneventful in 3 patients: the No-React® Injectable valve was completely resected and replaced in 1 patient by a 24 mm homograft, in 1 patient by a 25 mm Medtronic Hancock® prosthesis (Medtronic, Minneapolis, MN, USA) and in another by a 14 mm Contegra® (Medtronic) conduit. Three patients underwent high-pressure ballooning (Atlas, Bard, Tempe, AZ, USA) of the No-React® valve followed by PPVI with the Melody® valve (Medtronic): 1 patient as a two-stage procedure with 2 CP prestents (CCP 39 mm, bare CP 39 mm; NuMed,

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**Figure 4:** A 29-mm No-React® Injectable BioPulmonic™ valve 7 years after implantation (Patient 1): valved stent tilted with horizontal orientation, not aligned to the right ventricular outflow axis and with consecutive sub-valvular narrowing; stent-struts deeply anchored when attached to the wall, moderate degree of neointimal proliferation (A/B). Test-balooning (semi-compliant Cristal balloon (Balt, Montmorency, France) 25/50 mm) and simultaneously performed angiography via the longsheath unmasked considerable paravalvular leakage on the left-anterior margin (C/D). We also noted close proximity of the caudal struts to the LAD artery (not shown) and decided against percutaneous re-revalvulation in this setting. LAD: left-anterior descending.
Hopkinton, NY, USA; another as a one-stage with a bare Andra
prestent (AS XXL 43 mm; Andramed, Reutlingen, Germany) and
again as a two-stage in the third patient with two prestents
(custom-made CCP 55 mm and AS XXL 43 mm), respectively.
Both PVR and PPVI have so far delivered good results in the 6
retreated patients on short-term follow-up.

DISCUSSION

In this retrospective analysis, we report on our mid- to long-term
follow-up results after implantation of the No-React® Injectable
valve in 7 patients.

We documented disappointing longevity in conjunction with
freedom from re-replacement in just 14% after 7 years. The
reasons for replacement were severe neointimal reaction of the
No-React® valve in 3 patients and imperfect positioning from the
initial implantation (‘injection’) in 3 others. Interventional revalv-
ulation was feasible in 3 patients, whereas 3 required surgical valve
exchange. We observed no deaths or major morbidity following
the redo surgery and interventions.

The No-React® Injectable valve was introduced as a modern sur-
gical valve replacement for minimally invasive and even off-pump
procedures [1–6]. The potential advantages were ease of implant-
ation, favourable tissue constitution and a perfect landing zone for
a percutaneous valve-in-valve. We introduced the valve in our
clinical practice with these theoretical advantages in mind, and
were satisfied with the initial performance [3, 5]. However, we
decided to wait to see the mid-term results before using the pros-
thesis on a broader basis. As a matter of fact, we and others
observed difficulties with the introducer system and suggested
modifications with a more flexible one. We decided to wait for
this technical improvement which did not make it to clinical use
so far. In the meantime, we observed
initial problems with the few implanted prostheses and stopped
the programme.

The search for the perfect prosthesis for the pulmonary valve is
almost as old as congenital cardiac surgery itself [7–10]. A few
centres prefer mechanical prostheses in this context and have had
acceptable results. However, such valves are limited by the need for
life-long anticoagulation, moreover, valve thrombosis seems to be a
frequent event [11, 12]. Multiple xenograft prostheses and homo-
grafts have been tested and are being implanted via several access
routes. The surgical versus interventional valve implantation alter-
natives are discussed in multidisciplinary teams, and there are dif-
ferential indications. The surgical implantation of homografts of

Figure 5: A 29-mm No-React® Injectable BioPulmonic™ valve 7 years after implantation (Patient 4): obstruction at the level of the valve due to moderate tilt of the stent and neointimal proliferation resulting in an inner lumen of only 16.5–18 mm (A/B). Coronary angiography indicated the caudal strut-jags immediately next to the LAD (C/D). We refrained from percutaneous re-revalvulation due to the potential risk to the LAD after changing RVOT geometry via additional stenting. LAD: left-anterior descending; RVOT: right ventricular outflow.
bovine jugular vein graft (Contegra®, Medtronic) and other stented biological conduits (e.g. Hancock® valved conduit, Medtronic) has taken place with good long-term results [13, 14]. Homografts have performed quite favourably in pulmonary position [15]. The Contegra® has often been used with remarkable results due to the scarcity of homografts (especially small ones) and under urgent conditions [14]. All the reports on any type of right ventricle-to-pulmonary artery (RV-PA) replacement are better in mid-term follow-up terms with regard to freedom from reoperation or reintervention than our present series. However, some authors

Figure 6: A 23-mm No-React® Injectable BioPulmonic™ valve 5 years after implantation (Patient 5): dynamic sub-pulmonary narrowing (A), paravalvular flow and neointimal proliferation unmasked by test-ballooning with a 20/45 mm CBV (Balt), which occluded the valved stent completely at low inflation pressures correlating to an inner lumen around 17 mm (B). Deployment of a custom-made, 55 mm, covered 10-zig CP stent premounted on a 24/60 mm Balloon-in-Balloon system (NuMed) (C). After implantation of a second prestent (AS XXL 43 mm, Andramed), high-pressure ballooning up to 22 bar with a 24/20 mm Atlas balloon (Bard) and PPVI (Melody TPV, Medtronic), redilatation was performed with a 30/60 mm CBV balloon (D). Reasonable final result without residual paravalvular flow on angiography (E/F).
detected neointimal thickening together with supravalvular stenosis at the anastomotic site and preterm degeneration in conjunction with this valve type [16]. The different valve types are difficult to compare because of selection bias and surgical preferences.

PPVI has been the obvious option for over 10 years for many patients requiring RV-PA revalvulation [17]. This minimally invasive procedure is doable in specialized centres, as it carries a low risk of severe complications and has demonstrated acceptable mid-term results [18]. Concerns were raised after a higher rate of infective endocarditis was noted with this prosthesis [19]. Other typical drawbacks of this procedure are also the need to extensively pretreat the RV-PA portion, and possible damage to the nearby coronaries. Because of well-documented good results following use of PPVI, contemporary surgical valve implantation should prepare the region for the next interventional valve and for the implantation of proper conduits with appropriate diameters.

The No-React® Injectable valve was created as a sort of ‘in-between’ valve offering the advantages of percutaneous and surgical valves. Prior to implantation, the valve requires surgical manipulation before the correct position can be obtained. The introducing material has also needed improvement [3, 5]. In particular, deployment of the self-expandable No-React® stent system is accompanied by a notorious jump during its injection, carrying a relatively high risk for accidental dislodgement. This might be why some of the valves reveal poor alignment to the RVOT during catheterization. With much more experience handling the device and sufficient modification of the introducer material, easy, safe and off-pump implantation appears possible. However, the poor long-term results we have observed have led us to discontinue the use of this prosthesis in our clinic. In addition, from the interventionalist’s perspective, it reveals other major disadvantages and drawbacks. To minimize the risk of coronary artery compression, test-ballooning during coronary angiography is necessary before stent implantation into the RVOT tract and proximal pulmonary artery, respectively. The No-React® valve’s stent-hooks and strut-edges carry a considerable risk for perforation, especially when implanted in the native tissue of a dilated MPA or whenever stent oversizing is planned.

Also, the stiff No-React® stent does not always accommodate the geometry of the right ventricular-to-pulmonary artery junction; its self-expandable construction does not allow any reshaping or flaring, and is not breakable by means of high-pressure ballooning (up to 22 bars). These obstacles for an interventional valve-in-valve procedure were the reason for the need for surgery in three patients. Deorsola and Abbruzzese [6] found this prosthesis very helpful in young children. From our experience, we cannot support their judgement. We noticed that the smallest No-react® valve (15 mm) in a 10 kg infant was borderline feasible. Technically, small diameters are more demanding during implantation owing to the non-compliant behaviour of the stent-prosthesis.

During its production, the valve material is processed in a special manner to prevent the recipient’s body reaction to the material [20]. We have noted the thickening of some valves in catheterization, and found histological evidence of neointimal overgrowth on the explanted No-React® valves. Excessive neointimal formation has been described before in conjunction with the use of the No-React® material [21]. These are probably degenerative changes due to the shrinking valve leaflet and concurrent increased tissue proliferation (‘pseudo-intima’), as our histological analysis demonstrates. Crimping might contribute to this negative finding, as has been investigated in transcatheter aortic valves [22]. However, a neointimal reaction has not been reported to this extent in a series of explanted Melody® valves [23].

We identified the indication to replace the valve according to clinical findings, valvar gradient and incompetence at rest. Whenever we were unable to determine the reason for the symptoms in borderline gradients across the RVOT, we administered dobutamine stress during catheterization as an additional decision aid. There is evidence that ventricular failure often first reveals itself during exercise and stress-testing [24, 25].

Limitations

This is a small series, and our results should be judged with caution. We stopped implanting the No-React® valve after our initial positive experience in 5 in order to carry out this mid-term investigation. We do, however, wish to express a word of caution before studies are performed in larger patient cohorts. We are curious to hear about findings—especially long-term results—from other cohorts in whom this valve has been implanted. A major limitation is that we had no control group. However, for a statistically sound matching procedure, we had too few patients. Moreover, variation in the group was significant.

CONCLUSION

Our mid-term results after implantation of the No-React® Injectable Biopulmonic™ valve are disappointing. After less than 7 years, 6 of 7 implanted valves needed to be replaced. Technical problems with improper alignment of the prosthesis towards the RVOT on the one hand and neointimal formation even in appropriately positioned valves on the other hand were the main reasons for graft failure. Based on our results, we have come to the conclusion that the ‘No-React’ valve does not deliver what its name promises.

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Your August 2015 publication, ‘No-React® Injectable BioPulmonic™ valves re-evaluated’ [1] is part of a great case study on how not all minimally-invasive valves were designed or intended to be used in the same way. The device’s label is for implant in surgical implants. Heart 2015;101:788–93.

Conflict of interest: The author is a heart surgeon and the inventor of this valve.

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